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AIM AND SCOPE *World Journal of Clinical Cases* (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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What is the purpose of launching the *World Journal of Clinical Cases*?

Shuheï Yoshida

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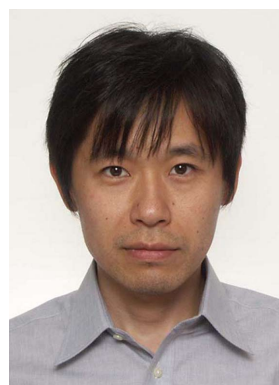


Figure 1 Editor-in-Chief of the *World Journal of Clinical Cases*. Shuheï Yoshida, MD, PhD, a Research Fellow in Gastroenterology, Harvard Medical School, Beth Israel Deaconess Medical Center, Dana 509, 330 Brookline Avenue, Boston, MA 02215, United States. He is also an Assistant Professor in Gastroenterology, Tokyo Women's Medical University, Yachiyo Medical Center, 477-96 Owada-Shinden, Yachiyo, Chiba 276-8542, Japan.

Abstract

The first issue of the *World Journal of Clinical Cases* (WJCC), whose preparatory work was initiated on October 26, 2012, will be published on April 16, 2013. The WJCC Editorial Board has now been established and consists of 520 distinguished experts from 55 countries. Our purpose of launching WJCC is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

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Key words: Clinical cases; Peer-reviewed; Open-access; Authors; Readers

Core tip: Evidence-based medicine (EBM) is the gold standard in current clinical treatments and essential for advancement of medicine. EBM attempts to objectively evaluate the quality of clinical research by critically assessing techniques reported by researchers in their publications. Therefore, high-quality clinical case studies published in clinical journals, which anyone can read, are extremely important. Information technology revolution brought us benefits that readers can easily access

such journals from home, on mobile devices, or even while traveling. It will also accelerate further progress in EBM. *World Journal of Clinical Cases* should be a leading journal based on EBM.

Yoshida S. What is the purpose of launching the *World Journal of Clinical Cases*? *World J Clin Cases* 2013; 1(1): 1-3 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/1.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.1>

INTRODUCTION

I am Shuheï Yoshida, MD, PhD, a Research Fellow in Gastroenterology, Harvard Medical School, Beth Israel Deaconess Medical Center, United States, and an Assistant Professor in Gastroenterology, Tokyo Women's Medical University, Yachiyo Medical Center, Japan (Figure 1). Together with Giuseppe Di Lorenzo, MD, PhD, Professor, from the Genitourinary Cancer Section and Rare-Cancer Center, University Federico II of Napoli, Italy; Jan Jacques Michiels, MD, PhD, Professor, from the Primary Care, Medical Diagnostic Center Rijnmond Rotterdam, Blood Coagulation, Internal and Vascular Medicine, Erasmus University Medical Center, The Netherlands; and Sandro

Vento, MD, from the Department of Internal Medicine, University of Botswana, Botswana. We will be the co-Editor-in-Chief for *World Journal of Clinical Cases* (*World J Clin Cases*, *WJCC*, ISSN 2307-8960, DOI: 10.12998). I am very pleased to announce that the first issue of *WJCC* will be published on April 16, 2013. The *WJCC* Editorial Board has now been established and consists of 520 distinguished experts from 55 countries. The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the “priority” and “copyright” of innovative achievements published, as well as evaluating research performance and academic levels. Evidence-based medicine (EBM) is the gold standard in current clinical treatments and essential for advancement of medicine. EBM attempts to objectively evaluate the quality of clinical research by critically assessing techniques reported by researchers in their publications. Therefore, high-quality clinical case studies published in clinical journals, which anyone can read, are extremely important. High-quality clinical case studies published in clinical journals benefit patients in the following ways: (1) Published clinical studies add novel treatment options to standard therapeutic strategies that may be on the cutting edge; and (2) Through clinical studies published in *WJCC*, patients can access to investigational agents, devices, imaging studies, technology, equipment, or novel diagnostic techniques at no additional cost.

AIM AND SCOPE

WJCC is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Autobiography, Case Report, Clinical Case Conference (Clinicopathological Conference), Clinical Management, Diagnostic Advances, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Clinical Practice, Meta-Analysis, Minireviews, Review, Therapeutics Advances, and Topic Highlight, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, geriatrics and gerontology, hematology, immunology, infectious diseases, internal medicine, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, peripheral vascular disease, psychiatry, radiology, rehabilitation, respiratory medicine, rheumatology, surgery, toxicology, transplantation, and urology and nephrology.

WJCC is dedicated to become an influential and prestigious journal in clinical cases, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJCC* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the study is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of *WJCC* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in science.

tific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers); (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-

quality clinical case conference; (11) Original Articles: To report innovative and original findings in clinical research; (12) Clinical Practice: To briefly report the novel and innovative findings in clinical practice; (13) Meta-Analysis: To evaluate the clinical effectiveness in clinical medicine by using data from two or more randomized control trials; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in *WJCC*, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of clinical medicine; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

CONCLUSION

Together, investigators who want to share any new finding or investigations, clinical experience on the application or improvements of diagnostic and therapeutic skills of clinicians, the *WJCC* will be a good place for you! As the Editor-in-Chief for *WJCC*, I am looking forward to your contributions to this attractive journal!

P-Reviewer Wang F **S-Editor** Wang JL
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Current concepts on spinal arthrodesis in degenerative disorders of the lumbar spine

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Abstract

Back pain is a common chronic disorder that represents a large burden for the health care system. There is a broad spectrum of available treatment options for patients suffering from chronic lower back pain in the setting of degenerative disorders of the lumbar spine, including both conservative and operative approaches. Lumbar arthrodesis techniques can be divided into sub-categories based on the part of the vertebral column that is addressed (anterior *vs* posterior). Furthermore, one has to differentiate between approaches aiming at a solid fusion in contrast to motion-sparing techniques with the proposed advantage of a reduced risk of developing adjacent disc disease. However, the field of application and long-term outcomes of these novel motion-preserving surgical techniques, including facet arthroplasty, nucleus replacement, and lumbar disc arthroplasty, need to be more precisely evaluated in long-term prospective studies. Innovative surgical treatment strategies involving minimally invasive techniques, such as lateral lumbar interbody fusion or transforaminal lumbar interbody fusion, as well as percutaneous implantation of transpedicular or trans-

facet screws, have been established with the reported advantages of reduced tissue invasiveness, decreased collateral damage, reduced blood loss, and decreased risk of infection. The aim of this study was to review well-established procedures for lumbar spinal fusion with the main focus on current concepts on spinal arthrodesis and motion-sparing techniques in degenerative disorders of the lumbar spine.

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Key words: Spinal arthrodesis; Lumbar spine; Motion-sparing implants; Intrebody fusion

Core tip: There is a broad spectrum of surgical techniques that can be performed in order to fuse lumbar motions segments. The aim of this study was to review well-established procedures for lumbar spinal fusion with the main focus on current concepts on spinal arthrodesis and motion-sparing techniques in degenerative disorders of the lumbar spine, including minimally invasive interbody fusion, total disc arthroplasty, nucleus replacement systems, percutaneous implantation of pedicle and facet screws, facet arthroplasty, and interspinous implants.

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INTRODUCTION

Back pain is a common chronic disorder that has been reported to affect more than a quarter of the adult population in the United States, representing a large burden for the health care system^[1]. Within the last decades health

care costs of back and neck pain have increased tremendously. In a recent report the increase in expenditures was estimated at 65% between 1997 (52.1 billions of US dollars) and 2005 (85.9 billions of US dollars)^[2].

There is a broad spectrum of available treatment options for patients with lower back pain due to degenerative disorders of the lumbar spine, including both conservative and operative approaches. Furthermore, novel and innovative surgical treatment strategies involving minimally invasive and motion-sparing techniques have emerged within the last decade. The aim of this study was to review well-established procedures for lumbar spinal fusion with the main focus on current concepts on spinal arthrodesis and motion-sparing techniques in degenerative disorders of the lumbar spine.

ANATOMY

The lumbar vertebral column is usually made up of five vertebral bodies (L1-L5), each providing a dense apophyseal ring at the top and bottom surfaces. The pedicles are bony processes projecting dorsally to merge into the two laminae, which fuse to one spinous process at the posterior midline. At the pediculo-laminar junction, the transverse process projects laterally on each side. Vertebral bodies articulation is executed *via* the intervertebral spinal disc as well as the superior and inferior articular processes extending from the superior and inferior laminar margins bilaterally. The superior articular process of the inferior lumbar vertebra articulates with the inferior articular process of the superior vertebral body to form the facet joint, also referred to as the zygapophyseal joint (Figure 1). The superior articular process forms the anterior part of the facet joint with a concavely shaped articular surface, compared to the convex shape of the inferior facet. The bony joint surfaces are covered by hyaline cartilage and lined by a synovial membrane. The lumbar spine can be further divided into three parts: the thoraco-lumbar junction (Th12-L1), the mid-lumbar spine (L1-L5), and the lumbo-sacral junction (L5-S1). Within the thoraco-lumbar junction, there is a transition from the rigid kyphotic thoracic to the more flexible lordotic lumbar spine, representing a zone of increased shear stress to the intervertebral motion segment. After exiting through the foramen magnum at the base of the skull, the spinal cord travels within the spinal canal, made up of the dorsal vertebral body surfaces, the pedicles, as well as the laminae. The abdominal aorta and the inferior vena cava travel anterior to the vertebral column and bifurcate to supply the pelvis and the lower extremities. The lumbar spinal roots exit the intervertebral foramen beneath the pedicle of the corresponding vertebral body into the pelvis to form the lumbar plexus, which travels through the posterior third of the psoas muscle with branches exiting at its anterior or lateral surfaces^[3-6].

While the lumbar plexus travels within the posterior third of the psoas in the majority of cases, recent studies

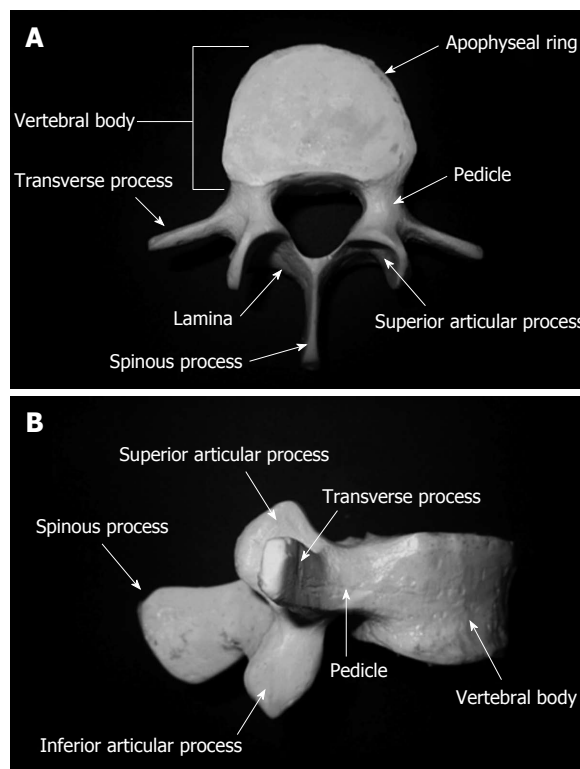


Figure 1 Schematic illustration of a typical lumbar vertebral body. A: View from above; B: View from the side.

have underlined its possible anatomical location posterior to the psoas muscle^[7].

LUMBAR ARTHRODESIS AND MOTION-SPARING TECHNIQUES

Lumbar spinal fusion is increasingly utilized to treat a broad spectrum of degenerative spine disorders, including scoliosis, spondylolisthesis, and spinal stenosis. Traditionally, fusion of a motion segment can be achieved by mechanical roughening and decortication of articular surfaces and packing the joint space with bone graft material, including iliac crest autograft, allograft material, or biologic adjuncts such as bone morphogenetic proteins (BMPs)^[4,8-16].

There is a wide spectrum of lumbar spinal arthrodesis techniques addressing different parts of the vertebral column. With regard to the well-established three-column theory of the spine^[17], plates, cages, and disc arthroplasty devices can be implanted with the aim to correctly align and stabilize the anterior two columns, while wiring systems, hook-based systems, pedicle screws, translaminar screws, facet replacement systems, and interspinous implants address the posterior column.

The selection of the appropriate surgical arthrodesis technique for lumbar spinal fusion is influenced by factors, such as the number of diseased motions segments, the affected number of columns per level, and the degree of instability, among others. Furthermore, to achieve

Table 1 Advantages and disadvantages of current procedures for the treatment of degenerative disorders of the lumbar spine

Surgical technique	Advantages	Disadvantages
ALIF	Direct visualization of disc space Small incisions and reduced tissue invasiveness if minimally invasive approach performed ^[27-30]	Intra-abdominal vascular and visceral injury ^[31,32]
PLIF	Avoiding intra-abdominal complications associated with anterior approach	Increased risk of surgical damage to neural structures, dural layer, and epidural veins ^[33-35]
LLIF	Avoiding surgical complications associated with anterior and posterior approaches Sparing of anterior longitudinal ligament (ligamentotaxis) ^[36] Stable implantation of device due to bilateral utilization of the dense apophyseal ring ^[36]	Limited surgical accessibility of L5-S1 level due to iliac crest Injury to lumbar plexus during transpsoas approach with post-operative approach-related neurological deficits ^[37-40]
TLIF	Minimally-invasive Reduced nerve root retraction ^[41] Circumferential fusion ^[27,41-43]	Less reduction in ROM compared to LLIF, if performed as stand-alone procedures ^[41]
Total disc arthroplasty	Reduced risk of adjacent segment disease due to preservation of motion ^[47] No fusion required ^[47]	Narrow spectrum of indications ^[48,49]
Nucleus replacement	Preservation of motion Multiple approach and revision options ^[53]	Risk of device migration, extrusion, and subsidence ^[53,54]
Sublaminar wiring	Can be implanted as an adjunct to other devices (hybrid) ^[4]	Risk of neurological injury ^[58,59]
Pedicle screws	Involvement of all three columns ^[4] Rigid segmental fixation ^[4] High fusion rates ^[4] Adequate deformity correction ^[4] Percutaneous approach possible ^[65-67]	High costs ^[4] Damage to neural and vascular structures ^[4] Adjacent segment disease ^[62]
Translaminar screws	Minimally-invasive percutaneous approach available ^[4,68,69]	Not indicated for multilevel arthrodesis ^[4,68,69]
Facet arthroplasty	Preservation of motion Reduce the risk of adjacent segment disease ^[71]	Complex anatomy of facet joints Narrow spectrum of indications
Interspinous implants	Preservation of motion	Narrow spectrum of indications

ALIF: Anterior lumbar interbody fusion; PLIF: Posterior lumbar interbody fusion; LLIF: Lateral lumbar interbody fusion; TLIF: Transforaminal lumbar interbody fusion; ROM: Range of motion.

adequate bony fusion, factors such as local and systemic bone quality, diabetes, smoking, and corticosteroid use, among others, have to be considered^[4]. The main advantages and disadvantages of current procedures for the treatment of degenerative disorders of the lumbar spine are summarized in Table 1.

In a recent systematic review on 26 articles including a total number of 3060 patients, Phillips *et al.*^[18] concluded that lumbar arthrodesis is a viable treatment strategy for patients with degenerative disc disease related low back pain who are refractory to non-surgical treatment, both with regard to pain reduction and functional improvement.

ANTERIOR SPINE

The implantation of anterior instrumentation systems has previously been shown to successfully restore immediate post-operative stability^[19], and to correct post-traumatic deformities such as progressive kyphosis^[20]. The spectrum of relative contraindications for the anterior approach includes severe osteoporosis and scarring due to previous abdominal surgery^[4]. Gurwitz *et al.*^[21] compared three different approaches for short-segment instrumentation in a lumbar spine burst fracture model: posterior instrumentation alone (VSP plates: Acromed, Cleveland, OH)

or with an anterior strut graft, and anterior instrumentation (Kaneda system: Acromed, Cleveland, OH) with an anterior strut graft. Posterior instrumentation alone indicated 76% less axial stiffness compared to the intact spine. Posterior instrumentation supplemented by anterior strut grafting revealed axial stiffness results that were not significantly different from the intact lumbar spine. Finally, anterior instrumentation with anterior strut grafting indicated 15% more axial stiffness than the intact spine. However, the three approaches showed 30%, 26%, and 24% decreased rigidity when compared to the intact spine. In their biomechanical study on anterior and posterior lumbar stabilization procedures, Flamme *et al.*^[22] compared three systems: anterior instrumentation alone [modular anterior construct system (MACS), Aesculap AG and Co. KG, Tuttlingen, Germany], MACS anterior instrumentation with intercorporeal Pyramesh cage augmentation (Medtronic Sofamor Danek, Memphis, TN), and posterior screw-rod instrumentation alone (SOCON: SOLID CONNECTION, Aesculap AG and Co. KG, Tuttlingen, Germany). When compared to the physiologic lumbar motion segments all three systems demonstrated increased stability and reduced mobility. The authors concluded that anterior instrumentation with intercorporeal cage augmentation results in comparable or even greater stability than posterior stabilization, with the exception of flexion/extension.

Interbody fusion

Since augmentation of the intervertebral space with bone graft alone has resulted in insufficient support of the anterior vertebral column of the lumbar spine with a resulting high rate of pseudarthrosis, intercorporeal implantation of cage devices has emerged in recent years^[23]. The principle of achieving intervertebral fusion with cage implantation is to expose the intervertebral disc space, to perform complete discectomy as well as end plate preparation (*i.e.*, removal of cartilage), and to implant a synthetic device. Commercially available cages can be loaded with bone graft supplements, including vertebral body and iliac crest aspirate, iliac crest bone graft (ICBG) material, β tricalcium phosphate, stem cell allografts, demineralized bone matrix, and biologic adjuncts, such as BMPs^[4].

Various techniques for intervertebral cage implantation have been described. The diverse spectrum of common interbody fusion techniques comprises anterior lumbar interbody fusion (ALIF), lateral lumbar interbody fusion (LLIF), transforaminal lumbar interbody fusion (TLIF), and posterior lumbar interbody fusion (PLIF), each characterized by a different approach to access the lumbar spine.

ALIF: Since the early 1930s, when the anterior approach for lumbar arthrodesis *via* bone grafting was first described as a surgical alternative for the management of spondylolisthesis^[24,25], the spectrum of conditions being addressed by the ALIF technique has widened. Currently, ALIF can be used to treat spondylolisthesis, lumbar instability, degenerative disc disease, and pseudarthrosis^[26,27]. *Via* either a retroperitoneal or a transperitoneal approach, the spine surgeon gains access to the lumbar intervertebral motions segments to excise the disk and insert a cage at the anterior part of the intervertebral space. A suggested advantage of ALIF over other interbody fusion techniques is direct visualization of the intervertebral space, potentially associated with improved post-operative outcome. In contrast to traditional invasive ALIF approaches, a minimally invasive surgical approach has been emerged recently, with the advantage of small incisions and reduced tissue invasiveness^[28-31]. ALIF has been reported to be associated with an increased risk of surgical collateral damage, such as intra-abdominal vascular and visceral injury^[32,33].

PLIF: The PLIF procedure, as originally described by Cloward^[34] in 1953, is characterized by sparing the facet joints, and by gaining access to the lumbar motion segment *via* laminotomy/laminectomy, followed by discectomy, decortication of vertebral body end plates, and the implantation of an interbody fusion device/graft. A suggested advantage of the posterior approach in PLIF is the avoidance of intra-abdominal vascular and visceral injury as seen in anterior approaches to the lumbar spine (*e.g.*, ALIF). However, PLIF is associated with an increased

risk of damage to neural structures, epidural vein injury potentially resulting in increased peri-operative blood loss, and dural laceration, among others^[34-36].

LLIF: Due to reduced risk of surgical collateral damage associated with the ALIF or PLIF approach^[32,33,35,36], the minimally-invasive LLIF procedure has recently been established to address lumbar motion segments L1-L5, as described by Ozgur *et al.*^[37] in detail. The implantation of LLIF cages at the L5-S1 level can be difficult due to the presence of the iliac crest potentially blocking the surgical access. The LLIF approach requires blunt dissection of the psoas muscle in order to insert minimally invasive tubular retractors. Following discectomy the procedure utilizes the dense apophyseal ring for device implantation, allowing a more stable fixation of the device and preventing subsidence. Furthermore, when compared to ALIF, the surgical approach in LLIF spares the anterior longitudinal ligament, leading to increased post-operative vertebral column stability and improved alignment *via* ligamentotaxis^[37]. However, due to the proximity of the lumbar plexus, which usually travels within the posterior third of the psoas muscle^[6,7], concerns regarding approach-related neurological adverse sequelae have arisen^[38-41]. Analysis of our unpublished data on 919 treated levels revealed that neurological deficits following LLIF, although high in the immediate post-operative setting, steadily decrease over time, which underlines the transiency of the majority of these deficits.

TLIF: TLIF is another minimally invasive approach to achieve lumbar arthrodesis, which has been reported to reduce the extent of nerve root retraction associated with the PLIF procedure^[42]. Unilateral facetectomy and/or laminectomy/laminotomy are followed by implantation of pedicle screws, discectomy at the appropriate level, gradual distraction of the intervertebral disk space, and surgical preparation of vertebral bony endplates. By careful retraction of the thecal sac and protection of the traversing nerve root, interbody fusion cages can be implanted through the intervertebral foramen, and the pedicle screws can be connected *via* a rod. Posterolateral fusion can further be achieved by decortication of the transverse processes and augmentation with ICBG. Due to surgeon's ability to address both the anterior as well as the posterior columns of the spine, TLIF has become a favorable procedure to achieve circumferential fusion^[28,42-44]. In their study on comparative effectiveness and cost-utility analysis comparing minimally invasive TLIF (MIS TLIF) *vs* the open TLIF procedure for degenerative spondylolisthesis, Parker *et al.*^[45] reported a similar post-operative patient-reported outcome for both techniques, but significantly less lengths of both hospital stay and return to the work force for MIS TLIF, resulting in a reduction in both societal and hospital costs.

Biomechanics of interbody cages: According to Ox-

land *et al*^[46], the implantation of anterior lumbar interbody cages alone provides stability of the vertebral column in flexion, axial rotation, and lateral bending, when compared to the intact spine, but no stabilization in extension. Posterior implantation of a titanium interbody cage has been reported to achieve higher stiffness, when compared to both the intact spine and the augmentation with bone graft alone, and to result in similar stiffness, when compared to posterior instrumentation supplemented by bone graft^[47]. In their biomechanical study, Cappuccino *et al*^[48] evaluated the range of motion (ROM) after the implantation of LLIF cages. The authors compared their results with current literature and concluded that the implantation of LLIF devices without supplemental instrumentation (*i.e.*, stand-alone LLIF) results in greater segmental reduction in ROM, when compared to stand-alone ALIF or TLIF procedures. Furthermore, the authors demonstrated that supplemental bilateral posterior instrumentation with pedicle screws results in the largest decrease of ROM.

Total disc arthroplasty

The principle of total disc arthroplasty (TDA) is to replace the degenerated disc by an intervertebral prosthesis with the theoretical advantage of preservation of ROM. Due to reduced shear stresses at the adjacent level based on preserved motion, a decreased risk for adjacent segment disease has been suggested. Furthermore, since no fusion is required, arthrodesis-associated adverse sequelae such as pseudarthrosis and donor site morbidity due to bone graft harvesting can be avoided^[49]. However, the surgical indications for performing TDA at the lumbar spine remain narrow. Previous studies have suggested young patients, with disc disease involving one motion segment, normal bone quality, intact facet joints, and absence of scoliosis and spinal instability (*e.g.*, spondylolisthesis, spinal fracture) as the ideal candidates to undergo lumbar TDA^[50,51]. In their prospective, randomized, multicenter study, Blumenthal *et al*^[52] revealed that the implantation of the CHARITÉ artificial disc (DePuy Spine, Raynham, MA) results in at least equivalent clinical outcomes, when compared to ALIF. Zigler *et al*^[53] compared ProDisc-L (Synthes Spine, West Chester, PA) lumbar TDA with circumferential fusion for the treatment of single-level lumbar degenerative disc disease. The authors concluded that ProDisc-L, with careful patient selection, achieves superior clinical results compared to circumferential fusion. The efficacy of ProDisc-L implantation was supported by a recent study on the long-term post-operative outcome. Although the results support both ProDisc-L and circumferential arthrodesis as adequate approaches to treat single-level degenerative disc disease, patients who had undergone TDA demonstrated more rapid improvement, with regard to post-operative pain, disability, and neurological function^[54].

Nucleus replacement

Nucleus replacement (nucleoplasty) devices can be func-

tionally divided into two major groups: elastomeric and mechanical nucleus devices, with elastomeric devices further being divided into hydrogel and non-hydrogel devices that are either injectable or preformed. Mechanical nucleus devices can further be sub-classified as one- or two-piece systems. The proposed advantages of nucleoplasty are the variety of minimally invasive surgical approaches that can be performed, and the multiple revision options after failed nucleoplasty, including lumbar disc arthroplasty and spinal fusion^[55]. Furthermore, as seen in other motion sparing techniques^[49], the risk of adjacent segment disease may also be reduced due to preservation of mobility of the addressed motion segment. However, the risk of device migration or extrusion, as well as subsidence remain a source of concern^[55,56]. The evaluation of post-operative outcome following NUBAC™ implantation, a novel nucleus disc device made of polyetheretherketone and two articulating pieces, revealed absence of major intra- and post-operative complications as well as significant post-operative decrease in visual analogue scale and Oswestry disability index parameters in addition to symptomatic improvement in all patients, underlining both the efficacy and safety of the approach, likely attributable to the reduced invasiveness of the procedure^[57]. However, further prospective studies on long-term outcomes and the influence on the adjacent motion segments are warranted.

POSTERIOR SPINE

Laminar wiring

One of the most common wiring procedures is the Luque technique, utilizing sublaminar wires for segmental spinal stabilization^[4,58-60]. This procedure has been associated with an increased risk of neurological injury, especially in the thoracic spine^[60,61]. Wires can also be used to attach the implanted rod to the spinous process ("Wisconsin method"^[62]), thereby avoiding the risk of injury to the spinal cord associated with the Luque technique^[60,61,63]. Currently, wiring systems are more commonly implanted supplemental to other fusion or stabilization devices such as pedicle screws, instead of being utilized alone (hybrid systems)^[4].

Pedicle screws

Transpedicular screw fixation, a common procedure aiming at the stabilization of the vertebral column, is the only available surgical technique that addresses all three columns of the spine. It has been reported to achieve rigid segmental fixation, high fusion rates, and deformity correction. Disadvantages include the high cost and the risk of damage to the thecal sac, the nerve roots, and major vascular structures^[4]. Furthermore, pedicular screw insertion has been shown to be associated with a higher risk of developing adjacent segment disease (12.2%-18.5%) compared to patients with a different instrumentation technique (posterior midline and interbody arthrodesis) or non-instrumented fusion (5.2%-5.6%)^[64]. When a

recent retrospective series evaluated adverse sequelae related to the implantation of transpedicular screws in 648 patients screw misplacement was evident in three cases, nerve root impingement in one case, leakage of cerebrospinal fluid in two cases, pedicular fracture in two cases, deep wound infection in four cases, screw loosening in two cases, and rod-screw disconnection in one case^[65]. In a recent meta-analysis, comparing different constructs in terms of mid- to long-term outcomes following instrumented posterior spinal fusion for adolescent idiopathic scoliosis, Cotrel-Dubousset instrumentation achieved higher degree of correction in the coronal plane, as well as better restoration of thoracic kyphosis and lumbar lordosis when compared to all-pedicle screw constructs. All-pedicle screw fixation was associated with the lower risk of pseudarthrosis, infection, neurologic deficit, and revision surgery^[66]. A novel technique for pedicle screw implantation is the percutaneous approach supplemental to an ALIF procedure for the treatment of spondylolisthesis. Advantages include reduced surgical time, blood loss and collateral tissue damage, high fusion rates, and low incidence of adjacent disc degeneration^[67-69].

Translaminar screws

Compared to transpedicular screw fixation, the translaminar approach has been shown to be associated with reduced soft tissue damage when screws are implanted *via* a minimally invasive percutaneous approach. However, translaminar screw technique is not indicated for multilevel arthrodesis since it does not provide enough strength of fixation^[4,70,71].

Facet arthroplasty

Replacement systems of the facet joint, such as the total facet arthroplasty system (TFAS) (Archus Orthopedics, Redmond, WA), can be implanted following posterior decompression in the setting of degenerative facet complex disease, and degenerative lumbar spinal stenosis^[72], with the aim to avoid the need for lumbar spinal fusion^[4]. By restoring the ROM at the operated motion segment to intact values and to almost physiologic kinematics at the adjacent levels, TFAS may reduce the risk of adjacent segment disease^[73]. TFAS is characterized by the transpedicular implantation of two straight metal stems into the inferior vertebral bodies and two bent metal stems into the superior ones. The two superior L-shaped metal stems are connected to a cross-arm with spherically-shaped ends that articulate with the bearing surfaces at the tops of the two inferior straight metal stems during flexion and extension^[72-74]. Due to financial problems the company had to discontinue distribution of the TFAS system, with a resulting lack of data regarding long-term outcomes. Other facet replacement systems, being characterized by individually sizing all articulating bony components in order to satisfactorily emulate the individual's anatomy of the facet joint, are currently under investigation. Clinical studies focusing on the long-term outcomes of these devices are warranted^[4].

Interspinous implants

Interspinous spacers, including the X-STOP device (Medtronic, Minneapolis, MN), have recently been introduced as motion-preserving implants for the treatment of lumbar degenerative conditions such as spinal stenosis, due to increase of flexion and prevention of extension at the motion segment level, in addition to distraction of the spinous processes^[4]. This concurs with the results of a randomized, controlled, prospective multicenter trial underlining the efficacy of the X-STOP interspinous spacer in the treatment of spinal stenosis. After 2 years of follow-up, patients treated with X-STOP showed an improvement of 45.5% in terms of disease symptom severity, compared to an improvement of only 7.4% recorded in conservatively treated patients^[75]. The Wallis System (Zimmer, Warsaw, IN) is implanted into the lumbar spine without permanent bony fixation ("floating" system) with the aim to decrease the risk of device loosening. It is recommended in the setting of disectomy for massive and/or recurrent disc herniation, adjacent segment disc degeneration, and chronic low-back pain due to mild degenerative disc disease (Modic I)^[76].

CONCLUSION

There is a broad spectrum of surgical techniques that can be performed in order to fuse lumbar motions segments. Advantages and disadvantages of each arthrodesis technique have to be taken into consideration during pre-operative surgical planning. The transition from open to minimally invasive surgical procedures, potentially supplemented by biologic adjuncts such as BMPs, is promising. The field of application and long-term outcomes of novel motion-sparing surgical techniques, such as facet arthroplasty, nucleus replacement, and lumbar disc arthroplasty, need to be more precisely evaluated in further, ideally prospective, studies.

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Proteinuria in paediatric patients with human immunodeficiency virus infection

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Core tip: Highly active antiretroviral therapy has decreased the mortality and morbidity of human immunodeficiency virus (HIV)-infected adults and children, too. Many of the antiviral drug used can cause side effects and in particular renal toxicity. A monitoring of renal function is useful for the management of HIV-infected patients.

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Abstract

In human immunodeficiency virus (HIV)-infected people kidney disease is as an important cause of morbidity and mortality. Clinical features of kidney damage in HIV-infected patients range from asymptomatic micro-albuminuria to nephrotic syndrome. The lack of specific clinical features despite the presence of heavy proteinuria may mask the renal involvement. Indeed, it is important in HIV patients to monitor renal function to early discover a possible kidney injury. After the introduction of antiretroviral therapy, mortality and morbidity associated to HIV-infection have shown a substantial reduction, although a variety of side effects for long-term use of highly active antiretroviral therapy, including renal toxicity, has emerged. Among more than 20 currently available antiretroviral agents, many of them can occasionally cause reversible or irreversible nephrotoxicity. At now, three antiretroviral agents, *i.e.*, indinavir, atazanavir and tenofovir disoproxil fumarate have a well established association with direct nephrotoxicity. This review focuses on major causes of proteinuria and other pathological findings related to kidney disease in HIV-infected children and adolescents.

INTRODUCTION

In human immunodeficiency virus (HIV)-infected people kidney disease has recently emerged as an important cause of morbidity and mortality. HIV, can cause severe kidney disease directly, including acute kidney injuries, thrombotic microangiopathies, HIV-associated nephropathy (HIV-AN), and HIV immune complex kidney disease (HIV-ICK). Likewise, many co-morbidity, such as tuberculosis, opportunistic and bacterial infections and sexually transmitted infections can cause a variety of kidney disorders that may affect the outcome of HIV infection. Rao *et al*^[1] divided the HIV-1-associated renal parenchymal diseases in four groups: (1) acute tubular dysfunction with electrolytes abnormalities and/or renal failure caused by infections and nephrotoxic drugs; (2) HIV glomerulopathies related to immunological abnormalities; (3) HIV-associated thrombotic microangiopathies; and (4) HIV-AN.

Before highly active antiretroviral treatment (HAART), an association of renal impairment with faster progres-

sion to acquired immunodeficiency syndrome and death in HIV-infected people was demonstrated^[2]. Hence, in the United States approximately 40% of all HIV-infected children presented renal complications. Among them, 10%-15% developed a renal disease named HIV-AN^[3,4]. HIV-AN has been described as a clinical and renal histological syndrome characterized by heavy proteinuria and rapid progression to end-stage kidney disease^[5,6]. Histopathological findings include collapsing glomerulopathy, global or focal glomerulosclerosis, microcystic transformation of renal tubules, interstitial inflammation and hyperplasia of podocytes^[7]. A genetic predisposition was supposed on the demonstration of the unique susceptibility of African-Americans to the development of this disease, although the responsible genes have not yet been identified^[8,9]. The finding of HIV-AN in children provided strong evidence that HIV-1 per se was capable of inducing renal disease independently of other confounding variables that are present in HIV-infected adults (such as heroin abuse)^[10].

Clinical features of kidney damage in HIV-infected patients range from asymptomatic microalbuminuria to full-blown nephrotic syndrome^[11]. Children with HIV-related kidney disease may also develop acute kidney injury, thrombotic microangiopathies (including atypical forms of haemolytic uraemic syndrome) and some may progress to chronic kidney disease (CKD)^[4]. The most common presentation is nephrotic syndrome, followed by anasarca and moderate range proteinuria. Edema and hypertension, in accordance with reports from adults, are rare in children with kidney disease^[5]. The lack of clinical features despite the presence of heavy proteinuria may mask the renal involvement. Indeed, it is important in HIV-infected patients to monitor renal function to early discover a possible kidney injury.

After the introduction of antiretroviral therapy, mortality and morbidity associated to HIV-infection have shown a substantial reduction, although a variety of side effects for long-term use of HAART, including renal toxicity, has emerged^[12,13].

Among more than 20 currently available antiretroviral agents, many of them can occasionally cause reversible or irreversible nephrotoxicity. Many of the nucleoside reverse transcriptase inhibitors, particularly older agents like didanosine, have been implicated as a cause of type B lactic acidosis, but this acid-base imbalance is not, strictly speaking, renal toxicity. Only three antiretroviral agents, *i.e.*, indinavir, atazanavir (ATV) and tenofovir disoproxil fumarate (TDF) have a well established association with direct nephrotoxicity.

Indinavir is an antiretroviral agent belonging to the protease inhibitor class. It was among the first agents used as a part of potent combination HAART and the most commonly protease inhibitor used in 1996, but nowadays, because of its inconvenient dosing, meal restrictions and nephrolithiasis, it is only rarely prescribed. Indinavir notoriously causes renal and urologic toxicity mediated by tubular crystallization^[14,15]. Guidelines recommend that

patients receiving indinavir drink at least 1.5 L of water a day and that periodic urinalysis and monitoring of serum creatinine concentration be performed.

ATV is a newer antiretroviral agent belonging to the protease inhibitor class characterized by an excellent tolerability and a potent efficacy in controlling HIV infection. It is poorly soluble in urine and easily precipitating at alkaline pH. In contrast to indinavir, clinically significant crystalluria and associated interstitial nephritis were not observed in patients treated with ATV, whereas several reports described ATV nephrolithiasis^[16,17]. Two recent publications estimated the relation between CKD and antiretroviral drug use in HIV-positive patients. Mocroft *et al*^[18] analysed a cohort of 225 subjects showing that 3.3% persons progressed to CKD during 21 482 persons-year follow-up, thus resulting in CKD incidence of 1.05 per 100 person-year follow up. After adjusting for traditional risk factor associated with CKD and other confounding variables, increasing cumulative exposure to ATV (IRR 1.21, 95%CI: 1.09-1.34) and lopinavir/r were associated with a significant increased risk rate of CKD. Dauchy *et al*^[19] in the Aquitaine cohort demonstrated that the use of ATV is associated with an increased risk of proximal renal tubular dysfunction (1.28 per year of exposure). Lastly Rockwood examined the development of renal stones in a cohort of HIV-infected individuals attending the Chelsea and Westminster Hospital Foundation Trust exposed to different antiretrovirals. The rate of development of renal stones in the ATV/r group ($n = 1206$) compared with efavirenz-lopinavir/r-darunavir/r combined group ($n = 4449$) was 7.3 per 1000 patients years of antiretroviral therapy exposure (95%CI: 4.7-10.8). Thus ATV/r renal stones should be considered as a potential comorbidity^[20].

TDF is a nucleotide reverse transcriptase inhibitor. It is currently widely used due to its excellent properties, combining good potency, tolerability and convenience, either as a single agent or co-formulated with emtricitabine or with emtricitabine plus efavirenz^[21]. TDF showed a relatively good safety profile in registrational clinical trials, but subsequently a number of reports have alerted about cases of tubular damage and occasionally of renal insufficiency in patients treated with TDF^[22-24]. The pathogenesis of renal damage caused by TDF remains unclear^[25,26]. Reviews of reported cases of TDF-associated nephrotoxicity suggest that it mostly manifests as proximal tubular injury with associated reduction in glomerular filtration rate (GFR). Patients often develop glycosuria, tubular proteinuria, lowered serum phosphate and increased serum creatinine. Some patients may develop frank Fanconi's syndrome or reduced bone mineral density. Thus, it is important to early and accurately diagnose TDF-associated nephrotoxicity^[27]. If many data are available for adult patients, the renal safety of TDF in HIV-infected children and adolescents has not been well documented. Although sporadic cases of renal toxicity have been reported in HIV-infected children treated with TDF, a report describes renal safety outcome after 96 wk of use of tenofovir in HIV-infected children and

adolescents. The findings suggest that 96-wk use of TDF is not associated with any impairment of glomerular and tubular renal function in children with normal renal function at baseline^[28]. According to another 60 mo follow-up study in HIV-infected children, adolescents and young adults treated with TDF, this antiretroviral drug has an excellent renal safety profile^[29]. It stands to reason that TDF renal safety needs to be further evaluated in children, in particular in those who may be at higher risk as a result of pre-existing renal disease and concomitant use of nephrotoxic drugs. Moreover, given the need for long-term exposure to antiretroviral therapy in HIV pediatric patients, the renal safety of TDF could be better defined by longer observational studies.

Early detection and treatment of potentially serious kidney problems are especially critical for people living with HIV, since many of these cases are reversible or their evolution can be slowed if recognized in time^[30,31].

NEPHROPATHY AND DIAGNOSTIC TESTS

With the exception of the rather dramatic clinical presentations seen with a severe or complete loss of kidney function, many kidney disorders are asymptomatic or the symptoms are non-specific, such as fatigue, loss of appetite, nausea, headache, *etc.* For this reason, many kidney disorders can only be recognized with laboratory tests. The biomarkers currently used to detect kidney injury or monitor kidney function have limited sensitivity or dubious accuracy and have not been well studied in HIV-infected people, according to a recent review by Post *et al.*^[32]. Other markers, which may provide a better and earlier indication of specific forms of kidney damage, including tenofovir-related proximal tubule damage, are being investigated.

HIV-infected people can present with the classic clinical features of the nephrotic syndrome, such as heavy proteinuria, edema and hypoalbuminemia. The renal disease may also be clinically manifested by persistent and isolated proteinuria^[4]. CKD is determined by the presence of kidney damage, indicated by albuminuria or proteinuria, or GFR below 60 mL/min per 1.73 m² for ≥ 3 mo^[33]. Kidney disease and GFR are directly correlated, and the latter typically decreases before the onset of symptoms of kidney failure^[34]. Several equations to calculate GFR exist. The Cockcroft-Gault equation, which uses the 24-h urine creatinine clearance as indirect reference method, was the first and most attractive formula validated in adults. However, the need of body weight in the equation has greatly limited its practicability for widely use in renal medicine. Subsequently, the modification of diet in renal disease (MDRD) equation adjusted for four variables (age, gender, serum creatinine and ethnicity) was validated by Levey *et al.*^[35]. In addition, the same author recommended that the constant factor used in the original equation should be re-expressed using a new constant, if creatinine measurement is standardized against Isotope Dilution-Mass Spectrometry (reference

method). Extensive evaluation of the MDRD study equation shows good performance in population with lower levels of eGFR but variable performance in those with higher levels^[36]. To overcome the above mentioned pitfalls, the MDRD equation was revisited again by its original author^[37] and modified into a new equation: the CKD epidemiology collaboration (CKD-EPI) equation. Therefore, it was suggested to replace the MDRD equation with CKD-EPI in clinical use in adults.

In children over 12 years of age, the Cockcroft-Gault equation is the most frequently used. For children under 12 years of age, Schwartz formula enables to calculate GFR using length in place of weight^[38]. Although these equations are used in clinical practice as well as in several studies conducted in HIV-infected children and adults to evaluate GFR, none of them have been really validated in these cohorts of patients^[27].

The diagnosis of kidney injury may include albuminuria and proteinuria testing. Proteinuria is believed to be the earliest and most consistent clinical finding for the diagnosis of HIV-AN^[39,40]. Han *et al.*^[11] have reported the presence of microalbuminuria as an early marker of HIV-AN in adults. Urine albumin-to creatinine ratios (ACR) or protein-to-creatinine ratios (PCR) are reproducible measurements of proteinuria. Micro and macroalbuminuria are defined by ACRs > 30 mg/g and > 300 mg/g, respectively, while significant proteinuria is defined by a PCR > 200 mg/g. While albuminuria is more specific to glomerular injury (such as is seen in HIV-AN), proteinuria, that predominately includes albumin with other proteins, can be an indicator of either a glomerular or tubular defect. The most widely available tests that screen for proteinuria and albuminuria are urine dipstick test. However, a recent study has demonstrated that the sensitivity of dipstick test, may be affected by urinary concentration^[41]. So dipstick tests may miss about one out of five people with kidney disease, and positive dipstick test results for proteinuria may have to be confirmed by other lab tests. Dipstick test has been efficiently used by Ray *et al.*^[3] in association with other tests to diagnose HIV-AN through the following criteria: (1) persistent proteinuria, defined as an albus-tix reading above 1+ or a urinary protein-to-creatinine clearance ratio more than 0.1 for more than 2 mo in the absence of acute infection episodes; (2) abnormal microscopic examination of the urinary sediment under similar conditions, which in some cases included the presence of urine microcysts; (3) presence of enlarged echogenic kidneys detected by renal ultrasonography in at least two different studies performed 2 mo apart; and (4) black race and clinical history consistent with the typical diagnosis of HIV-AN (*i.e.*, nephrotic-range proteinuria without significant oedema and/or severe hypertension). Nephrotic range proteinuria has been defined by Ramsuran *et al.*^[42] as a PCR of ≥ 2.0 and by Chaparro *et al.*^[43] as a PCR of > 1.0 .

Proteinuria in children is an important prognostic factor for HIV-associated renal disease, and it needs to be assessed in follow-up to diagnose concurrent potentially progressive renal disease. As much as one third of the

Table 1 Features of proteinuria in different human immunodeficiency virus-associated kidney diseases in children

Type of proteinuria	Laboratory findings	Clinical findings
Glomerular proteinuria	Proteinuria: Urine protein to creatinine ratio > 200 mg/g Microalbuminuria: Urine albumine to creatinine ratio > 30 mg/g Macroalbuminuria: Urine albumine to creatinine ratio > 300 mg/g	HIV associated nephropathy
Tubular proteinuria	Proteinuria: Urine protein to creatinine ratio > 200 mg/g Urine albumine to creatinine ratio < 30 mg/g Proteinuria: Urine protein to creatinine ratio > 200 mg/g Urine albumine to creatinine ratio < 30 mg/g Glycosuria with normal glycemia Increased fraction excretion of phosphorus Reduced fraction excretion of uric acid	Infections or atazanavir use Fanconi syndrome associated with tenofovir use

HIV: Human immunodeficiency virus.

population may present proteinuria, but no more than 10% generally have a real nephropathy, defined as nephrotic-range proteinuria, which may benefit of HAART or angiotensin blockade therapy. Surveillance of quantitative proteinuria in conjunction with imaging and chemical indicators of renal dysfunction is very much warranted. It seems reasonable to propose nephrotic range proteinuria as a major criterion for defining the clinical nephropathy in children and would be a clear indication for renal biopsy and initiation of HAART in naive patients^[44,45]. Biopsy diagnosis can reveal the typical histological features of minimal change nephrotic syndrome, mesangioproliferative glomerular lesions, and “lupus-like” renal lesions^[3,10,39,46,47]. Other patients show renal changes consistent with the diagnosis of HIV-AN or HIV-ICK^[47]. Thus, performing a renal biopsy is the only way to establish a definitive diagnosis.

People with kidney disease localized in the renal tubule such as Fanconi's syndrome may have mild proteinuria composed of other proteins but rarely of albumin. The presence of renal tubular disorders in HIV-infected African American and Venezuelan patients has been recognized through hypercalciuria with a potential for nephrocalcinosis, and less frequently with crystalluria, hyperchloremia, and metabolic acidosis^[3,10,39]. Tubular disorders may induce sodium, potassium, and phosphate wasting states. Elevated fractional urinary excretion of phosphate is perhaps an earlier marker of proximal tubular dysfunction and might be useful in monitoring for TDF toxicity.

Besides proteinuria, there are a number of other biomarkers that could potentially be more specific for tubular inflammation or damage and that may serve as earlier and better indications of which patients are likely to experience tenofovir-associated toxicity. Post *et al.*^[32] note that since the proximal tubule is supposed to reabsorb substances such as low molecular weight proteins, increased excretion of these in the urine could indicate tubular dysfunction^[48,49]. Tests for these markers are not yet affordable or widely available and research into the use of these substances as biomarkers for renal tubule disorders is still in its infancy. Therefore it would be worth underline that a urine high PCR in conjunction with a normal or low urine albumine-to-creatinine ratio may identify patients with renal tubular disorders^[50]. Thus, the assess-

ment of these markers may be very useful to discover the proximal tubular dysfunction induced by TDF exposure.

In the meantime, studies using these markers as evidence of kidney damage should be interpreted with caution.

Table 1 is provided to summarize the different features of proteinuria in different HIV-associated kidney diseases in children.

CONCLUSION

A prompt diagnosis of nephrotoxicity due to antiretroviral therapy in HIV-infected patients allows to take rapid steps to mitigate damage to the kidney. It is also important to distinguish it from other causes of HIV-associated renal diseases. The collaboration with a nephrologists, the close monitoring of renal function and the biopsy in case of progressive renal disease allow to establish an accurate diagnosis.

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Endoscopic papillary balloon dilation for difficult common bile duct stones: Our experience

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Abstract

AIM: To evaluate the efficacy and safety of endoscopic balloon dilation (EBD) performed for common bile duct (CBD) stones.

METHODS: From a computer database, we retrospectively analyzed the data relating to EBD performed in patients at the gastrointestinal unit of the Sandro Pertini Hospital of Rome (small center with low case volume) who underwent endoscopic retrograde cholangiopancreatography (ERCP) for CBD from January 1, 2010 to February 29, 2012. All patients had a proven diagnosis of CBD stones studied with echography, RMN-cholangiography and, when necessary, with computed tomography of the abdomen (for example, in cases with pace-makers). Prophylactic therapies, with gabexate mesilate 24 h before the procedure and with an antibiotic (ceftriaxone 2 g) 1 h before, were administered in all patients. The duodenum was intubated with a side-viewing endoscope under deep sedation with intravenous midazolam and propofol. The patients were placed in the supine position in almost all cases. EBD

of the ampulla was performed under endoscopic and fluoroscopic guidance with a balloon through the scope (Hercules, wireguided balloon®, Cook Ireland Ltd. and CRE®, Microvasive, Boston Scientific Co., Natick, MA, United States).

RESULTS: A total of 14 patients (9 female, 5 male; mean age of 73 years; range 57-82 years) were enrolled in the study, in whom a total of 15 EBDs were performed. All patients underwent minor endoscopic sphincterotomy (ES) prior to the EBD. The size of balloon insufflation depended on stone size and CBD dilation and this was performed until it reached 16 mm in diameter. EBD was performed under endoscopic and fluoroscopic guidance. The balloon was gradually filled with diluted contrast agent and was maintained inflated in position for 45 to 60 s before deflation and removal. The need for precutting the major papilla was 21.4%. In one patient (an 81-year-old), EBD was performed in a Billroth II. Periapillary diverticula were found only in a 74-year-old female. The adverse event related to the procedures (ERCP + ES) was only an intra procedural bleeding (6.6%) that occurred after ES and was treated immediately with adrenaline sclerotherapy. No postoperative complications were reported.

CONCLUSION: With the current endoscopic techniques, very few patients with choledocholithiasis require surgery. EBD is an efficacious and safe procedure.

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Key words: Choledocholithiasis; Endoscopic balloon dilation; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Mechanical lithotripsy

Core tip: Choledocholithiasis is frequently found in the adult population. Endoscopic sphincterotomy (ES) is considered the standard therapy for the treatment of this condition. However, several complications are associated with ES. Endoscopic balloon dilation (EBD)

is actually recognized as an alternative to ES for the extraction of difficult bile duct stones. Reading the literature, we have found that most of the studies use small diameter balloons (6-10 mm), while the ones using larger balloons (from 12-20 mm) are rare. The aim of this retrospective study was to evaluate the efficacy and safety of large EBD performed for common bile duct difficult stones.

Zippi M, De Felici I, Pica R, Traversa G, Occhigrossi G. Endoscopic papillary balloon dilation for difficult common bile duct stones: Our experience. *World J Clin Cases* 2013; 1(1): 19-24 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/19.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.19>

INTRODUCTION

Choledocholithiasis is found in about 10%-15% of the adult population^[1]. Since 1974, when Classen *et al*^[2] and Kawai *et al*^[3] introduced the endoscopic sphincterotomy (ES), this procedure has become the standard therapy for the treatment of various biliary diseases, especially common bile duct (CBD) stones. Several complications associated with ES have been reported: early ones, such as acute pancreatitis, hemorrhage, duodenal perforation, acute cholangitis, and late ones, such as recurrence of stones and papillary stenosis^[4]. Balloon dilation of the biliary sphincter has been introduced as an alternative to sphincterotomy for the extraction of bile duct stones^[5,6]. Endoscopic balloon dilation (EBD) was first described by Staritz *et al*^[7] in 1983. EBD is still not widely embraced, especially due to the fear of complications, in particular acute pancreatitis. However, EBD does not have the short term complications of bleeding and perforation and it may preserve the biliary sphincter, with a decrease in long term complications. There are several controversies regarding EBD, such as the difficulty of removing larger stones because of the smaller biliary opening, the more frequent need for mechanical lithotripsy (ML) and the higher incidence of pancreatitis after the procedure compared with ES^[8,9]. Most of the studies used small diameter balloons (6-10 mm). Studies using larger balloon (esophageal/pyloric/colonic dilatation balloons, from 12-20 mm) are rare^[10,11]. In particular, EBD is performed for large stones (a stone measured more than 2 cm), hard stones (a stone difficult to be crushed by ML or to remove after papillary balloon dilation) and for confluence stones (multiple stones or stones located at the hepatocholedochal junction).

The aim of this retrospective study was to evaluate the efficacy and safety of EBD performed for CBD difficult stones.

MATERIALS AND METHODS

Patients

Starting from a computer database, we retrospectively analyzed the data relating to EBD performed in patients at

the gastrointestinal unit of the Sandro Pertini Hospital of Rome (small center with low case volume) who underwent endoscopic retrograde cholangiopancreatography (ERCP) for CBD from January 1, 2010 to February 29, 2012. All patients had a proven diagnosis of CBD stones studied with echography, RMN-cholangiography and, when necessary, with computed tomography of the abdomen (for example, in cases of pace-makers).

Prophylactic therapies, with gabexate mesilate 24 h before the procedure and with an antibiotic (ceftriaxone 2 g) 1 h before, were administered in all patients.

Endoscopic therapy

The duodenum was intubated with a side-viewing endoscope (TJF 140 or 145®, Olympus Optical, Hamburg, Germany) under deep sedation with intravenous midazolam and propofol. The patients were placed in the supine position in almost all cases. During the ERCP, the arterial oxygen saturation, pulse rate and blood pressure were continuously monitored. During the procedure, oxygen supplementation through nasal cannulae was used for all patients. ES, using appropriate sphincterotomy (Ultratome XL, triple lumen sphincterotomy® and Ultratome, double lumen sphincterotomy®, Microvasive, Boston Scientific Co., Natick, MA, United States) was performed *via* a hydrophilic guide wire (Jagwire 0.025-inch or 0.035-inch®, Microvasive, Boston Scientific Co., Natick, MA, United States) to achieve controlled cutting. The length of ES performed depended on stone size. In cases of difficult cannulation, a precut technique was performed using a needle-knife sphincterotome (Microknife XL, triple lumen Needle Knife®, Microvasive, Boston Scientific Co., Natick, MA, United States). EBD of the ampulla was carried out using a balloon through the scope (Hercules, wire guided balloon®, Cook Ireland Ltd. and CRE®, Microvasive, Boston Scientific Co., Natick, MA, United States). The size of the balloon's insufflation depended on the stone's size and CBD dilation and it was performed until achieving a 16 mm diameter. EBD was performed under endoscopic and fluoroscopic guidance. The balloon was gradually filled with diluted contrast agent and it was maintained inflated in position for 45 to 60 s before deflation and removal. After EBD, stone clearance was routinely performed under fluoroscopic guidance using a basket (Retrival stainless steel basket umbrella 5 Fr or 7 Fr, Innoflex®, Innovamedica, Milan, Italy) and balloon catheter (Extractor XL triple lumen retrieval balloon®, Microvasive, Boston Scientific Co., Natick, MA, United States). In cases of difficult stone extraction with these techniques, we adopted ML (Soehendra lithotripter®, Wilson-Cook Ireland Ltd.). As extracorporeal shock wave lithotripsy is not available at our center, when complete stone extraction was not achieved, a biliary plastic stent (Cotton-Huibregtse® Biliary stent, Cook Ireland Ltd.) or a naso-biliary tube (Flexima nasobiliary catheter®, Microvasive, Boston Scientific Co., Natick, MA, United States) was positioned for bile duct drainage. Post-ERCP complications and their severity were defined according to the 1991 consensus guidelines^[4].

Table 1 Main patient characteristics

No.	Pre-cut	CBD dilation	Stone (mm)	EBD (mm)	ML	Stent	NBD	Complications
1	---	Yes	15 ¹	10	Yes	---	---	---
2	Yes	Yes	30	10	---	---	---	---
3	Yes	Yes	10 ¹	12	---	---	---	---
4	---	Yes	10 ¹	12	---	---	---	---
5	---	Yes	20 ¹	12	---	---	---	---
6	---	Yes	20 ¹	12	Yes	---	---	---
7	---	Yes	20 ¹	12	---	---	---	---
8	---	Yes	15	10	---	---	---	---
9	---	Yes	40	12	---	---	---	---
10	---	Yes	25 ¹	13	Yes	10 Fr	---	Bleeding
11	---	Yes	25 ¹	16	---	10 Fr	6 Fr	---
12	---	Yes	15 ¹	12	---	---	---	---
13	Yes	Yes	20	12	---	---	---	---
14	---	Yes	20 ¹	12	---	---	---	---
15	---	Yes	35	16	Yes	---	6 Fr	---

¹Multiple. CBD: Common bile duct; EBD: Endoscopic balloon dilation; ML: Mechanical lithotripsy; NBD: Naso-biliary drainage.

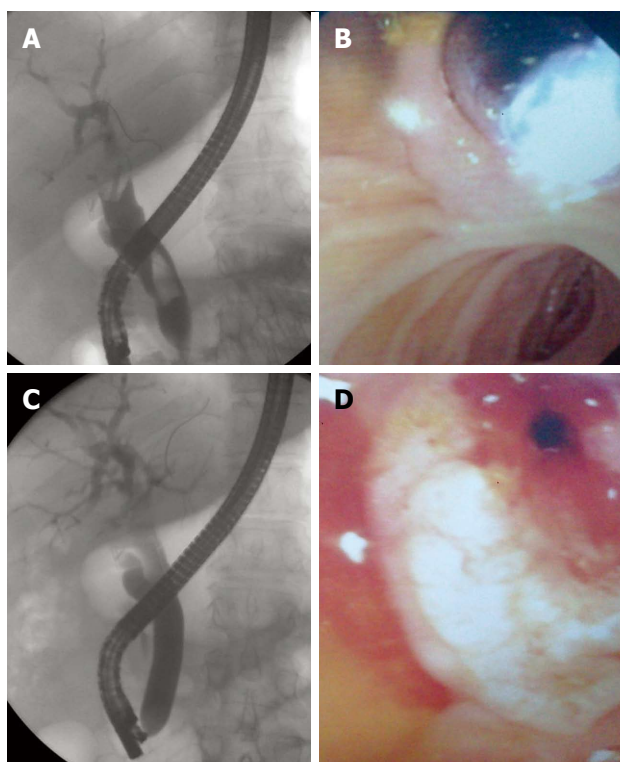


Figure 1 Endoscopic papillary large balloon dilation performed in a 58-year-old female. A: Cholangiogram shows a large dilated common bile duct with two stones of about 2 cm each; B: Endoscopic view of the inflated balloon which it is located across the papilla after minimal endoscopic sphincterotomy; C: Fluoroscopic image of balloon dilation (16 mm diameter); D: Large biliary orifice after the procedure.

RESULTS

Characterization of the population studied

A total of 14 patients (9 female, 5 male; mean age of 73 years; range 57-82 years) were enrolled in the study, in whom a total of 15 EBDs were performed. The main patient characteristics are summarized in Table 1. All patients underwent minor ES prior to the EBD. The size

of balloon insufflation depended on stone size and CBD dilation and this was performed until it reached 16 mm in diameter (Figure 1). The need for precutting the major papilla was 21.4% (3/14 ERCPs-EBD). In one case of an 81-year-old male, EBD was performed in a Billroth II (B-II) surgery. Periapillary diverticula (PAD) were found only in a 74-year-old female. Stone removal was achieved in a single session in 78.6% (11/14 ERCPs-EBD). Four patients required ML (26.6%), two stent insertions (13.3%) and two Silverman needle biopsy placement (13.3%).

Complications

The adverse event related to the procedures (ERCP + ES) was intra procedural bleeding in 1 case (6.6%) which occurred after ES and was immediately treated with adrenaline sclerotherapy (1:10 000 dilution, 10 mL), with no further intervention, and no postoperative complications were reported.

DISCUSSION

The success rate of stone extraction following EBD ranges from 85% to 100%^[7]. In patients with small stones (> 10 mm), EBD allows successful stone extraction, generally without the need for ES or ML. Bergman *et al.*^[12], in a prospective randomized controlled trial, assessed the outcome of 101 patients with CBD stones treated with EBD or ES. The authors concluded that the success rate of EBD was similar to ES, with no difference in the rate of early complications, such as pancreatitis. However, in patients with difficult stones (> 10 mm or number > 3), the success rate of EBD and ES is comparable but lithotripsy is required in about 50% of cases and an additional sphincterotomy or repeat ERCP in 15%-30% of patients^[12]. A systematic review underlines that EBD is less successful than ES^[13]. In our series, we performed ML in 4 cases, followed by the temporary placement of a plastic stent in one and naso-biliary drainage in another.

However, EBD seems to have several advantages over ES. The function of the biliary sphincter is preserved after EBD, while it is permanently lost after ES^[14]. Regarding this consideration, Bergman *et al*^[15] showed that the biliary sphincter was absent for up to 17 years after ES. This condition leads to chronic reflux of gastroduodenal contents into the biliary system, with subsequent bacterial colonization and inflammation. The potential benefit of EBD is in preventing this kind of reflux, even if until now, it is still controversial whether EBD is more efficacious in preventing bacterial contamination of the biliary tract than ES. Recently, Natsui *et al*^[16] investigated the bacterial flora in the bile after these two procedures (EBD and ES). The authors concluded that EBD has the possibility of suppressing bacterial contamination of the biliary tract compared with ES in patients with small stones.

The risk of bleeding seems to be decreased in EBD compared to ES. In fact, while bleeding has been reported in 2%-5% of patients undergoing ES for bile duct stones^[17], no significantly bleeding has been observed in over 1000 reported EBD procedures^[12,15,18,19]. This characteristic makes EBD a safe procedure, especially in patients with an increased risk of bleeding, such as those with cirrhosis who have a six to eight fold risk of bleeding after ES^[17,20]. In our cohort of patients, we had only 1 case of mild bleeding that occurred after ES and was successfully treated with sclerotherapy.

It is not clear whether or not this procedure is associated with a major risk of post-procedure pancreatitis since the available published studies report conflicting data. The meta-analysis of randomized, controlled trials by Baron *et al*^[21] showed that the early complication rate of EBD was comparable to ES for removing CBD stones during ERCP. In particular, the rate of pancreatitis was higher in the EBD group compared to the ES group (7.4% *vs* 4.3%, $P = 0.05$). The mechanism of post-EBD hyperamylasemia and pancreatitis is not clear, even if it is implicated in the compression of the pancreatic duct. In fact, Bergman *et al*^[22] underline how the balloon compression of the papilla or the pancreatic duct orifice may provoke peripapillary edema or sphincter of Oddi spasm, leading to hyperamylasemia or pancreatitis. In this regard, a randomized controlled trial demonstrated that a 5 min dilation time rather than the conventional 1 min time resulted in an adequately loosened sphincter of Oddi and consequently reduced the risk of post ERCP pancreatitis and improved its efficacy^[23].

We have not reported such complications but we want to underline that all our patients underwent prophylactic therapy, with gabexate mesilate 24 h before the procedure. Bergman *et al*^[24] reported a randomized trial of EBD and ES for removing bile duct stones in patients with a prior B-II gastrectomy. Compared to patients with a normal anatomy, patients with a prior B-II gastrectomy had a significantly increased risk of bleeding after ES. Early complications occurred in 19% of the patients who underwent EBD compared to 39% of the patients who underwent ES^[24].

In 2003, Ersoz *et al*^[10] introduced the technique of endoscopic papillary large balloon dilatation (EPLBD) using a balloon larger than 12 mm after mid-incision ES for the removal of large CBD stones. Starting from that, multiple studies showed that EPLBD alone or in combination with other techniques can be useful for managing difficult biliary stones^[25-28]. Several studies on EPLBD have demonstrated a relatively high technical success rate (74%-99%) for the removal of large bile duct stones and also for patients with PAD and relatively low rates of pancreatitis, without recurring to ML^[10,29,30]. Recently, the incidence of biliary complications have been reported to be significantly lower in patients after EPLBD than in those after ES and this outcome appeared most markedly in patients who also underwent cholecystectomy^[31].

Some authors have suggested that the stone recurrence rate may also be higher with EPLBD than with ES and ML^[32]. However, the results of a Japanese multicenter trial with a mean follow up of 6.7 years demonstrated that there is a lower risk of stone recurrence following EPLBD when compared with ES^[33]. Another study that evaluated the short term clinical outcomes after removing CBD stones using EPLBD showed a recurrence rate of 24.0% with a mean follow-up period of 10.8 ± 4.5 mo^[34].

EBD and EPLBD are considered safe procedures for patients with an increased risk of bleeding. In fact, EPLBD is especially attractive in patients who are at risk for bleeding after ES or in those with altered anatomy, such as patients with a B-II gastrectomy in whom a full sphincterotomy cannot be successfully achieved. Choi *et al*^[35] evaluated the efficacy and safety of EPLBD for removal of bile duct stones in patients with B-II gastrectomy. In all cases, stones were successfully removed without significant complications, such as bleeding, pancreatitis or perforation.

According to the study of Youn *et al*^[36], EPLBD with a large balloon of over 15 mm with ES is an effective and safe procedure with a very low probability of severe post-procedural pancreatitis. The authors found five cases of not severe post-EPLBD pancreatitis. This complication was not associated with larger balloon size (17.0 ± 2.4 mm) but was associated with longer procedure time (30.0 ± 3.5 min) and smaller dilation of the CBD (17.6 ± 6.7 mm).

To date, there are no data on the optimal duration of papillary balloon dilation after a biliary sphincterotomy. Paspatis *et al*^[37] compared effectiveness and complications of the endoscopic papillary balloon dilation for 60 s *vs* 30 s after ES. A total of 124 patients were prospectively randomized to either the 60 s dilation group (G60, $n = 60$) or the 30 s dilation group (G30, $n = 64$). The complete removal of bile duct stones was similar between the two groups (86% *vs* 85%, $P = 0.9$), such as the rates of post-ERCP pancreatitis (3.1% *vs* 3.3%, $P = 0.9$). The authors concluded that 30 s papillary balloon dilation, performed after ES for the management of bile duct stones, is equally effective as the 60 s papillary balloon dilation. In our cohort of patients, we maintained the inflated balloon in position for 45 to 60 s before deflation and removal.

In conclusion, therapeutic ERCP, including in a low-

volume center, represents the first line management option for CBD stones. With the current endoscopic techniques, very few patients with choledocholithiasis require surgery. The data emerging from our study confirm that EBD, performed for large CBD stones, is an efficacious and safe procedure.

COMMENTS

Background

Endoscopic sphincterotomy (ES) was always considered the standard therapy for the treatment of common bile duct (CBD) stones but this procedure may fail in cases of difficult stones (large, hard and confluence). Endoscopic balloon dilation (EBD) is actually recognized as an alternative to ES for the treatment of these conditions. Many studies have reported the use of small diameter balloons (6-10 mm), while the ones using larger balloons (from 12 to 20 mm) are rare.

Research frontiers

EBD is not still widely embraced, especially due to the fear of complications, in particular, of acute pancreatitis. However, EBD does not have the short term complications of bleeding and perforation compared to ES and it may preserve the biliary sphincter with a decrease in long term complications.

Innovations and breakthroughs

For the extraction of difficult bile duct stones, the dilation of the biliary orifice with a large balloon after a small ES appears to be a promising technique.

Applications

The study results suggest that large EBD is an efficacious and safe procedure that could be used for treating difficult CBD stones.

Terminology

EBD is a procedure performed under endoscopic and fluoroscopic guidance in which the balloon is inflated with diluted contrast agent and is located across the papilla. The size of the balloon's insufflation depends on the stone size and CBD dilation; mechanical lithotripsy (ML) is a method of stone extraction performed under fluoroscopic guidance. MLs are devices designed to break stones which have been captured within a basket.

Peer review

The authors report the results of 14 patients who underwent endoscopic papillary balloon dilatation for difficult CBD stones. The patients had good outcomes, without major short and long term complications.

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Gastric hyperplastic polyps causing upper gastrointestinal hemorrhage in a young adult

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The patient presented to Northwestern Memorial Hospital in July 2011. The polyps were resected by clip-assisted snare polypectomy. Histopathologic assessment of the resected polyps demonstrated multiple, non-ulcerative hyperplastic polyps measuring 1.3-1.8 cm in size, without evidence of dysplasia or malignancy. This case describes a young adult patient with multiple, large gastric polyps causing overt gastrointestinal bleeding. This is a rare presentation in a young individual, as these polyps are typically identified in patients older than 60 years of age and less commonly, pediatric populations.

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Key words: Gastrointestinal hemorrhage; Hyperplastic polyps; Endoscopy; Polyp; Therapeutic endoscopy

Core tip: While uncommon, gastric hyperplastic polyps may be the source of overt upper gastrointestinal hemorrhage in young individuals and must be included in the differential of such symptoms.

Secemsky BJ, Robinson KR, Krishnan K, Matkowskyj KA, Jung BH. Gastric hyperplastic polyps causing upper gastrointestinal hemorrhage in a young adult. *World J Clin Cases* 2013; 1(1): 25-27 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/25.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.25>

Abstract

Here, we report a case of a young man who presented with a significant upper gastrointestinal bleed treated by endoscopic removal of multiple hyperplastic polyps. Gastric hyperplastic polyps are a relatively uncommon cause of overt gastrointestinal bleeding. While most hyperplastic gastric polyps are asymptomatic, they may present with abdominal pain, iron deficiency anemia or gastric outlet obstruction. These polyps are associated with conditions such as *Helicobacter pylori* gastritis and atrophic autoimmune gastritis, which predispose the epithelium to chronic inflammation and epithelial repair.

INTRODUCTION

Hyperplastic gastric polyps are epithelial proliferations that primarily occur in the antrum of the stomach. On endoscopy, these polyps appear as smooth, dome-shaped lesions. Larger lesions tend to become lobulated and pedunculated, with frequent erosion of the surface epithelium. Histologically, hyperplastic polyps consist of elongated, dilated and distorted gastric foveolar epithelium

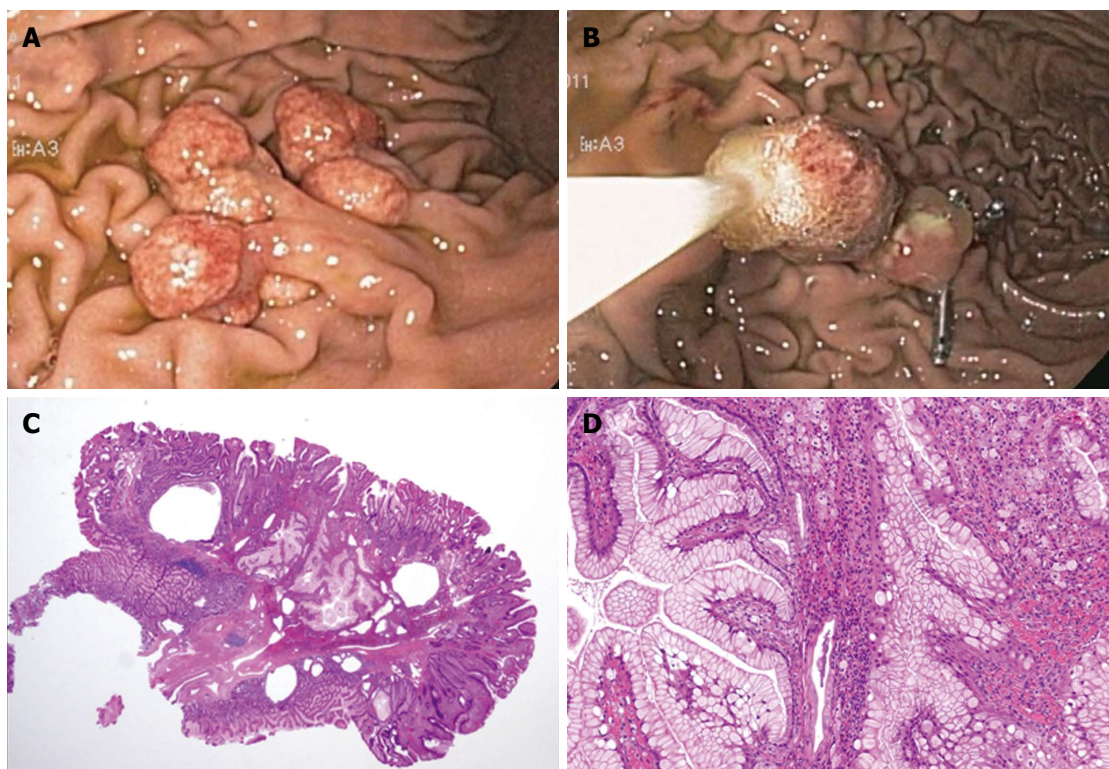


Figure 1 Endoscopic and microscopic evaluation of multiple gastric polyps. A: Endoscopic images demonstrate 5 pedunculated polyps ranging in size from 1.0-1.8 cm clustered in the body of the stomach; B: These polyps were removed using clip-assisted snare polypectomy; C: Microscopic evaluation of one of these polyps reveal a pedunculated lesion with hyperplastic and dilated foveolar glands (HE stain, 10 × magnification); D: At higher magnification, there is increased inflammation in the lamina propria with a small collection of foamy histiocytes (HE stain, 200 × magnification).

and can be associated with local edema and rarely foamy histiocytes^[1-4].

While most hyperplastic gastric polyps are asymptomatic, they may present with abdominal pain, iron deficiency anemia or gastric outlet obstruction^[3-6]. These polyps are associated with conditions such as a *Helicobacter pylori* (*H. pylori*) and atrophic autoimmune gastritis, which predispose the epithelium to chronic inflammation and epithelial repair.

CASE REPORT

A 32-year-old male with a personal history of colonic adenoma and a family history of colon polyps presented with a 3-d history of hematemesis and melena. Initial laboratory evaluation was notable for a hemoglobin drop from 14 to 9.6 g/L. He underwent an upper endoscopy that revealed five large (> 1 cm in diameter), highly vascular, pedunculated polyps localized at the greater curvature. The remainder of the stomach was normal. The polyps were resected by clip-assisted snare polypectomy. Histopathologic assessment of the resected polyps demonstrated non-ulcerative hyperplastic polyps measuring 1.3-1.8 cm in size, without evidence of dysplasia or malignancy (Figure 1). Biopsies did not reveal *H. pylori* or atrophic autoimmune gastritis. No further bleeding occurred during a 6-mo follow-up period. Repeat endoscopy 1 mo after admission revealed two additional hyperplastic polyps at the previous site, which were again removed.

DISCUSSION

Non-neoplastic gastric polyps are benign epithelial proliferations that often require no intervention. However, these polyps may be symptomatic or can grossly mimic malignant tumors^[7]. In these clinical scenarios, such polyps are commonly removed *via* endoscopy. Non-neoplastic gastric polyps can be solitary or numerous in number, and are rarely associated with a number of genetic conditions including Peutz-Jeghers Syndrome, Familial Juvenile Polyposis, and Cronkhite-Canada Syndrome^[1,7]. These polyps are usually asymptomatic and thus go undiscovered in the majority of the population. However, the prevalence of gastric polyps ranges as low as 0.5% to 7% in patients undergoing routine endoscopy^[5,8].

Once found to be the most prevalent type of polyp in the stomach, hyperplastic polyps are now increasingly uncommon due to the eradication of *H. pylori* and resulting decrease in non-atrophic gastritis in industrialized nations^[2-5]. In one large-scale study reviewing over 100 000 endoscopies conducted between 2007-2008, hyperplastic polyps made up only 17% of all discovered gastric polyps^[5]. Fundic gland polyps, characterized as small, sessile gastric lesions associated with antacid use, are now thought to be the most prevalent gastric polyp^[5,9-11].

This case describes a young adult patient with multiple, large gastric polyps causing overt gastrointestinal bleeding. This is a rare presentation in a young individual, as these polyps are typically identified in patients older

than 60 years of age and less commonly, pediatric populations. Furthermore, outside of the setting of anticoagulation or antiplatelet therapy, gastric polyps are typically associated with occult, rather than overt gastrointestinal bleeding^[1-3,5].

In contrast to normal or hyperplastic mucosa, molecular evaluation of hyperplastic polyps have demonstrated rare cases of p53 protein overexpression and neoplastic features such as dysplasia and carcinoma. Polyps with neoplastic foci have also shown increases in Ki-67 labeling indices, demonstrating an increase in proliferative activity^[5]. These observations are suggestive of a dysplasia-carcinoma sequence in the malignant transformation of hyperplastic polyps and argue for a complete eradication of such lesions^[1,6,11,12].

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Saphenous graft on transesophageal echocardiogram masquerading as an abnormal vascular communication into the right atrium

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INTRODUCTION

Cardiovascular disease is the leading cause of death in the United States. The number is expected to increase substantially. As a result, significant advancements have been made to diagnosed, treat and also to prevent this epidemic. More than 150 000 people undergo coronary artery bypass grafting each year in the United States^[1-4]. Many of these patients will have routine follow ups and among them, several will have subsequent imaging studies to evaluate improvement, or unfortunately, disease progression. Echocardiography is and has been a great tool for the evaluation of cardiac anatomy and function. Postoperative patients for valve replacements and or coronary bypass grafts have offered interesting and challenging studies that often show the limitations of echocardiography^[1,5]. Magnetic resonance imaging (MRI) is a non-invasive modality which can be used for direct visualization of coronary artery bypass grafts. Along with spin-echo and gradient-echo (cine-MRI), they provide information on graft morphology and patency with a 90% accuracy^[3,6,7].

CASE REPORT

We present a case of a 72-year-old male with past medical history of moderate aortic stenosis, coronary artery disease status post five vessel coronary artery bypass grafting with left internal mammary artery to left anterior descend-

Abstract

An unknown aberrant flow in the right atrium observed on doppler with transesophageal echocardiogram (TEE) in a patient with prior coronary bypass. TEE revealed normal size left ventricle with severely dilated left atrium. There was moderate aortic regurgitation and moderate aortic stenosis noted. Patient was incidentally found to have an abnormal vascular communication noted to the right atrium. To further evaluate this finding, the patient underwent cardiac magnetic resonance angiography which revealed that the tubular structure noted on TEE was actually a graft that was abutting onto the coronary sinus, and the flow anomaly was really the graft coming up and running adjacent to the coronary sinus.

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Key words: Vascular; Communication; Echocardiogram; Saphenous vein graft; Magnetic resonance imaging

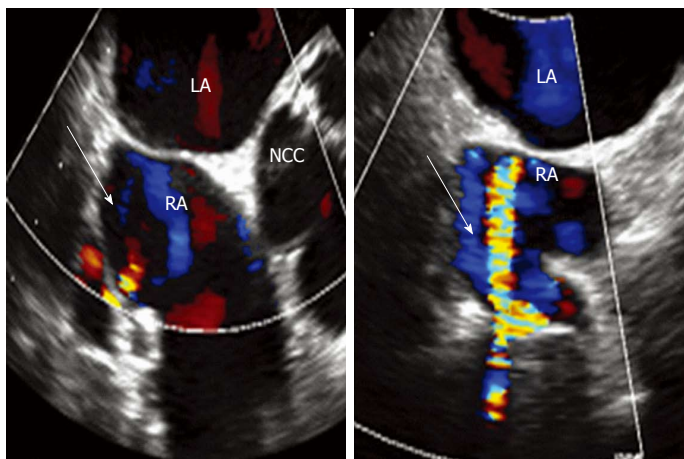


Figure 1 Transesophageal echocardiogram-mid esophageal view, short axis, at -30 degree view, with slight clockwise rotation. White arrow points to the abnormal vascular communication noted to the right atrium on transesophageal echocardiogram. LA: Left atrium; RA: Right atrium; NCC: Noncoronary cusp.

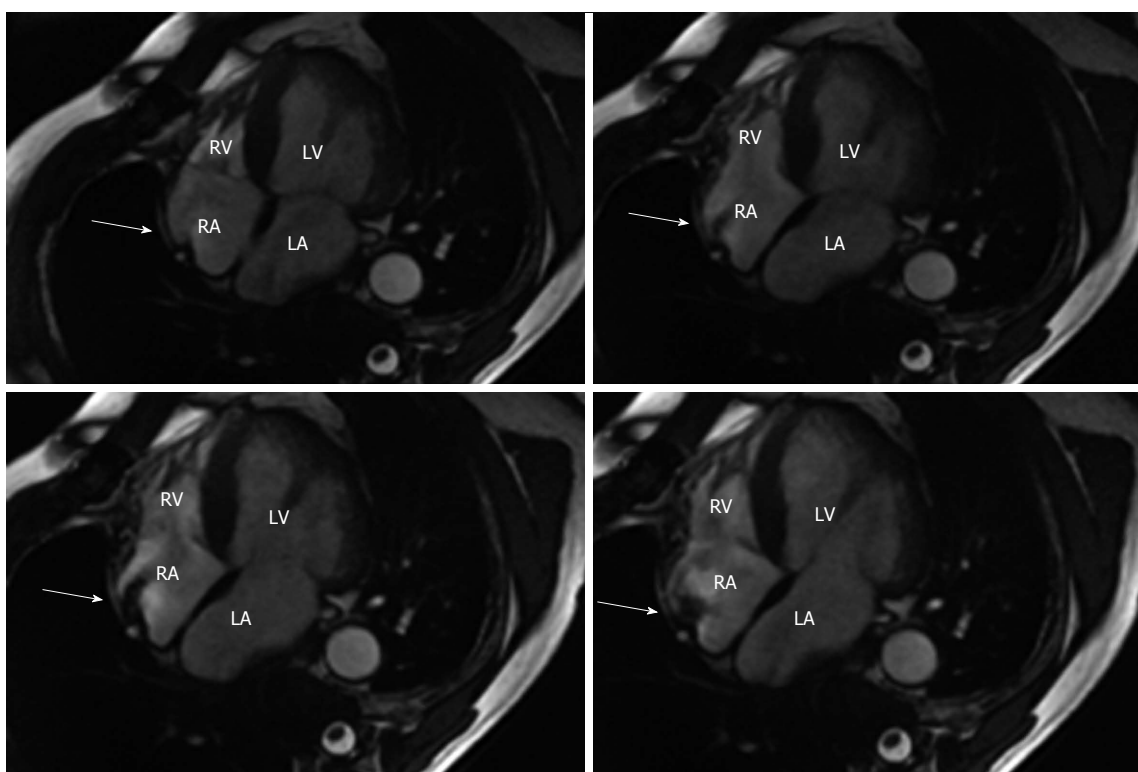


Figure 2 Magnetic resonance angiography-transverse view of the heart with visualization of all four chambers. White arrow points to the flow anomaly, which was really the graft coming up and running adjacent to the coronary sinus. RV: Right ventricle; LV: Left ventricle; LA: Left atrium; RA: Right atrium.

ing, saphenous vein graft to the third obtuse marginal branch, saphenous vein graft to right coronary artery, saphenous vein graft to first diagonal, and saphenous vein graft to ramus intermedius. Patient was evaluated at the cardiology clinic for further stratification of aortic stenosis and underwent left atrium transesophageal echocardiogram (TEE). TEE revealed normal size left ventricle with severely dilated left atrium. There was moderate aortic regurgitation and moderate aortic stenosis noted. Patient was incidentally found to have an abnormal vascular communication noted to the right atrium (Figure 1). To further evaluate this finding, the patient underwent cardiac

magnetic resonance angiography (MRA) which revealed that the tubular structure noted on TEE was actually a graft that was abutting onto the coronary sinus, and the flow anomaly was really the graft coming up and running adjacent to the coronary sinus (Figure 2).

DISCUSSION

This case shows one way a graft can appear on TEE, which was confusing until MRA and clinical correlation were accomplished. This case also illustrates the importance of correlating graft locations when performing TEE

and also to utilize cardiac MRA if needed to better define unusual presentations of sapheno-venous graft adjacent to atrial chambers.

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Low ADAMTS-13 in plavix induced thrombotic thrombocytopenic purpura

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INTRODUCTION

Greater than 600 000 percutaneous coronary interventions (PCI) are performed each year in the United States. With each PCI, patients are usually placed on more than one antiplatelet regimen because of its proven benefit. The very first agent available was aspirin, which inhibited thromboxane A₂, an agent that causes platelet aggregation, thus reducing cardiac events post PCI. Following aspirin, further studies examined two other drugs that were available at the time: dipyridamole and cilostazol, both of which inhibits phosphodiesterase differently to illicit the same inhibition of platelet aggregation. Dipyridamole was found to be more efficacious in reducing stroke, but not acute coronary syndrome and thus never made into guidelines. Cilostazol proved beneficial in acute coronary syndrome, but had more adverse side effects and thus, there are no clear guidelines to specify its use in PCI patients. More recently, P2Y₁₂ receptors antagonist have entered the market with astonishing efficacy. P2Y₁₂ receptors are a class of purinergic receptors that exert various affects, like platelet aggregation, when activated by nucleotides, specifically adenosine diphosphate. Ticlopidine was the first P2Y₁₂ antagonist approved for use. Initially approved for the management of stroke, it was later found efficacious in acute coronary syndrome and became incorporated into the American Heart Association (AHA) and the American College of Cardiology guidelines. Unfortunately, due to its hematologic side effects, causing neutropenia and thrombotic thrombocytopenic purpura, the use of ticlopidine was taken out of the 2011 AHA guidelines^[1]. Clopidogrel, like ticlopidine, is a thienopyridine derivative which works by inhibiting adenosine diphosphate induced platelet aggregation. Clopidogrel has for the most part replaced ticlopidine as

Abstract

Thrombotic thrombocytopenia purpura (TTP) was first described in 1924 as a "pathologic alteration of the microvasculature, with detachment or swelling of the endothelium, amorphous material in the sub-endothelial space, and luminal platelet aggregation leading to compromise of the microcirculation". Ticlopidine induced TTP has been highly associated with autoimmune induced reduction in ADAMTS-13 activity. These findings, to a lesser extent, have also been found in clopidogrel induced TTP. We report a case of clopidogrel associated TTP in a patient that presented with acute stroke, renal failure, and non-ST elevation myocardial infarction.

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Key words: Plavix; Thrombotic thrombocytopenic purpura; Antiplatelet therapy

Cao LB, Jones C, Movahed A. Low ADAMTS-13 in plavix induced thrombotic thrombocytopenic purpura. *World J Clin Cases* 2013; 1(1): 31-33 Available from: URL: <http://www.wjgnet.com>

the drug of choice for patients undergoing arterial stenting because the clopidogrel *vs* aspirin in patients at risk of ischaemic events trial helped show that there is less risk for neutropenia and thrombotic thrombocytopenia purpura (TTP) with the use of clopidogrel than ticlopidine^[2]. However, with the rise in clopidogrel associated TTP in the recent years, more special consideration should be taken into account when selecting an antiplatelet therapy, especially now that we have other options of P2Y¹² antagonist like prasugrel (Effient) and Ticagrelor (Brilinta), which have their own drawbacks like increased bleeding with low body weight, and dyspnea, ventricular pauses and increased serum uric acid, respectively^[1,3].

CASE REPORT

A 67-year-old male with past medical history of hypertension, diabetes mellitus, coronary artery disease status post coronary artery bypass, ischemic heart failure with an ejection fraction of 25% with biventricular pacemaker presented to a local hospital with complaints of left sided weakness in both his upper and lower extremities that quickly progressed to bilateral lower extremity weakness with frequent falls. He was transferred to our intensive care unit with a platelet of 14 000, a creatinine of 7.8, and a diagnosis of acute stroke. His home medications included aspirin, plavix, lisinopril, spironolactone, atorvastatin, glargine and aspart insulin. His home antiplatelet therapy was held on arrival due to his thrombocytopenia and drop in hemoglobin of 7.9 from a baseline of 11. Cardiac markers were positive with a peak troponin of 25.0, a creatine kinase MB of 30 and an index of 4.6. A ventricular paced rhythm was observed on electrocardiographic. Patient had denied any recent illness, and no prior medical history of autoimmune disease, human immunodeficiency virus, or malignancies. However, he claims of being started on plavix 2 wk earlier for known coronary disease. Peripheral blood smear showed schistocytes, lactic dehydrogenase was found to be 1182 and haptoglobin was 2, thus suggesting microangiopathic hemolytic anemia. ADAMTS-13 was less than 5%, complement C3 was decreased slightly at 85 and C4 was normal at 16, thus supporting TTP. Further Coombs testing was not done. Prothrombin time was 11.2, partial thromboplastin time was 30 and fibrinogen was 397, which did not support disseminated intravascular coagulation. Patient was immediately started on IV methylprednisolone 40 mg *iv* on day one for TTP, and he subsequently received 4 d of plasmapheresis with dramatic improvement in his platelet count and hemoglobin (Figure 1). He never had chest pain or dyspnea and was always hemodynamically stable. As his cardiac enzymes normalized with the onset of TTP treatment, no further intervention was done. With no further residual weakness and normal labs, our patient was discharged home on PO prednisone.

DISCUSSION

TTP was first described in 1924 (Moschcowitz syndrome)

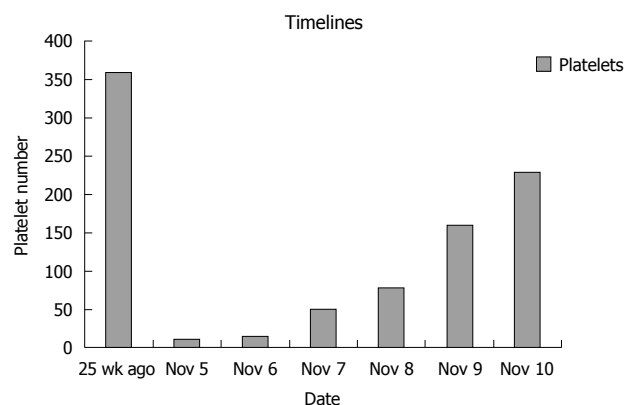


Figure 1 Timeline of platelet levels while patient underwent treatment with methylprednisolone 40 mg *iv* and plasmapheresis (platelet numbers equate to $\times 1000$).

as a “pathologic alteration of the microvasculature, with detachment or swelling of the endothelium, amorphous material in the sub-endothelial space, and luminal platelet aggregation leading to compromise of the microcirculation”. There are two types: (1) Familial type (Upshaw-Schulman syndrome), which is rare, occurring in early childhood, and chronically relapsing but self-limiting; and (2) Sporadic or acquired type, which covers the majority of the cases^[3]. Clopidogrel induced TTP occurs at a rate of about four per million patients taking the medication with a mortality rate of 10%-20%, and is 15 times more likely to occur within the first 2 wk of drug use^[4,5]. Complications include severe thrombocytopenia, hemolytic anemia, fluctuating or focal neuro-deficits from central nervous system ischemia, renal failure and fever. Von Willebrand factor (vWF) plays a role in platelet-platelet and platelet-endothelial cell interactions. Large vWF multimers are the most potent in platelet clumping, and are constantly secreted from endothelial cells. ADAMTS-13 is a naturally occurring protease that acts to cleave these large vWF multimers, thus preventing uncontrolled platelet aggregation. Ticlopidine induced TTP has been highly associated with autoimmune induced reduction in ADAMTS-13 activity. These findings, to a lesser extent, have also been found in clopidogrel induced TTP. Our patient had severely low ADAMTS activity level of $< 5\%$ (normal is $> 66\%$). Thus, treatment with steroids, and plasma exchange has been very effective^[5-9]. Prompt recognition of this disease is important to survival. Therapeutic plasma exchange initiated within 3 d of TTP onset significantly increases survival. Delay in therapy will not only increase mortality, but also rate of relapse. Our patient responded appropriately after 4 cycles of plasma exchange.

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Intracystic hemorrhage in a non-endometriotic mullerian vaginal cyst

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Abstract

The commonest type of simple vaginal cyst is the Mullerian cyst. These are typically lined by columnar epithelium and contain serous or mucinous fluid. If blood is found in the cyst, the source is usually due to the presence of endometrial elements in the cyst wall. The cyst is then termed an endometriotic cyst. In this case report, we have described a woman with a symptomatic 3 cm upper vaginal cyst who underwent surgical excision of the cyst. The cyst cavity was found to be full of old dark blood and mucous, however the wall contained no endometrial tissue and was lined by columnar epithelium which stained positive for mucous with mucicarmine. No cause for the intracystic hemorrhage was identified. We conclude that intracystic hemorrhage can occur in a simple Mullerian vaginal cyst in the absence of endometrial components.

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Key words: Vaginal cyst; Mullerian cyst; Endometriotic cyst; Hemorrhagic cyst; Endometriosis

Core tip: The commonest type of simple vaginal cyst is the Mullerian cyst. These are typically lined by columnar epithelium and contain serous or mucinous fluid. If blood is found in the cyst, the source is usually due to the presence of endometrial elements in the cyst wall. It is then termed an endometriotic cyst. We describe a simple Mullerian vaginal cyst containing blood in which no endometrial tissue was found. No cause for the intracystic hemorrhage was identified. We conclude that intracystic hemorrhage can occur in a simple Mullerian vaginal cyst in the absence of endometrial components.

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Rivlin ME, Meeks GR, Ghafar MA, Lewin JR. Intracystic hemorrhage in a non-endometriotic mullerian vaginal cyst. *World J Clin Cases* 2013; 1(1): 34-36 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/34.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.34>

INTRODUCTION

Vaginal cysts are relatively common and of these the commonest type found in the upper vagina is the Mullerian cyst arising from paramesonephric duct remnants^[1]. Mullerian cysts are usually lined by columnar endocervical-like cells but may be lined by endometrial or fallopian type epithelium^[2]. The cyst fluid has been described as serous, mucinous or purulent-like^[3]. We have not found a reference to intracystic blood other than with the endometriotic cyst. We report a case of intracystic blood in a Mullerian cyst lacking any endometrial component.

CASE REPORT

A 21-year-old nulliparous woman on oral contraceptives presented with a 3-year history of a vaginal cyst which was discovered on routine examination and was managed expectantly. Significant in her past history was a laparoscopy at age 19 for pelvic pain with essentially normal findings other than a 2 cm ovarian cyst which was biopsied and showed ovarian stroma. There was no evidence of endometriosis.

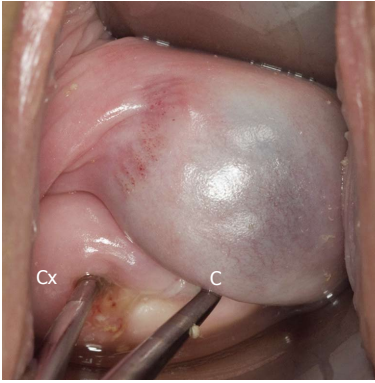


Figure 1 Operative photograph showing vaginal cyst antero-lateral to the cervix. C: Cyst; Cx: Cervix.

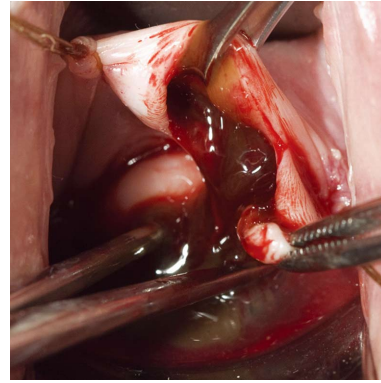


Figure 3 Operative photograph showing blood and mucus draining from cyst after incision.

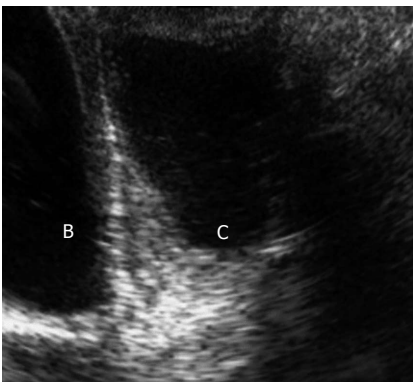


Figure 2 Pelvic ultrasound showing cyst separate from bladder. C: Cyst; B: Bladder.

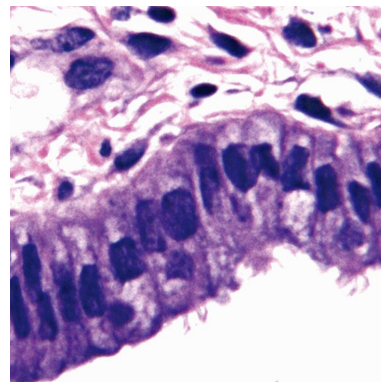


Figure 4 Photomicrograph showing cyst lining of tall columnar secretory endocervical-like epithelium (HE, $\times 400$).

She now felt that the cyst was causing discomfort with tampon use and intercourse sufficient for her to request its removal. A 3 cm cyst was seen on speculum examination in the left vaginal fornix at the 2-o'clock position antero-lateral to the cervix (Figure 1). The remainder of the pelvic examination was unremarkable. Pelvic sonogram noted a 3 cm. Echogenic fluid filled simple cyst anterior to the cervix with no connection to uterus or bladder (Figure 2). The pelvic organs were otherwise normal. Renal sonography showed normal urinary tracts. At surgery, on entry into the cyst cavity, 3 mL of dark old blood mixed with mucus was drained (Figure 3).

The cyst wall was excised and on microscopy found to be lined by columnar cells with intra-cytoplasmic mucus resembling endocervical epithelium (Figure 4).

DISCUSSION

Focal ciliated cells were also seen but no Bartholin gland tissue or vaginal adenosis was noted. Mucicarmin stain for mucus was positive. The pathologic findings were compatible with a diagnosis of a Mullerian cyst of endocervical type.

Vaginal cysts are usually asymptomatic and benign. They do not require excision unless they cause problems,

pain and dyspareunia being the commonest complaints^[2]. It is possible that the onset of symptomatology in our patient was related to the accumulation of blood in the cyst cavity. The finding of old blood in a vaginal cyst is highly suggestive of the presence of endometrial tissue in the cyst wall. Endometriotic cysts are uncommon. There were 6 in Evans series of 42 cases and 1 in Kondi-Pafitis series of 40 patients^[1,3]. Endometriosis is defined as the ectopic implantation of endometrial glands and stroma. As regards the diagnosis of endometriosis in the vaginal area, 2 of the following 3 findings must be seen: endometrial glands, endometrial stroma and hemosiderin laden macrophages^[2]. Distortion and destruction of the epithelium by hemorrhage is often present and there may be evidence of endometriosis elsewhere^[1].

Another vaginal lesion that may contain glandular epithelium in the vagina is vaginal adenosis. This is attributed to incomplete replacement of vaginal columnar epithelium by squamous epithelium during embryogenesis. This lesion is often found in diethylstilbestrol exposed women and usually has a red grape-like mucosal appearance^[2]. Another extremely rare condition, unilateral hematocolpos with ipsilateral renal agenesis was excluded by the negative laparoscopic pelvic examination and the sonographic demonstration of normal urinary tracts^[4].

The absence of endometrial glands, stroma and hemosiderin laden macrophages in our patient excluded the diagnosis of endometriosis and the clinical appearance made the diagnosis of vaginal adenosis highly unlikely. Therefore the finding of hemorrhage in our patients' simple Mullerian cyst is difficult to explain. Possibly local trauma may have been a factor, however the cyst was relatively avascular. It seems unlikely that endometrial tissue was destroyed by hemorrhage as there was no evidence of fibrosis or scarring in the cyst wall, furthermore laparoscopy 2 years prior, showed no evidence of pelvic endometriosis. We conclude that intracystic hemorrhage can occur in a simple Mullerian cyst in the absence of endometrial components.

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Hodgkin's lymphoma coexisting with liver failure secondary to acute on chronic hepatitis B

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Abstract

Acute on chronic liver failure (ACLF) is rarely the initial manifestation of a malignant process or precipitated by the initiation of anti-viral treatment with a nucleoside or nucleotide agent. We report an unusual case of ACLF temporally associated with initiation of Entecavir for treatment of chronic hepatitis B. Early Hodgkin's lymphoma (HL) was unmasked with initiation of the anti-viral treatment which may have exacerbated ACLF. To the best of our knowledge, this has not been described in the literature. In reviewing our patients clinical course and liver autopsy, he developed a severe acute exacerbation of his chronic hepatitis B virus coinciding with the institution of antiviral therapy and the underlying HL perhaps modulating the overall degree of hepatic injury.

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Key words: Entecavir; Hepatic flare; Fulminant hepatic failure; Chronic hepatitis; Acute liver failure; Hodgkin's lymphoma

Palta R, McClune A, Esrason K. Hodgkin's lymphoma coexisting with liver failure secondary to acute on chronic hepatitis B. *World J Clin Cases* 2013; 1(1): 37-40 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/37.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.37>

INTRODUCTION

Chronic hepatitis B virus (HBV) is a worldwide clinical problem. The natural progression of HBV is determined by the hosts' immune system and viral replication. HBV flares can be elicited by withdrawal of an immunosuppressive therapy, exposure to another hepatitis or malignancy or can occur spontaneously due to an intensification of the hosts' immunologic response to the HBV virus^[1]. The pathogenesis of hepatic flares are suspected to be due to changes in immunologic control of viral replication which precipitate an increase in T-cell reactivity to the hepatitis virus. Antiviral treatment viral restores T-cell responsiveness allowing for suppression of viral replication and may precipitate hepatic flares early in treatment. Withdrawal of anti-viral therapy can allow for development of viral mutations^[1]. Entecavir and Tenofovir are potent HBV inhibitors with a high barrier to resistance and have been noted to achieve virological response in patients with severe acute exacerbations of chronic HBV^[2].

Hepatic involvement by Hodgkin's lymphoma (HL) typically manifest with large tumor infiltration leading to hepatocyte destruction, duct necrosis and subsequent liver failure. The diagnosis of Hodgkin's disease requires presence of mononuclear Reed-Sternberg cells. Hepatic involvement of HL usually indicates Stage IV disease and rarely presents as the initial manifestation of acute liver failure (ALF)^[3].

CASE REPORT

A 57-year-old Asian physician with a history of verti-

cally transmitted inactive chronic hepatitis B diagnosed in 1985 presented for routine health examination in August 2010 and liver tests were noted to be abnormal: aspartate aminotransferase (AST) 77 IU/L and alanine aminotransferase (ALT) 79 IU/L.

Two months later, AST and ALT had risen to 83 IU/L and 102 IU/L, respectively. HBV DNA level was > 110 000 000 IU/mL. Hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen negative and hepatitis B e antibody positive. Hepatitis B core immunoglobulin (IgM) negative, hepatitis B core IgG positive. International normalized ratio (INR) was normal. Abdominal ultrasound was unremarkable. Repeat laboratory examination demonstrated AST 165 IU/L, ALT 230 IU/L and total bilirubin (T.bili) 1.1 mg/dL. Entecavir 0.5 mg daily was initiated. Follow-up labs 1 mo later demonstrated AST 917 IU/L and ALT 1225 IU/L, INR 1.6, T.bili 2.4 mg/dL and a lower HBV DNA level of 3 198 626 IU/mL.

He presented 6 wk later with complaints of abdominal pain and jaundice. On physical examination, his heart rate was 110-125 beats per minute with normal blood pressure. He had no stigmata of chronic liver. Mild abdominal tenderness noted with minimal ascites and no palpable masses. Lymphadenopathy was not appreciated. Edema and asterixis were absent.

AST and ALT were 1169 IU/L and 1472 IU/L, respectively, INR 2.2 and T.bili 5.7 mg/dL. HBV DNA was 322 029 IU/mL. Serological tests for hepatitis A, hepatitis C, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, Wilson's disease, autoimmune liver disease, thyroid disease, α 1 anti-trypsin deficiency and hemochromatosis were all within normal limits. Serum and urine toxicology screens were negative. Hepatitis E IgG and IgM were negative.

Abdominal ultrasound suggested early cirrhosis with splenomegaly and a patent portal vein. Non-contrast computed tomography (CT) scan of abdomen confirmed a mildly nodular liver surface compatible with early cirrhosis, a mildly enlarged spleen and small to moderate ascites. No masses, gallbladder stones or biliary dilatation was seen. Asymmetrical right external iliac adenopathy and right inguinal adenopathy were noted on CT scan. Chest X-ray (CXR) was normal. Transthoracic echocardiogram demonstrated an ejection fraction of 65%-70% with right ventricular systolic pressure measured at 24-29 mmHg.

Six weeks after initiation, Entecavir was held in the emergency department given a concern for a potential side effect of the medication. The patient was started on N-acetylcysteine intravenously and on vitamin K. Only a minimal amount of ascites was visualized on ultrasound, therefore a paracentesis was not performed. Empiric piperacillin and tazobactam was initiated for presumed spontaneous bacterial peritonitis (SBP).

The aminotransferases improved but the bilirubin and INR continued to rise. Blood and urine cultures were negative. He was transferred to University of California Los Angeles (UCLA) for orthotopic liver transplant evaluation.

To prevent worsening hepatic failure and to prevent the emergence of a drug-resistant mutation secondary to abrupt discontinuation of Entecavir therapy, he was started on Tenofovir 300 mg daily at the UCLA Medical Center. Repeat HBV DNA level of 5 IU/mL. Paracentesis was positive for SBP and Ceftriaxone was initiated. The ascites culture and cytology were negative. Repeat CT scan of the abdomen/pelvis at UCLA confirmed cirrhosis. No hepatic masses or biliary dilatation were noted. Ascites, splenomegaly and bilateral small pleural effusions were present.

His mental and respiratory status deteriorated, necessitating intubation and mechanical ventilation. He developed fevers and CXR demonstrated increasing pulmonary vascular congestion. Antibiotic coverage was broadened to intravenously vancomycin and piperacillin/tazobactam.

Three days after intubation, sedatives were held in order to assess his mental status. Non-contrast head CT scan did not demonstrate any abnormalities. He remained unresponsive with a spontaneous gag and cough reflex. Non-contrast CT scan of the chest demonstrated diffuse ground glass opacities bilaterally with consolidation throughout the lungs consistent with Acute Respiratory Distress Syndrome (ARDS). Prominent mediastinal lymph nodes measuring up to 10 mm were also visualized but attributed to be most likely reactive changes to ARDS. Non-contrast brain CT demonstrated interval development of malignant cerebral edema.

Patient's overall clinical status deteriorated further requiring multiple vasopressor support and continuous renal replacement therapy. The patient's family withdrew care. Cause of death was acute on chronic liver failure (ACLF) complicated by multisystem organ failure and acute brain stem herniation.

Autopsy was limited to the liver. The liver was small with micro-nodular cirrhosis. Histology demonstrated diffuse hepatocyte necrosis with florid reactive bile duct proliferation and acute collapse of hepatic parenchyma. Immunohistochemistry was negative for hepatitis B surface and core antigens. Histological examination of a single 0.7 cm subcapsular nodule on the superior surface of the liver revealed mixed inflammatory infiltrative cells composed of small mature lymphocytes and scattered atypical multinucleated cells consistent with Reed-Sternberg cells. Immunohistochemical studies were positive for CD20, CD30, fascin, Epstein-Barr virus-encoded small RNA, consistent with HL.

DISCUSSION

Chronic HBV affects more than 350 million people worldwide. Complications of HBV include development of hepatocellular carcinoma or decompensated cirrhosis. In rare instances, chronic HBV patients can develop spontaneous severe acute exacerbations of the disease that result in hepatic failure and death^[2]. Acute flares of HBV are caused by withdrawal of immunosuppressive

medications, antiviral therapy and HBV genotypic variations. Occasionally, acute exacerbations are spontaneous^[1].

We report a case of fatal ACLF associated with undiagnosed HL and initiation of anti-viral treatment.

Review of the literature did not reveal any reports implicating HL as a catalyst for acute on chronic hepatic failure. However, HL has been associated with fulminant hepatic failure (FHF)^[3,4].

HL can lead to liver dysfunction through several mechanisms^[3-6] which include (1) tumor infiltration of hepatic vasculature, bile ducts and/or hepatic parenchyma; (2) vanishing bile duct syndrome from cytokine release; (3) as a paraneoplastic phenomenon; and by (4) withdrawal of chemotherapeutic agents in HBV positive individuals. In cases where HL is implicated with FHF, patients typically have been treated with chemotherapy and ALF is secondary to reactivation of HBV^[7]. To the best of our knowledge, HL has never been implicated as an eliciting factor to an acute exacerbation of chronic HBV.

HL most commonly presents as painless lymphadenopathy with hepatic manifestations usually occurring in advanced stage disease. Liver test abnormalities or ALF is rarely seen as the initial manifestation of HL and often only detected post-mortem^[8-12].

FHF can present in 5%-8% of patients with HL^[8,13,14], although, in reported cases, the patients usually had established malignancies^[9-12]. Most reports of FHF in HL implicate diffuse hepatic infiltration as the etiology^[13]. Rarely, is FHF an initial presentation of non-metastatic HL^[8,14-16].

An 18-year retrospective review of ALF patients by Rowbotham *et al*^[3] reported that 18 out of 4020 patients (0.44%) were found to have ALF secondary to malignant infiltration. HL was seen in only 0.07% (3 of 4020) cases. In the three cases where HL was implicated as the cause of ALF, two had previously been diagnosed with HL and had a history of chemotherapy.

Recommended treatment for patients with an acute flare of HBV is early initiation of oral nucleoside analogs to suppress HBV DNA viral replication^[1,2]. Early suppression may decrease the number of hepatocytes expressing HBV antigens thereby reducing the target burden for the immune response, allowing the flare to settle. Nucleoside analogs lack a direct immunologic effect and have a rapid effect on viral replication as compared to Interferon therapy^[1]. Anti-viral therapy has not impacted short-term survival but has improved long-term outcomes by preventing future exacerbations and ongoing liver injury^[1,2].

Entecavir is a potent nucleoside analogue with low rates of antiviral resistance (< 1% at 2 years in treatment-naïve subjects) and has been widely adopted for routine use in patients with HBV infection^[13].

Several studies have documented the benefits of entecavir therapy in ACLF in HBV. Shu *et al*^[17] reported that entecavir improved overall survival in 84 HBeAg negative patients. Jochum *et al*^[18] reported that entecavir improved outcomes in 6 patients with ACLF. In 5 out of 6 of these

cases, seroconversion to anti-HBsAg was achieved with normal or trace amounts of HBV DNA within 3 mo. Chen *et al*^[19] reported improved survival among 352 patients with ACLF after initiation of lamivudine, entecavir or telbivudine. Wong *et al*^[20] suggested long-term survival benefit among ACLF if anti-viral therapy (specifically lamivudine) was initiated early (bilirubin less than 20 mg/dL).

In 2011, Wong *et al*^[20] reviewed short and long term mortality in a small cohort of patients with ACLF who were treated with entecavir compared to lamivudine. Entecavir use was independently associated with increased short-term mortality but had a higher virological and biochemical response at week 48. The cause of increase in short-term mortality is not understood.

In conclusion, ACLF is an uncommon but well recognized complication of hepatitis B. In many instances, the eliciting trigger is identifiable and treatment with anti-viral therapy is beneficial for long-term mortality. Patients HL typically manifest their disease with systemic symptoms or diffuse hepatic infiltration and rarely present with FHF^[6,11]. HL without prior treatment with chemotherapy has not been implicated as a trigger for an acute exacerbation of HBV.

This report is a case of fatal acute on chronic hepatic failure that may have been accelerated by undiagnosed HL and/or initiation of anti-viral treatment. In reviewing our patients clinical course and liver autopsy, he developed a severe acute exacerbation of his chronic HBV coinciding with the institution of antiviral therapy and the underlying HL perhaps modulating the overall degree of hepatic injury.

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Fulminant sepsis after liver biopsy: A long forgotten complication?

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INTRODUCTION

Percutaneous liver biopsy is an important diagnostic tool for the evaluation of liver disease. It is considered safe with an overall mortality and morbidity rate of 0.015% and 0.29%, respectively^[1]. The most important complication is bleeding related to liver biopsy with an incidence of 0.016%^[2]. Infectious complications are nowadays considered as extremely rare^[3]. We report on a patient with fulminant sepsis following percutaneous liver biopsy.

CASE REPORT

A 74-year-old male patient was admitted to our hospital for further diagnostic work-up of recurrent episodes of cholangitis with fever and elevated liver enzymes. A year ago the patient had undergone cholecystectomy because of cholecystitis. The further medical history was remarkable for a stroke without neurological residuals and asymptomatic peripheral arterial disease. The patient was on a dose of 100 mg aspirin per day, which was stopped 7 d prior biopsy.

The laboratory work-up (Table 1) revealed elevated liver enzymes and a slight elevation of inflammatory markers. Sonography of the liver displayed mild intra- and extrahepatic cholestasis. Since endoscopic retrograde cholangiopancreatography (ERCP) showed a large juxta-papillary duodenal diverticulum, we thought that the recurrent bouts of cholangitis were, at least in part, caused by an intermittent obstruction of the bile flow and ascending bacterial infection caused by the diverticulum.

We performed an ERCP and found a moderate dilated common bile duct (9 mm). A 7 Fr double pigtail plastic-

Abstract

We report on a 74-year-old patient with recurrent cholangitis and a large juxta-papillary duodenal diverticulum. Despite drainage of the common bile duct by an endoscopically placed stent, the elevated liver enzymes normalized only partially. To rule out other possible causes of liver injury, a percutaneous liver biopsy was done. After the liver biopsy the patient developed fulminant septic shock and died within 24 h. We discuss the possible causes of the septic shock following percutaneous liver biopsy in our patient and give a concise overview of the literature.

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Key words: Liver biopsy; Cholangitis; Septic shock

Core tip: This case report deals with a patient in whom percutaneous liver biopsy was performed for further work-up of elevated liver enzymes. Immediately after biopsy, the patient developed fulminant sepsis and died. Possible reasons that might have caused sepsis in this patient as well as strategies to prevent sepsis/infection following percutaneous liver biopsy are discussed.

Table 1 Laboratory values, median (range)

	First presentation	Before percutaneous liver biopsy
GGT (U/L)	641 (10-71)	283 (10-71)
Alkaline phosphatase (U/L)	181 (40-129)	131 (40-129)
ALT (U/L)	109 (10-41)	25 (10-41)
Bilirubin (mg/dL)	3.4 (0.1-1.1)	1.5 (0.1-1.1)
C-reactive protein (mg/dL)	54.3 (0.0-0.5)	9.4 (0.0-0.5)

GGT: Gamma-glutamyl transpeptidase; ALT: Alanine transaminase.

stent was therefore placed in the common bile duct to ensure drainage. To minimize the risk of ascending biliary infections, a papillotomy was not performed. During the procedure we observed a short episode of flush. After the ERCP the patient developed chills and fever, which resolved promptly with antibiotic treatment.

Further course

Following stent implantation the elevated liver enzymes declined but did not fully normalize (Table 1). Since ultrasound showed that the intra- and extra-hepatic cholestasis had completely resolved, we employed an extended laboratory work-up to exclude autoimmune or viral liver disease.

Autoantibodies [antineutro-phil cytoplasmic antibody (ANCA), anti-nuclear, antimitochondrial autoantibodies, smooth muscle antibodies, anti-liver kidney microsomal] as well as immunoglobulines, ferritin and markers of viral liver disease were unremarkable.

To rule-out ANCA-negative primary sclerosing cholangitis or toxic liver damage we performed a percutaneous liver biopsy. The biopsy was carried out under sterile conditions with a Menghini needle (Hepafix, Braun Melsungen, Germany) after local anesthesia with Scandicaine. The laboratory tests prior liver biopsy (Table 1) showed neither clotting abnormalities nor elevated markers of inflammation like white blood cell count and C-reactive protein.

Immediately after the biopsy the patient had a short episode of flush, lasting a few seconds only.

One hour after the biopsy, the patient developed chills and a temperature of 39.6 °C. Blood pressure dropped to 90/50 mmHg. Chest X-ray at this moment showed no abnormalities. Sonography of the liver revealed no bleeding or other abnormalities. The patient was transferred to an intensive care unit, blood cultures were taken immediately after admission and antibiotic treatment with Piperacillin/Tazobactam was started. Even though the patient developed fulminant sepsis with multi-organ failure.

Despite invasive ventilation, continuous veno-venous haemofiltration, administration of fresh frozen plasma and catecholamines the patient's condition deteriorated rapidly and he died 24 h after the liver biopsy in fulminant septic shock.

Further findings

Because of the unexplained sepsis and the rapid deteriora-

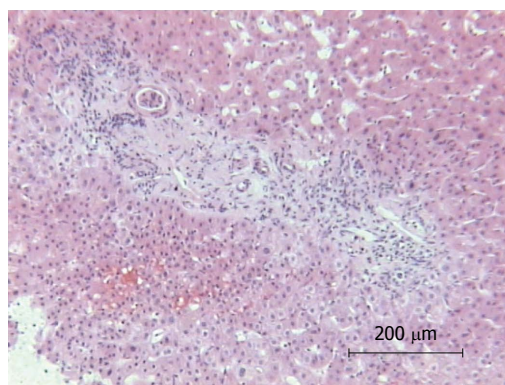


Figure 1 Minor and moderate inflammatory lymphocytic infiltrate in portal tract and periportal parenchyma. Mild sclerosing portal and periportal inflammation.

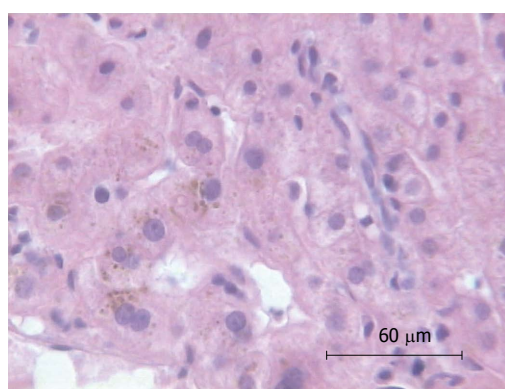


Figure 2 Focally fatty change and discrete cholestasis in liver cells.

tion of the patient's condition after liver biopsy, an autopsy was performed. The autopsy demonstrated cholangitis but the puncture side and canal showed no abnormalities. Another infection site from which a bacterial sepsis could have been arose was not found. The histology of the liver specimen revealed chronic sclerosing cholangitis (Figures 1 and 2). There were no signs of toxic or other liver disease.

In the blood cultures that were taken 6 h after liver biopsy *Clostridium perfringens*, *Enterococcus faecalis*, *Proteus mirabilis*, *Citrobacter braakii* and *Citrobacter freundii* were found.

DISCUSSION

In our report, we describe a patient with fatal septic shock following percutaneous liver biopsy.

Liver biopsy is considered a safe procedure with complications in only 0.29% of cases^[1]. The most important complications are pain and haemorrhage. Infrequent complications are shock, pulmonary embolism, arteriovenous fistula, haemobilia and ileus^[4]. Infectious complications are considered as extremely rare^[3].

Transient bacteremia following liver biopsy has an estimated incidence of 2% to 13%^[5-7]. Most often only single microorganisms like *Escherichia coli* (*E. coli*) or *Klebsiella spp.* are found. However, clinically evident infectious complications following liver biopsy are considered a rare event. In

a large retrospective analysis of 68 276 biopsies, the risk of infectious complications was approximately 1 in 10 000 liver biopsies^[3].

To our best knowledge, there have been no published cases of sepsis following percutaneous liver biopsy in the last 15 years. In contrast, looking back two or three decades, septicemia following liver biopsy was described by several authors. Morris *et al*^[8] reported fever and/or a positive blood culture in 3 out of 125 patients who underwent liver biopsy. LoIudice *et al*^[4] found three patients with septicemia following liver biopsy in a series of 797 patients. Murray *et al*^[9] as well as Navarro *et al*^[10] published each one case report of patients with sepsis following liver biopsy. *E. coli* was found in the blood culture of most patients. Blood cultures positive for *Streptococcus viridans*, *Klebsiella spp.* and *Clostridium welchii* have also been reported. In the majority of the affected patients, liver biopsy revealed cholangitis or pericholangitis as the underlying disease. Large bile duct obstruction without cholangitis does not seem to be a risk factor for sepsis following liver biopsy^[8]. These findings were emphasized by a study of 950 liver biopsies in 136 patients who had undergone liver transplantation^[11]. The authors found infectious complications in six patients. Of these six patients, five had undergone choledochojunostomy. Blood cultures of the affected patients were positive for *E. coli*, *Klebsiella spp.*, *Streptococcus faecium*, *Clostridium spp.* and *Enterobacter aerogenes*. None of the five patients with choledochojunostomy and infectious complications after biopsy had clinically evident signs of cholangitis before liver biopsy. Biliary obstruction was excluded in all patients by a T-tube or transhepatic cholangiogram. Since mainly microorganisms of the enteric flora were found, the authors concluded that due to the choledochojunostomy, an enteric flora without clinically evident signs of infection colonized the transplanted liver.

Another group published conflicting results. They retrospectively compared 46 liver transplant patients with choledochojunostomy with a total of 192 liver biopsies with 46 liver transplanted patients with choledochostomy with a total of 118 biopsies. There were no significant differences between the two groups regarding infectious complications^[12]. The authors tried to explain the conflicting findings by a difference in the length of the small bowel segment used for the choledochojunostomy.

One could only speculate why there have been no cases of sepsis following liver biopsy reported in the last years. Most likely-due to advances in imaging and laboratory methods in recent years-the majority of patients with cholangitis are correctly diagnosed without a liver biopsy and hence biopsy is nowadays seldom performed in patients with cholangitis.

Although sepsis following liver biopsy is considered a rare event, the pathogenetic relationship between liver

biopsy and septic shock appears well substantiated in our patient.

At the time of the liver biopsy, the patient had no clinically or laboratory evident signs of cholangitis, nor was biliary obstruction present. Nevertheless, autopsy and the liver biopsy revealed cholangitis. In addition, the blood cultures were positive for bacteria, which are typically found in cholangitis. We hypothesize that the patient had recurrent bouts of ascending cholangitis caused by biliary obstruction due to the large juxtaepapillary duodenal diverticulum. The liver biopsy then induced propagation of infection by establishing the communication between the infected focus and the blood vessels.

To avoid septic complications in patients with suspected cholangitis undergoing liver biopsy in the future, antibiotic prophylaxis prior biopsy in these patients should be discussed.

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Treatment of a patient with congenital analbuminemia with atorvastatin and albumin infusion

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Core tip: Congenital analbuminemia is characterized by low plasma albumin and compensatory hypercholesterolemia, which may increase cardiovascular risk. We report a case of congenital analbuminemia (1.0 g/dL) in a 38-year-old male with hypercholesterolemia (range: 406-475 mg/dL) and severe arterial dysfunction [no brachial artery flow-mediated dilation (FMD)]. Long-term, cholesterol-lowering treatment with atorvastatin was associated with the appearance of peripheral edema. Two-months of infusion with albumin improved FMD (7%) and reduced serum cholesterol (273 mg/dL). Statin treatment, together with periodical albumin infusions, may contribute to the safe reduction of cardiovascular risk.

Abstract

Congenital analbuminemia is a rare autosomic recessive inherited disorder characterized by low plasma albumin and hypercholesterolemia, which may increase cardiovascular risk. Patients are essentially asymptomatic, apart from ease of fatigue, minimal ankle oedema and hypotension. There is no accepted strategy for safely treating both hypercholesterolemia and analbuminemia in order to eventually decrease the atherosclerotic risk. We report a case of congenital analbuminemia (1.0 g/dL) in a 38-year-old male with hypercholesterolemia (range: 406-475 mg/dL) and severe arterial dysfunction [no brachial artery flow-mediated dilation (FMD)]. Long-term, cholesterol-lowering treatment with atorvastatin was associated with the appearance of peripheral edema. Two-months of infusion with albumin improved FMD (7%) and reduced serum cholesterol (273 mg/dL), supporting the hypothesis of a compensatory role of hypercholesterolemia. Statin treatment, together with periodical albumin infusions, may contribute to the safe reduction of cardiovascular risk.

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Key words: Analbuminemia; Hypercholesterolemia; Atorvastatin; Albumin infusion; Endothelial dysfunction

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INTRODUCTION

Congenital analbuminemia is a rare autosomic recessive inherited disorder in which the subject has no or little plasma albumin^[1-3]. Analbuminemia is attributable to defects in the gene coding for albumin which is located on chromosome 4 and is split into 15 exons by 14 intervening introns^[4,5]. Multiple mutations causing analbuminemia have been identified in the homozygous state^[6-8]. The estimated prevalence is less than one in a million and to date, fewer than 50 cases have been reported worldwide. Although it is extremely rare, analbuminemia may teach us important pathophysiological lessons.

Albumin is the major plasma protein and the most important for maintaining plasma colloid oncotic pressure and preventing systemic edema^[9]. It is also an important circulating antioxidant and a transporter of many

less soluble metabolites^[9]. Surprisingly, the absence of albumin is tolerable and most patients are detected fortuitously. In fact, patients are essentially asymptomatic, apart from ease of fatigue, minimal ankle oedema and hypotension^[10-13].

In these patients the body is able to compensate for the lack of albumin through the synthesis of immunoglobulins and other serum proteins such as ceruloplasmin, fibrinogen and transferrin, but particularly through an increased secretion of apolipoprotein-B from the liver^[14,15]. Patients have enhanced plasma low density lipoprotein-cholesterol (LDL-C) levels, normal or reduced high density lipoprotein-cholesterol (HDL-C) and normal triglycerides, possibly leading to premature atherosclerosis and cardiovascular events^[16-18]. Indeed, hypoalbuminemia is strongly associated to cardiovascular disease in patients with nephrotic syndrome and in hemodialysis patients, where an inverse association between albumin and both total and LDL-C is observed^[19]. Based on this, congenital analbuminemia should be associated with premature atherosclerosis^[20] and thrombotic events although, no data on atherosclerotic risk have been reported so far.

Consequently, there is no accepted strategy for safely treating both hypercholesterolemia and analbuminemia in order to eventually decrease the atherosclerotic risk.

CASE REPORT

Previous medical history

A 38-year-old Italian man was admitted with severe hypercholesterolemia and congenital analbuminemia. Born in 1973 from healthy and non-sanguineous parents, he received replacement therapy with human serum albumin for the presence of mild oedema in his lower limbs and eyelids^[21]. At 1 mo old he was admitted to the children's hospital where laboratory examinations revealed a reduced serum total protein of 3.2 g/dL and almost undetectable albumin but with normal urinary protein excretion and a remarkable increase in serum cholesterol (222 mg/dL). During hospitalization, he received replacement therapy with human albumin and was discharged at 6 mo of age, free of oedemas and in good general condition. He was followed for 8 years with periodic laboratory check ups, which showed an absence of the albumin peak in protein electrophoresis, thus confirming the initial diagnosis of congenital analbuminemia associated with severe hypercholesterolemia (total cholesterol > 400 mg/dL). Evaluation of the child's family revealed no members with hypoalbuminemia or familial hypercholesterolemia.

Clinical presentation

After 21 years of life without any major clinical complication, the patient was referred to our outpatient clinic for the treatment of hypercholesterolemia. His past clinical history was unremarkable except for some lipotymic events and the presence of mild ankle oedema during the

hot season after standing for a long time. He had taken no medications regularly. The physical examination was within normal limits with no signs of oedema of the lower limbs, and no pleuric or ascitic effusion. His arterial blood pressure was 110/70 mmHg, with a body weight of 80 kg and a body mass index of 24.7 kg/m². Resting and exercise electrocardiogram, arterial blood pressure monitoring, mono/bidimensional echocardiogram, echocolor doppler studies of the carotids and of peripheral arteries were without pathological findings and confirmed the absence of clinical signs of atherosclerotic complications. However, on several occasions the brachial artery flow-mediated dilation (FMD) test^[22], a surrogate marker of atherosclerotic disease, confirmed the existence of severe arterial dysfunction (absence of post-ischemic arterial dilatation). No tendon xanthomas were detected.

Repeated laboratory examination revealed serum total protein ranging from 5.0 to 5.2 g/dL and serum albumin from 1.0 to 1.2 g/dL. Cellulose-acetate electrophoresis revealed the absence of an albumin peak. Renal function tests, urinalysis and urinary protein excretion were normal. The patient showed a remarkable elevation in serum total-cholesterol (range, 406-475 mg/dL), LDL-C (range, 317-379 mg/dL) and apolipoprotein-B (> 200 mg/dL) with normal HDL-cholesterol and triglyceride levels. Serum lipoprotein(a), assessed by monoclonal-based enzyme-linked immuno-absorbent assay, had the remarkably high value of 90.5 mg/dL (normal < 30 mg/dL). No corneal arcus or other signs of dyslipidemia were present.

Our patient is the first case of congenital analbuminemia attributable to compound heterozygosity for 2 new mutations in the exons 10 and 11 of albumin gene^[5].

Response to atorvastatin treatment

The patient received a American Heart Association step-1 low-cholesterol, low-saturated-fat diet on his first visit, without any significant decrease in serum lipids over a 5-mo period (total cholesterol from 409 to 397 mg/dL; LDL-C from 336 to 328 mg/dL, apolipoprotein-B from 225 to 203 mg/dL). Treatment with atorvastatin was then started at the initial daily dose of 10 mg, increased to 20 mg at week 5 and to 40 mg at week 21^[23]. Baseline and on-treatment lipid and lipoprotein data are reported in Table 1. After 6 mo of drug treatment, total and LDL-C dropped by 37.7% and by 50.6% respectively and HDL-C increased by 13.4%. Moreover, apolipoprotein-B and lipoprotein(a) were decreased by 18.7% and 19.7% respectively while apolipoprotein-A1 was increased by 65.0%. The treatment was safe and well tolerated with no increases in creatine-kinases or in liver enzymes. Total and LDL-C, apolipoprotein-B and lipoprotein(a) reached pre-treatment values only 2 wk after stopping atorvastatin. Based on the above favourable results, long-term treatment with atorvastatin 40 mg was prescribed.

Response to albumin infusions

After 2 years on 40 mg/d atorvastatin treatment, the pa-

Table 1 Changes in serum lipid profile during treatment with atorvastatin at increasing dosages

Time	Treatment	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	Apo A1 (mg/dL)	Apo B (mg/dL)	Lp (a) (mg/dL)	ALT (UI)	AST (UI)	CK (U/L)	Alb (g/L)
Week 20	Diet	409	97	53	336		225		20	26	195	1.1
Week 0	Diet	397	85	52	328	124	203	90.5	18	18	162	0.8
Week 1	At 10 mg	384	144	45	310				25	30	193	0.8
Week 2	At 10 mg	307	104	52	234				18	20	181	0.8
Week 3	At 10 mg	284	122	45	214				21	22	138	0.7
Week 4	At 10 mg	261	111	44	194	162	151	85.3	21	15	147	0.7
Week 5	At 20 mg	303	100	60	223				14	20	160	0.8
Week 6	At 20 mg	290	99	61	209				20	20	147	0.7
Week 8	At 20 mg	240	130	49	165			80.0	19	21	123	0.8
Week 10	At 20 mg	263	93	45	199				22	15	123	0.8
Week 12	At 20 mg	264	84	36	211				25	20	192	0.7
Week 14	At 20 mg	264	88	47	199				23	17	172	0.8
Week 16	At 20 mg	250	83	49	184			76.6	22	17	142	0.7
Week 18	At 20 mg	279	119	42	213				17	17	131	0.7
Week 20	At 20 mg	272	90	57	197	224	160		23	24	195	1.0
Week 21	At 40 mg	243	90	59	166	199	165	72.6	25	30	189	0.7
Week 26	Diet	375	113	52	300			89.6	19	15	153	
Week 28	Diet	435	124	51	359	224	206		22	10	137	0.6

TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein-cholesterol; LDL: Low density lipoprotein-cholesterol; Apo: Apolipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatine phosphokinase; Alb: Albumin.

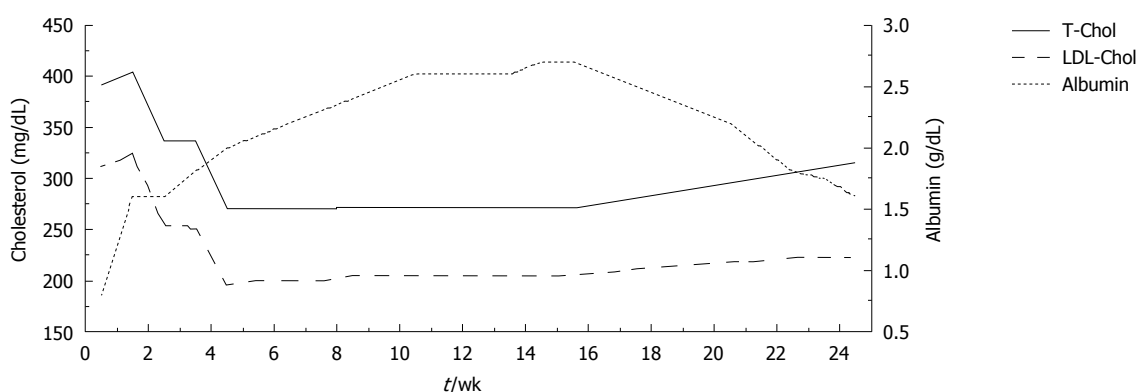


Figure 1 Variation of plasma albumin (g/dL) and of total and low density lipoprotein cholesterol (mg/dL) during albumin infusions and after albumin discontinuation. LDL: Low density lipoprotein; TC: Total cholesterol.

tient complained of severe bilateral, gravity-dependent, oedema and painless swelling of the ankles and lower legs.

At that time serum cholesterol and albumin were 360 mg/dL and 0.8 g/dL, respectively. Therefore, statin therapy was stopped and oral furosemide (25 mg/d) treatment was prescribed.

In addition, starting 1 mo later, human albumin (20 g) was infused over a period of 8 wk (two infusions during the first week and one per week thereafter). During the treatment course, blood samples were taken immediately before each albumin infusion in order to evaluate long-term changes in serum lipids and albumin. Serum albumin levels rose remarkably from 0.8 to 2.7 g/dL, while a progressive decrease in total and serum cholesterol was observed (total cholesterol from 391 to 273 mg/dL; LDL-C from 312 to 196 mg/dL) (Figure 1). No alterations in liver and kidney function were observed after the peripheral infusion of albumin.

Albumin infusion was also associated with recovery from symptoms of peripheral oedema and an increase in FMD (from 0% to 7%).

During the 4 mo after albumin discontinuation, a mild, progressive increase of total and LDL-C was observed (total cholesterol up to 333 mg/dL; LDL-C up to 249 mg/dL) which was paralleled by a progressive decrease of serum albumin (from 2.7 to 1.4 g/dL).

DISCUSSION

So far, more than 50 analbuminemia-causing homozygote or compound heterozygote mutations of the albumin gene have been reported^[24]. The majority of patients do not have major clinical complications and can live fairly normal lives. In fact, the lack of albumin is compensated by a severe hypercholesterolemia which is mainly caused by an increased rate of production of apo-B-containing lipoproteins in the liver and to a lesser extent by a decrease

in LDL catabolism^[17,18]. Hypercholesterolemia, whether primary or secondary, is recognized as the most important risk factor for premature atherosclerosis and there is overwhelming evidence that lowering cholesterol decreases cardiovascular risk. Indeed, in our patient, the presence of severe arterial dysfunction, as assessed by the absence of post ischemic brachial artery dilation, was demonstrated on several occasions.

There are only two other cases in the literature of short-term treatment of hypercholesterolemia in human analbuminemics^[18]. They relate to two South African adult patients who were treated with lipid-lowering diet and simvastatin at up to 40 mg day for a period of 20 wk. based on general experience with simvastatin, one patient responded as anticipated (LDL-C-48.3%), but the other responded less than expected (LDL-C-38.3%). However, both patients experienced a three- to fivefold increase in creatine-kinase.

In our patient a 21-wk period of drug treatment with atorvastatin, with the dose increasing in stages from 10 to 40 mg, resulted in a 50.6% reduction of serum LDL-C, eventually reaching a value close to the goal of 160 mg/dL. Short-term treatment was safe and well tolerated, and no clinical complaints or biochemical signs of hepatotoxicity, myopathy or dysproteinemia developed. However long-term lipoprotein cholesterol-lowering treatment led to a progressive decrease of oncotic pressure, due to the reduction of the compensatory hypercholesterolemia, with the consequent development of severe swelling of the ankles and lower legs.

Treatment with albumin infusions reversed peripheral edema and decreased serum cholesterol, supporting the hypothesis that severe hypercholesterolemia may represent a compensatory mechanism for the deficit of albumin.

We also observed an improvement in FMD after albumin infusion, suggesting a role for low albumin in eliciting artery dysfunction. As oxidative stress unfavourably influences FMD^[25], this favourable change may be interpreted as a combined antioxidant and cholesterol-lowering effect of albumin. Therefore, we suggest a direct correlation between albumin infusion and the improvement in FMD.

In conclusion, we describe a patient with analbuminemia in whom statin reduced serum cholesterol but was associated with the appearance of peripheral edema. Albumin infusions were also effective in reducing serum cholesterol and ameliorating artery dysfunction. Long-term atorvastatin therapy together with periodic albumin infusions may contribute to decreasing cardiovascular risk safely in this clinical setting.

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Schwannoma of the rectum: A case report and literature review

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dimensons. No recurrence of the lesion was observed after 6 mo of follow-up.

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Key words: Rectum; Schwannoma; Immunohistochemistry; S-100 protein; Treatment

Core tip: Schwannomas of the colon and rectum are tumors that are rarely detected. For achieving a definitive histopathological diagnosis, the use of an appropriate immunohistochemical panel is request. Although schwannomas are considered to be benign tumors, their risks of recurrence must be not ignored. The best therapeutic option is complete surgical removal. In the present study, we describe a case of a rectal schwannoma occurred in a 72-year-old man, presented as a small sessile polypoid lesion, which was successfully removed *in toto* by hot-biopsy, during the same procedure. No recurrence of the lesion was observed after 6 mo of follow-up.

Abstract

Schwannoma is a tumor originating from the Schwann cells. Gastrointestinal schwannomas are uncommon stromal tumors of the intestinal tract and, in particular, rectal schwannomas are extremely rare. In fact, it is well established that schwannomas appear more frequently in the stomach and in the small intestine, while location in the colon or in the rectum is uncommon. Reading the literature, only few cases of rectal schwannoma have been reported. Their diagnosis is confirmed by the immunohistochemical panel (S-100 protein). When these tumors are located in the colon and in the rectum, radical excision with wide margins is mandatory, due to their tendency to recur locally or become malignant, if left untreated. In the present study, we describe a case of a rectal schwannoma occurred in a 72-year-old man, presented as a small polypoid lesion, which was successfully removed *in toto* by hot-biopsy, during the same endoscopy, due to the

Zippi M, Pica R, Scialpi R, Cassieri C, Avallone EV, Occhigrossi G. Schwannoma of the rectum: A case report and literature review. *World J Clin Cases* 2013; 1(1): 49-51 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/49.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.49>

INTRODUCTION

Schwannomas are rare tumors derived from the cells of Schwann that form the neuronal sheath. Generally these are benign tumors, which, if left untreated, have the tendency to recur locally and become malignant^[1,2]. These lesions are classified in gastrointestinal autonomic nerve tumours (GANTs) and were described for the first time by Herrera *et al*^[3] in 1984. There are many synonyms for neurogenic tumors of the gastrointestinal tract, such as

schwannoma, neurinoma, neurofibroma, neurogenic fibroma, neurilemoma and plexiform neurofibromatosis. Usually, these different names are used with the intent of relating them to the structure from which they originate^[4]. The correct name of gastrointestinal schwannoma is based on the evidence showing that this neoplasm originates from Schwann cells in the neurons of the myenteric plexus^[5,6].

Although rare, schwannomas must be included in the differential diagnosis from other intestinal mesenchymal neoplasms, such as smooth muscle tumors, neurofibromas, and gastrointestinal stromal tumors (GISTs)^[7]. Primary schwannoma of the colon and rectum, not associated with systemic neurofibromatosis (von Recklinghausen disease), are extremely rare^[8].

CASE REPORT

A 72-year-old man was referred to our unit for performing a colonoscopy due to abdominal pain. The medical history of the patient included a type 2 diabetes mellitus and arterial hypertension. The therapy was assumed at the moment for these diseases. There was no family history of inflammatory bowel disease or cancer and no previous abdominal surgery. Physical examination of the patient revealed good general condition. Laboratory tests were normal. A colonoscopy disclosed evidence of a small sessile polypoid lesion, of about 1.5 cm in diameter, in the left lateral wall of the rectum, approximately at 1 cm from the superior anal margin. No other lesions were found in the other colon segments, including the cecum, except for a diverticular disease of the sigmoid colon. This lesion was removed *in toto* by hot-biopsy (Figure 1). The related histopathological findings showed typical features of schwannoma, with Antoni A/verocay bodies (cells forming a typical palisade arrangement in a well-organized pattern) and Antoni B (small lacunar foci with loss of palisade architecture; Figure 2A) and strong positivity for S-100 protein at immunohistochemical assay (Figure 2B). After 6 mo, a follow-up colonoscopy, performed with methylene blue staining, disclosed no evidence of recurrence of the lesion.

DISCUSSION

GANTs are uncommon stromal tumours accounting for 0.1% of benign tumours of the gastrointestinal tract^[5]. The most frequent site for GANTs include the stomach followed by duodenum, jejunum, ileum^[9], rarely they are located in the colon, and in the literature we have found only few reported cases of rectal schwannomas^[2,6,9-16]. Moreover, Gibson *et al*^[17] have studied 26 colorectal sessile polyps containing S-100 positive neural proliferations in the lamina propria, not associated with type 1 neurofibromatosis (NF1). The authors proposed to define them as “mucosal Schwann cell hamartoma”, to avoid confusion with the neural lesions that have significant associations with inherited syndromes. In particular, schwannoma has the same incidence in men and women with a mean



Figure 1 In case of a rectal schwannoma, the colonoscopy disclosed evidence of a little polypoid lesion in the left lateral wall of the rectum.

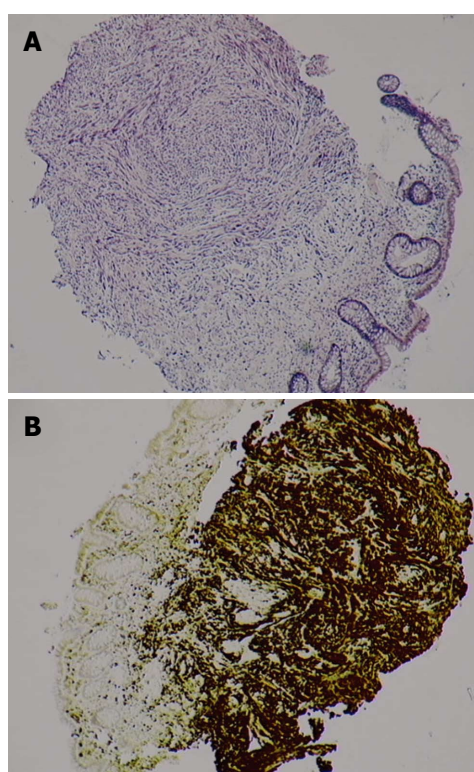


Figure 2 In case of rectal schwannoma, the tumor, located in the submucosa, has a nodular well-defined structure (haematoxylin and eosin, ×20). The structure that consists in proliferation of Schwann-like cells, showing a palisading arrangement (A), being marked by S-100 protein (B).

age of 60-65 years^[18]. Their size may vary and a case of a rectal schwannoma of about 12 cm has been reported^[11]. Schwannomas are mostly asymptomatic or can present non-specific symptoms such as pain, fatigue and fever. Sometimes, rectal bleeding and signs of colonic obstruction may occur^[18].

Schwannomas should be differentiated from other intestinal mesenchymal neoplasms. In fact, the most accurate diagnosis is based on immunohistochemical test^[6]. Especially, it is difficult to distinguish schwannoma from leiomyoma and GIST. Generally, gastrointestinal schwannomas are not encapsulated, and this finding may

help to distinguishes them from schwannomas in peripheral nervous system. On histopathological examination these kind of tumors have a lymphoid cuff with germinal centre. They may resemble GISTs but the presence of lymphoid cuff helped in diagnosing of schwannomas. The tumor cells of schwannoma are positive for S-100 protein, as in our case, and negative for smooth muscle markers, such as actin and desmin, which are positive in myogenic tumors. Although these are considered as benign tumors, the risks of recurrence of local and of distant metastases are 30% and 2%, respectively^[19,20]. The mainstay management of these tumors is based prevalent on surgery with radical excision.

In conclusion, rectal schwannoma is a rare tumor with a benign behaviour and a good prognosis.

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Liver failure in an obese middle-aged woman after biliointestinal bypass

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Author contributions: Cotticelli G and de Sio I made substantial contributions to the conception and design of the study; Funaro A, Sgambato D, Del Prete A, de Sio C and Romano L were involved in the acquisition, analysis and interpretation of data; Federico A, Gravina A and Miranda A were involved in drafting the manuscript and critically revising it for important intellectual content; Loguercio C and Romano M approved the final version for publication.

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Abstract

Obesity is considered an emerging epidemic that is often associated with non-alcoholic fatty liver disease. Among the therapeutic options for morbid obesity, bariatric surgery plays an important role when conventional therapies fail. The effects of bariatric surgery on liver function and morphology are controversial in the literature. Liver failure has been reported after jejunoileal bypass (JIB), biliopancreatic diversion and gastric bypass. Biliointestinal bypass (BIB) is considered an effective procedure among recently introduced bariatric surgery techniques. It is a clinically safe, purely malabsorptive operation in which the blind intestinal loop of the JIB is anastomosed to the gallbladder, allowing a portion of bile to transit into excluded intestinal tract. BIB is the only procedure, to our knowledge, to have

no liver side effects reported in the literature. We report the case of a young obese woman who developed liver failure 8 mo after BIB. She had a rapid weight loss (70 kg) with a reduction in body mass index of 41% from January to September 2012. Because of a severe hepatic decompensation, she was referred to a transplantation centre. We strongly believe that the most important pathogenetic mechanism involved in the development of liver injury is the rapid weight loss that produced a significant fatty liver infiltration.

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Key words: Bariatric surgery; Biliointestinal bypass; Liver failure; Non-alcoholic fatty liver disease; Obesity; Rapid weight loss

Core tip: Biliointestinal bypass (BIB) is considered an effective procedure among recently introduced bariatric surgery techniques. Liver failure has been described after jejunoileal bypass, biliopancreatic diversion and gastric bypass; however, no case of liver injury has been reported after BIB in the literature, to our knowledge. We present a case of liver failure that developed 8 mo after biliointestinal derivation in a young obese patient, who subsequently required a liver transplantation.

Sgambato D, Cotticelli G, de Sio I, Funaro A, Del Prete A, de Sio C, Romano L, Federico A, Gravina A, Miranda A, Loguercio C, Romano M. Liver failure in an obese middle-aged woman after biliointestinal bypass. *World J Clin Cases* 2013; 1(1): 52-55 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/52.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.52>

INTRODUCTION

Currently, obesity is considered an emerging epidemic,

often associated with non-alcoholic fatty liver disease (NAFLD)^[1]. A wide spectrum of conditions ranging from fatty liver to non-alcoholic steatohepatitis (NASH) is included in NAFLD. Conventional therapies often do not induce significant, life-changing weight loss, so alternative surgical approaches have been developed for the treatment of morbid obesity. New therapeutic surgical procedures include restrictive bowel surgery, aimed at reducing oral intake by limiting gastric volume, and surgery that promotes malabsorption, such as the Fobi-Cappella gastric bypass (GB) and the Scopinaro biliopancreatic diversion (BPD) operations and biliointestinal bypass (BIB). There are also mixed procedures that apply both techniques simultaneously, such as sleeve gastrectomy with duodenal switch. A laparoscopic approach has been described in the literature for the surgical treatment of morbid obesity, and this approach has been associated with a reduction in surgical site infection rate by 70%-80%, compared with open surgery, across general abdominal surgical procedures^[2]. The jejunoileal bypass (JIB) was abandoned in the 1980s due to a high rate of early and late liver complications, ranging from acute hepatic failure to cirrhosis^[3]. Among recently introduced bariatric surgeries, BIB is the only procedure in which no liver side effects have been described in the literature. This procedure is a clinically safe, purely malabsorptive operation in which the blind intestinal loop of the JIB is anastomosed to the gallbladder, allowing a portion of bile to transit into excluded intestinal tract. The cholecystojejunal anastomosis eliminates stasis in the bypassed bowel and reduces the amount of bile salts malabsorbed compared with the JIB. We report the case of a young obese woman who developed liver failure 8 mo after BIB. Due to severe hepatic decompensation, she was referred to a transplantation centre.

CASE REPORT

A 42-year-old woman was admitted to our hepatology unit for jaundice, asthenia and diarrhoea. She underwent BIB for severe obesity: body mass index (BMI) 54 in January 2012. Abdominal ultrasound (US) performed before the surgery revealed a bright liver pattern (slight NAFLD), and no evidence of liver cytolysis or abnormal functional tests were detected. Serum markers for hepatitis B virus, hepatitis C virus and other causes of liver damage (AMA, ANA, ASMA, anti-LKM1, α 1-AT, copper, ceruloplasmin, iron and transferrin) were negative. No alcohol abuse was reported. Her lipid profile was characterised by high levels of total cholesterol (2.45 g/L, normal values 0.60-2.00 g/L) and triglycerides (2.00 g/L, normal values 0.20-1.75 g/L). No paracetamol or other drug consumption was detected. She was not under total parenteral nutrition. A liver biopsy was not performed during the surgical procedure. After the operation, the patient underwent periodic nutritional controls, and the intake of vitamins and proteins was recommended. She experienced a rapid weight loss (70 kg) with a reduction

in BMI of 41% from January to September 2012. During this period, she had only diarrhoea, a well-known side effect of bariatric malabsorptive operations. In September 2012, she presented with jaundice and severe asthenia and was admitted to the surgery unit where she had received the previous operation. Upon admission, a physical examination revealed jaundice, pale mucosae and splenomegaly. The laboratory data revealed: anaemia [hemoglobin (Hb) 72 g/L, normal values 126-160 g/L; red blood cell (RBC) $2.23 \times 10^6/\text{mm}^3$, normal values $4.20\text{-}5.40 \times 10^6/\text{mm}^3$; mean corpuscular volume (MCV) 102 fL, normal values 81.0-99.0 fL], a low platelet (PLT) count (54 000/ μL , normal values 13 000-400 000/ μL), clotting alterations [international normalized ratio (INR) 1.90, normal values 0.8-1.2], hyperbilirubinemia (total bilirubin 0.14 g/L, normal values < 0.01 g/L, with a direct bilirubin of 0.06 g/L, normal values < 0.002 g/L), hypoalbuminemia (31 g/L, normal value 35-55 g/L), hepatocytolysis [aspartate aminotransferase (AST) 135 U/L, normal values 5-32 U/L; alanine aminotransferase (ALT) 150 U/L, normal values 5-33 U/L], a low cholinesterase value (3220 U/L, normal values 5320-12 920 U/L), and negative for markers of viral hepatitis. D-Dimer, antithrombin III and fibrinogen values excluded a disseminated intravascular coagulation. Hemocultures for aerobic and anaerobic pathogens were repeatedly negative. Therefore, due to the severe anaemia, a blood transfusion was performed. Abdominal US showed: hepatomegaly with a bright liver pattern (mild steatosis), 20 mm portal vein diameter, and splenomegaly (lateral diameter 20 cm). Abdominal computed tomography confirmed the US findings. Endoscopic exams (esophagogastroduodenoscopy and colonoscopy) produced negative results. The patient also underwent a bone marrow biopsy that revealed non-specific low dysplasia. Clinical, laboratory and imaging data might have suggested that the patient had Banti Syndrome (*i.e.*, congestive splenomegaly with hypersplenism secondary to liver cirrhosis, portal or spleen venous thrombosis). Doppler ultrasonography (USG) of the portal system might have helped in the diagnosis. There are several studies demonstrating that changes in the hepatic artery resistance index, phasicity of right hepatic vein blood flow, or velocity of portal vein blood flow are inversely related to the degree of fatty infiltration of the liver. However, Doppler USG was not performed. As an alternative, transient or dynamic elastography might have helped in detecting hepatic fibrosis, but this procedure was also not performed. Thirty days after the admission to the surgery division, she was moved to our hepatology unit. Upon admission, a physical examination, similar to the one performed at the surgery division, was performed. The laboratory data were as follows: white blood cell (WBC) $6.03 \times 10^3/\text{mm}^3$ (normal values $4.20\text{-}10.80 \times 10^3/\text{mm}^3$), Hb 96 g/L, RBC $3.08 \times 10^6/\text{mm}^3$, MCV 95 fL, PLT 75 000/ μL , INR 1.89, total bilirubin 0.07 g/L with a direct bilirubin of 0.03 g/L, albumin 37 g/L, AST 31 U/L, ALT 45 U/L, cholinesterase 3018 U/L, alkaline phosphatase (ALP) 61 U/L (normal values 35-108 U/L), γ -glutamyltransferase (GGT)

Table 1 Laboratory data

Date	WBC ¹ (/mm ³)	RBC (/mm ³)	Hb (g/L)	PLT (/μL)	INR	Total bilirubin (g/L)	Albumin (g/L)	ALP (U/L)	GGT (U/L)
September 27	5.30	2.23	72	54	1.90	0.14	31	56	22
October 24	3.60	2.64	82 ²	42	2.06	0.07	36	62	30
November 06	6.30	3.08	96 ²	75	1.89	0.07	37	61	28
November 20	3.24	3.04	94 ²	63	2.13	0.06	29	52	18

¹The differential was normal; ²The patient received blood transfusions. RBC: Red blood cell; WBC: White blood cell; Hb: Hemoglobin; PLT: Platelet; INR: International normalized ratio; ALP: Alkaline phosphatase; GGT: γ-glutamyltransferase.

28 U/L (normal values 5–36 U/L), total cholesterol 0.71 g/L [high density lipoprotein (HDL) 0.37 g/L, normal values > 0.45 g/L; low density lipoprotein (LDL) 0.21 g/L, normal values < 1.29 g/L] and triglycerides 0.49 g/L. Arterial blood gas analysis showed mixed metabolic and respiratory acid-base disturbances (pH 7.478, pCO₂ 33.0 mmHg, pO₂ 72.2 mmHg, HCO₃⁻ 25.4 mmol/L, Na⁺ 136.6 mmol/L, K⁺ 1.83 mmol/L, Cl⁻ 107 mmol/L).

She underwent abdominal US at our USG section, which confirmed the bright liver pattern, with posterior acoustic attenuation and poor visualisation of vascular structures (mild-high steatosis) with splenomegaly (lateral diameter 24 cm) and a dilated spleno-portal axis. Because cirrhosis has been described in these patients, a liver biopsy might have been important for diagnosis. However, we neither performed a percutaneous liver biopsy due to the severe coagulative injury nor performed a transjugular liver biopsy even though this procedure has been reported to be potentially well tolerated in this setting. During hospitalisation, liver function worsened, and 7 d after admission, the laboratory data were as follows: WBC $3.24 \times 10^3/\text{mm}^3$, Hb 94 g/L, RBC $3.04 \times 10^6/\text{mm}^3$, MCV 96.2 fL, PLT 63 000/μL, INR 2.13, albumin 29 g/L, cholinesterase 2052 U/L, bilirubin 0.15 g/L, ALP 52 U/L, GGT 18 U/L, total cholesterol 0.55 g/L (HDL 0.32 g/L, LDL 0.14 g/L), and triglycerides 0.49 g/L. Changes in the laboratory data are presented in Table 1. Due to the rapid liver decompensation, we sent the patient to a transplantation unit. She underwent orthotopic liver transplantation with a reversal of the bariatric surgery. Her subsequent condition was characterised by a satisfactory clinical improvement. Unfortunately, we have no data concerning hepatic histological findings.

DISCUSSION

The prevalence of obesity has increased dramatically over the last decades with NASH becoming more frequent. Among therapeutic options for morbid obesity, bariatric surgery plays an important role when conventional therapies fail. The effects of bariatric surgery on liver function are controversial in the literature. Moreover, the progression and/or regression of hepatic steatosis after bariatric surgery is poorly understood^[4].

Several trials suggest that bariatric surgery improves liver morphology in patients with pre-existing histological liver alterations such as steatosis or steatohepatitis.

According to Dixon *et al*^[5] who examined the effects of weight loss on NAFLD in 36 selected obese patients, steatosis, lobular inflammation, centrolobular fibrosis and ballooning degeneration improved significantly after bariatric surgery. Moreover, a significant reduction in the prevalence of metabolic syndrome (from 70% to 40%) and a marked improvement in liver steatosis, inflammation and fibrosis after GB were described by Mattar *et al*^[6]. Concerning the effects of bariatric surgery on cardiometabolic risk factors and weight loss, BIB seems to produce, for a longer period, marked improvements in HOMA I, Tot-C/HDL-C ratio and body composition compared to restrictive bariatric surgery procedures^[7]. However, several authors highlight the occurrence of hepatic complications after bariatric surgery. In particular, the risk of liver decompensation or cirrhosis is one of the reasons JIB has been abandoned. Piringer *et al*^[8] described the case of an obese woman who developed severe NAFLD 23 years after JIB. A multicentre Belgian survey reported that 10 patients were listed for liver transplantation due to severe hepatocellular failure after bariatric surgery. Nine of the patients had undergone a Scopinaro operation, and one had a JIB; the hepatic failure was observed after a median time of 5 years following surgery^[9].

Several cases of early hepatic failure after bariatric surgery are described in the literature. D'Albuquerque *et al*^[4] studied three patients, 20 to 38 years old, with no history suggestive of liver failure, who developed liver decompensation for which transplantation was considered, 7 to 24 mo after GB or BPD. Castillo *et al*^[10] reported a case of morbid obesity in a patient who developed subacute hepatitis resulting in hepatic failure 1 year after BPD. A patient, who developed steatohepatitis and, subsequently, died of fatal hepatic failure after BPD, has been described by Grimm *et al*^[11]. More recently, Sagredo *et al*^[12] described a 28-year-old obese woman who developed acute liver failure 11 mo after gastroplasty with intestinal resection and a gastro-jejunal anastomosis. A liver biopsy performed after the surgery revealed severe steatohepatitis and fibrosis.

No cases of liver decompensation after BIB have been described in the literature, to our knowledge. We report the case of a young obese woman who developed liver failure 8 mo after BIB. We hypothesise that multiple factors might have contributed to liver damage after bariatric surgery, such as hormonal, autoimmune and/or inflammatory factors. First, the non use of the intestinal loop

may lead to bacterial overgrowth with the production of toxic polymers and inflammatory cytokines. The excluded mucosal barrier can be damaged and these molecules may be absorbed into the portal venous system, facilitating hepatic injury. However, bacterial overgrowth is observed less in BIB than in other surgical bariatric procedures because of the transit of bile salts into the excluded intestinal loop. Nyhlin *et al.*^[13] observed that patients with BIB had a significantly lower elimination time of bile acid than those with JIB. Moreover, the authors suggest that BIB surgery to treat obesity seems to be advantageous over JIB in reducing the postoperative loss of bile acid and choleretic diarrhoea, without influencing weight loss. Secondly, when a long jejunoileal loop is excluded by intestinal transit, several nutritional supplements are not absorbed, and this condition has a negative impact on liver function. Moreover, because of the rapid weight loss that occasionally follows bariatric surgery, a surplus of fatty acids reaches the liver, exceeding the liver's ability to metabolise them. Thus, we also hypothesise that liver failure after bariatric surgery may be the consequence of an acute or subacute fatty liver infiltration.

In the case we described, the actual liver damage mechanism is not clear because a liver biopsy was not performed due to the severe coagulative injury. However, while all of the mechanisms described above may have played a role in the development of hepatic decompensation, the rapid weight loss could represent the most important pathogenetic mechanism in our case. In fact, the BMI was 54 kg/m² before the surgery and 34 kg/m² 8 mo after, and our patient lost approximately 70 kg during the same period.

In conclusion, we suggest strict monitoring of liver function in the management of obese patients before and after bariatric surgery, including adequate supplementation with specific nutrients to prevent rapid weight loss and consequent liver injury.

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Can neck swelling lead to spinal cord compression?

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tant neck swelling. Admitted to our division with severe tetraparesis he underwent a cervical spine computed tomography scan that showed a large cervical mass measuring 11 cm × 27 cm × 17 cm with SCC, extending from the occiput to C7. Emergency spinal cord decompression was performed leading to minor neurological improvement. Poor outcome was due to the unusual clinical sign that led to late diagnosis and treatment.

Costi E, Roca E, Spanu F, Nicolosi F, Nodari G, Fontanella M, Panciani PP. Can neck swelling lead to spinal cord compression? *World J Clin Cases* 2013; 1(1): 56-58 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/56.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.56>

Abstract

Spinal cord compression (SCC) caused by cervical spinal canal invasion of a pulmonary sarcomatoid carcinoma metastasis has never been reported previously. A 59-year-old man, with a history of pulmonary carcinosarcoma, developed over several weeks important neck swelling. Admitted to our division with severe tetraparesis he underwent a cervical spine computed tomography scan that showed a large cervical mass measuring 11 cm × 27 cm × 17 cm with SCC, extending from the occiput to C7. Emergency spinal cord decompression was performed leading to minor neurological improvement. Poor outcome was due to the unusual clinical sign that led to late diagnosis and treatment.

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Key words: Carcinosarcoma; Spinal cord compression; Spine surgery; Tetraparesis; Pulmonary sarcomatoid carcinoma

Core tip: Spinal cord compression (SCC) caused by cervical spinal canal invasion of a pulmonary sarcomatoid carcinoma metastasis has never been reported previously. A 59-year-old man, with a history of pulmonary carcinosarcoma, developed over several weeks impor-

INTRODUCTION

Spinal cord compression (SCC) is a well-known occurrence in cancer patients that can lead to permanent neurologic impairment. Prompt diagnosis is mandatory and surgery should be performed at the onset of symptoms. Up to 30% of cancer patients develop metastases (mts) in the spine and SCC is generally observed in almost 15% of them. In adults, SCC is mainly due to solid tumors and lung cancers are responsible for 15% to 20% of cases. Thoracic and lumbosacral account for about 75% of the locations, whereas cervical mts are less common^[1]. Pulmonary sarcomatoid carcinomas (PSC) are rare and SCC in case of PSC has never been observed. In this article we report a case of neck swelling and progressive neurological impairment in a patient affected by pulmonary carcinosarcoma.

CASE REPORT

A 59-year-old man with a history of pulmonary lobectomy performed 6 mo before for carcinosarcoma presented over a period of several weeks progressive neck swelling (Figure 1). Several physicians evaluated the cervical mass, but no further investigations were prescribed. At last the



Figure 1 Patient on the operating table in prone position. Important swelling is noted on the right side of the patient's neck. The blue line designs a hypothetical midline as the cervical spinous processes couldn't be palpated.

patient developed severe tetraparesis and was admitted to our Neurosurgical Division.

An emergent cervical spine computed tomography (CT) scan which showed (Figure 2) the presence of a mass measuring 11 cm × 27 cm × 17 cm, extending from the occiput to C7 and antero-laterally to the right. The lesion entered the spinal canal between C1 and C2 with marked SCC extending caudally for 7 cm. The patient underwent partial tumor debulking and laminectomy from C1 to C4 with complete spinal cord decompression resulting in a minor neurological recovery and persistence of severe paraparesis. The metastatic lesion opened itself a breach in the ligamentum flavum between C1 and C2 entering the spinal canal, compressing the spinal cord without any dural or bony infiltration.

The histopathological findings showed the presence of atypical cellular elements with a mixture of carcinomatous and mesenchymal components. The epithelial component showed marked nuclear pleomorphism and a mitotic index $> 15 \times 10$ high-power fields (HPF); the cells of the stromal component were also characterized by marked pleomorphism and high mitotic index $> 15 \times 10$ HPF. Immunohistochemical investigations have shown intense and diffuse positivity for EMA (Dako) and cytokeratin AE1/AE3 (Dako) in the cells of the epithelial component but not in those of the spindle stromal component. The positivity for vimentin (Menarini) was found for the elements of both cellular components. The spindle cells of the stromal component also tested negative for smooth muscle actin (Sigma), S-100 (Dako) and myosin (Dako). The initial post-operative stay was uneventful and the patient was transferred to the Rehabilitation Division of our Hospital.

DISCUSSION

Pulmonary carcinosarcoma is a rare tumor that accounts for 0.3% to 1% of all pulmonary cancers, being a subgroup of PSC^[2]. Currently, PSC are defined as poorly differentiated non-small-cell carcinomas containing a component with sarcoma or sarcoma-like (spindle or giant cell) component. The recent establishment of World

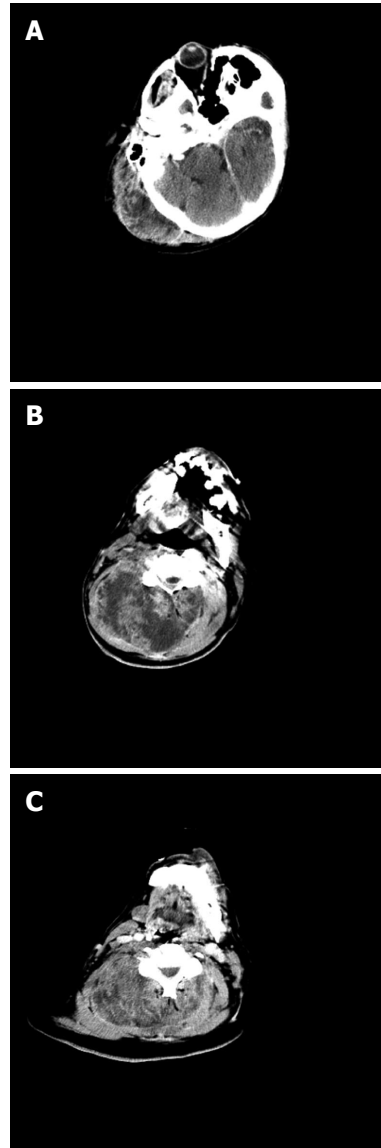


Figure 2 Cervical contrast-enhancement spine computed tomography. A: Occipital axial-scan with evidence of a right mass lesion in the pericranial soft tissues; B: Axial-scan passing through the body of C3. Note the almost complete replacement of the paravertebral muscles with the tumor; C: Axial-scan passing through C5.

Health Organization criteria classify pulmonary sarcomatoid carcinoma into carcinosarcoma, pleomorphic carcinoma, and spindle cell carcinoma^[3]. On the basis of morphologic, behavioral, and genotypic/phenotypic attributes PSCs are segregated into a distinct clinicopathologic entity.

The sarcomatous or sarcomatoid component of these tumors probably derives from the activation in carcinoma cells of an epithelial-mesenchymal transition program leading to sarcomatous transformation or metaplasia (conversion paradigm)^[4]. The sarcomatous component involves poorly differentiated osteosarcoma, chondrosarcoma, or rhabdomyosarcoma.

The carcinomatous component is non-small-cell lung carcinoma, including squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma. The clinical charac-

teristics, preoperative diagnostic methods, and prognostic factors of the pulmonary carcinosarcoma are still not completely understood.

Metastatic disease is frequent and it is most common to lymph nodes, followed by adrenal glands, kidneys, bones, liver and rarely brain. To the best of our knowledge, this is the first case of cervical metastasis from lung carcinosarcoma, with invasion of the spinal canal and compression of the spinal cord.

The metastatic carcinosarcoma showed high aggressiveness that led to the rapid onset of SCC. A fairly general symptomatology, cervical pain and fatigue, led to late diagnosis of spinal canal invasion and SCC leading to the development of a serious neurological condition before adequate diagnostic tests were performed. Therefore, it is important to achieve an early diagnosis to prevent SCC and tardive onset of severe symptoms. In this case neck magnetic resonance imaging would have been the best diagnostic imaging study for the correct visualization of the lesion's relationship with the surrounding structures but wasn't performed because the exam was not available at the time of presentation.

Considering the rapid onset of tetraparesis and the short amount of time between the onset and diagnosis we decided to perform emergent spinal cord decompression to allow the best neurological recovery possible for the patient leaving staging momentarily in stand-by. Unfortunately only partial neurologic recovery was obtained and the patient had severe paraparesis by post-operative day 4.

Therapeutic strategies are few, and there is limited information on treatment options such as systemic chemotherapy and radiotherapy. Nevertheless, the aggressive nature and poor differentiation of this tumor render the treatment difficult resulting in poor prognosis.

In conclusion, in case of diagnosis of pulmonary carcinosarcoma, vertebral or paravertebral metastases should always be considered in order to avoid irreversible neurological damage, moreover if a fairly aspecific physical finding such as neck swelling is observed. Therefore, a close follow-up is mandatory in order to undertake all possible therapeutic strategies ahead of time.

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Tumour induced osteomalacia due to a sinonasal hemangiopericytoma: A case report

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Core tip: Tumour induced osteomalacia (TIO) is a rare and often unrecognized cause of hypophosphatemia. We report on a case of TIO due to a hemangiopericytoma originating from the left nasal sinus. The patient was a 55-year-old male with a 3-year history of left hip pain and an undisplaced left hip fracture. Our case highlights the importance of considering TIO when assessing patients with low serum phosphate.

Jamal SA, Dickson BC, Radziunas I. Tumour induced osteomalacia due to a sinonasal hemangiopericytoma: A case report. *World J Clin Cases* 2013; 1(1): 59-63 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/59.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.59>

Abstract

Tumour induced osteomalacia (TIO) is a rare and often unrecognized cause of hypophosphatemia. We report on a case of TIO due to a hemangiopericytoma originating from the left nasal sinus. The patient was a 55-year-old male with a 3-year history of left hip pain and an undisplaced left hip fracture. Biochemical testing demonstrated low levels of serum phosphate and serum 1,25-dihydroxyvitamin D, and an elevated level of fibroblast growth factor 23. Octreotide scanning demonstrated uptake in the left nasal sinus area and a computed tomography scan revealed a left nasal sinus mass. The patient underwent surgical resection of the mass and histology was consistent with a sinonasal hemangiopericytoma. His serum phosphate levels normalized almost immediately after surgery and he had complete resolution of hip pain. Our case highlights the importance of considering TIO when assessing patients with low serum phosphate.

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Key words: Phosphate; Osteomalacia; Tumour; Fibroblast growth factor 23

INTRODUCTION

Tumour induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by hypophosphatemia and abnormal vitamin D metabolism. TIO is typically caused by small endocrine tumours that secrete the phosphaturic hormone fibroblast growth factor 23 (FGF23)^[1,2]. A lack of awareness among clinicians about the existence of TIO, combined with the fact that once TIO is recognized as a possible diagnosis the instigating tumour may be difficult to locate, means that most patients with TIO can have symptoms for up to 10 years before a definitive diagnosis is made^[3,4].

CASE REPORT

We report here on a 55-year-old Caucasian male who was referred to our osteoporosis clinic in February 2010 due to concerns of ongoing fractures despite bisphosphonate therapy. The patient reported that he was in good health until 2007 when he suffered a left "undisplaced hip fracture" after falling in the bathtub. His primary care practitioner made a diagnosis of osteoporosis and prescribed alendronate 70 mg weekly, vitamin D 800 IU

Table 1 Laboratory investigations

Calcium (2.20 to 2.60) ¹ (mmol/L)	2.26
Phosphate (0.8 to 1.45) (mmol/L)	0.44
Magnesium (0.70 to 1.05) (mmol/L)	0.88
Creatinine	70
25(OH)D (nmol/L)	76
Alkaline phosphatase (40-120) (IU/L)	315
PTH (1.4 to 7.6) (pmol/L)	7.2
1,25(OH)D (39-193) (pmol/L)	32
Fractional absorption of phosphate (%)	14
FGF23 (8-54) (pg/mL)	194

¹Indicates normal range. PTH: Parathyroid hormone; FGF23: Fibroblast growth factor 23.

once daily and calcium citrate 650 mg twice daily. He continued to take these agents up to the time of assessment in our clinic. The patient stated that after his initial fall in 2007 he had at least three more falls, all on the left side, and repeat radiographs demonstrated a persistent undisplaced left hip fracture. After his initial fall in 2007, he developed left sided groin/hip pain aggravated by walking and in 2008 he started using a cane to assist with ambulation. He denied generalized fatigue, weakness, and weight loss, and had no active medical problems. He did not smoke or take glucocorticoids. He did not drink alcohol, but reported that he was a prior binge drinker, consuming 24 drinks per day for 10 years; his last drink was 15 years ago. There was no family history of any bone disease. Physical examination was normal. Specifically, he was a well looking man with normal muscle strength in the upper and lower proximal muscle groups. Bone mineral density (BMD) testing by dual energy X-ray absorptiometry showed a lumbar spine T score of -0.6 (1.147 g/cm³); a right femoral neck T score of -3.4 (0.624 g/cm³) and a right total hip T score of -3.5 (0.638 g/cm³). Laboratory testing revealed persistently low levels of serum phosphate, elevated levels of serum alkaline phosphatase, and serum levels of calcium, creatinine, parathyroid hormone (PTH) and 25(OH) vitamin D that were in the normal range. Further laboratory testing demonstrated low serum 1,25(OH)D levels and an increase in serum FGF23, also unchanged with repeated testing. Tubular reabsorption of phosphate was calculated and found to be decreased (Table 1). Prostate specific antigen testing was negative, serum bicarbonate and urine electrolytes were normal. Radiographs of the right and left femurs revealed Looser's zones (Figure 1).

The patient was advised to stop the alendronate, and was started on phosphate Sandoz 500 mg *bid*, rocaltrol 1 mg/d and underwent octreotide scanning which demonstrated nonspecific uptake in the sinus area consistent with sinusitis (Figure 2). On further questioning, the patient reported that he had a longstanding history of "chronic sinusitis" but had not had any specific testing or treatments for this condition.

Computed tomography (CT) scan of the sinuses demonstrated a left posterior nasal cavity mass associated with bony remodelling. An open biopsy of the mass revealed a subepithelial neoplasm composed of spindle cells with a



Figure 1 Bilateral radiographs of femurs. Arrows indicate Looser's zones.

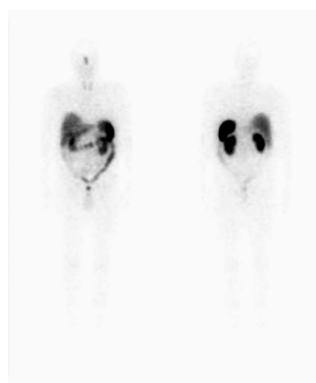


Figure 2 Octreotide scan demonstrating uptake in the sinus area.

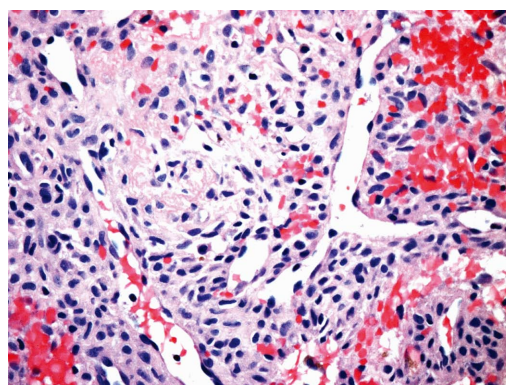


Figure 3 Photomicrograph demonstrating spindle cell neoplasm with prominent thin-walled branching vasculature. The tumour is comprised of short fascicles of cells with pale eosinophilic cytoplasm and bland ovoid nuclei. There is conspicuous extravasation of erythrocytes (haematoxylin and eosin, × 200).

fascicular pattern. The cytoplasm was ample and eosinophilic. The nuclei were ovoid with mild atypia and the mitotic activity was not readily identified. Occasional hyalinised blood vessels, some of which contained "stag-horn"-like branching, were noted. Interstitial haemorrhage and hemosiderin deposition were present. There was no evidence of necrosis or significant pleomorphism (Figure 3). Immunohistochemistry revealed expression of BCL-2; however, the tumour was negative for smooth muscle

actin, desmin, CD34, S-100, and keratin (AE1/AE3). The patient received neoadjuvant radiation therapy (50 Gy in 25 fractions from September 21 to October 26, 2011) and had the mass surgically resected in December 2011. The resection specimen contained reactive changes compatible with the neoadjuvant therapy effect, but it was otherwise similar to the initial biopsy. There was no evidence of myxochondroid matrix or dystrophic calcification to suggest phosphaturic mesenchymal tumour, mixed connective tissue variant; hence, the findings were most in keeping with a variant of a sinonasal hemangiopericytoma-like tumour. Phosphate Sandoz and rocaltrol were discontinued postoperatively.

The patient was reassessed in our osteoporosis clinic in March 2012. At that time he reported feeling well with no hip/groin pain. He had stopped using a cane for ambulation a month prior to the clinic visit. Compared to values in 2010, serum phosphate was in the normal range and BMD testing demonstrated a lumbar spine T score of 2.5 (1.523 g/cm²; increased by 29%), a femoral neck T score of -1.7 (0.844 g/cm²; increased by 25%) and total hip T score of -1.7 (0.855 g/cm²; increased by 35%).

DISCUSSION

Epidemiology of TIO

TIO was first recognized as a disease by Prader *et al.*^[5] in 1959. Prader *et al.*^[5] reported on an 11.5-year-old girl who developed severe rickets over 1 year. Studies of kidney function were normal with the exception of decreased tubular phosphate absorption. Subsequently, a giant cell granuloma was identified on a rib which, when removed, resulted in healing of her rickets. Prader *et al.*^[5] suggested that there was likely an unidentified “substance” secreted by the granuloma that resulted in the development of the patient’s rickets and when the tumour was removed the “substance” was also removed, and her rickets resolved. The unidentified substance was most likely a phosphaturic agent - specifically FGF23. Since Prader’s publication, there have been over three hundred cases of TIO reported in the literature, mainly in association with small endocrine tumours that secrete FGF23.

Phosphate homeostasis

Serum phosphate plays a key role in cell membrane composition, energy metabolism, and bone mineralization. Not surprisingly then, the symptoms of hypophosphatemia in adults can include fatigue, weakness, bone pain and fractures.

About 2/3 of dietary phosphate is absorbed in the intestine (duodenum and ileum). The absorbed phosphate is primarily stored in the bone with a small amount in the circulation. The circulating phosphate is filtered by the glomerulus and 85%-95% of filtered phosphate is reabsorbed in the proximal tubule of the kidney. It is noteworthy that renal phosphate reabsorption can only increase up to a threshold and thereafter phosphate is excreted in the urine. Phosphate levels are maintained by an ongoing interaction between the intestine, bone and

kidney. Low levels of phosphate stimulate calcitriol production which increases gut reabsorption of calcium and phosphate and causes the release of calcium and phosphate from the bone. The increase in serum calcium, together with the increase in calcitriol, inhibits PTH secretion which allows an increase in the tubular reabsorption of phosphate and an increase urinary calcium excretion^[6].

Causes of low phosphate levels can be categorized into three major groups: intracellular shifts (the redistribution of phosphorous from extracellular fluid into cells), decreased intestinal absorption and increased urinary excretion. Each of these causes is associated with a long differential diagnosis that has been reviewed in other publications in detail^[7-9]. Briefly, intracellular shifts include treatment of diabetic ketoacidosis, refeeding of malnourished patients with anorexia, tumour consumption, sepsis and hungry bone syndrome. Decreased intestinal absorption is most commonly due to vitamin D deficiency or vitamin D resistance. Increased urinary excretion can be due to primary renal transport defects (Falconi syndrome), excess PTH (primary and secondary hyperparathyroidism), excess FGF23 production (from bone or from tumour), production of other phosphaturic proteins from tumours, or overproduction of klotho which is a cofactor required for FGF23 signaling.

FGF23

FGF23 is an essential regulator of phosphate homeostasis. FGF23 binds to FGF receptor 1c and its coreceptor klotho, and activation of this receptor complex inhibits reabsorption of phosphate by reducing expression of sodium-phosphate transporters in the proximal tubule^[10,11]. FGF23 also decreases the synthesis of 1,25-dihydroxyvitamin D [1,25(OH)₂D] in the renal proximal tubules. Both of these effects serve to lower serum phosphate levels. Hyperphosphatemia leads to an increase in the secretion of FGF23 by osteocytes while hypophosphatemia decreases FGF23 secretion. This explains why most cases of hypophosphatemia are associated with an increase in synthesis of 1,25(OH)₂D unless they are FGF23 dependent.

Causes of FGF23-dependent hypophosphatemia include a small number of inherited conditions, most of which develop in childhood or adolescence, such as: X-linked hypophosphatemia, autosomal dominant hypophosphatemia, and autosomal recessive hypophosphatemia. The other cause of FGF23-dependent hypophosphatemia is TIO. Over the past 10 years assays for FGF23 have become widely available and this has resulted in an increase in the recognition and diagnosis of FGF23-related hypophosphatemia^[12].

Diagnosis

The laboratory evaluation of TIO includes serum measurements for phosphate, calcium, alkaline phosphatase, creatinine, PTH and 1,25(OH)₂D and a fasting 2-h urine for measurement of phosphate, creatinine, calcium, amino acids and glucose. In addition, the tubular reabsorption of phosphate (TmP/GFR) should be calculated: 1 - urine phosphorous × serum creatinine/urine creatinine × se-

rum phosphorus (all measured in milligrams per deciliter). Note that when the serum phosphate is low the tubular reabsorption of phosphate should be relatively high, and in renal phosphate wasting the tubular reabsorption of phosphate is lower than expected given the serum value.

Because complete surgical resection can cure TIO, localizing the tumour is critical. These tumours are often found in the craniofacial region or extremities. Thus, a careful physical examination should be focused in these areas. Conventional imaging with magnetic resonance imaging (MRI) or CT scans can be used to image areas of clinical suspicion. Some tumours associated with TIO express somatostatin receptors and can be detected using a radiolabeled somatostatin analog (octreotide scan)^[3,13]. Other imaging techniques that have been used in locating these tumours include: whole body MRI, positron emission tomography, and selective venous sampling for FGF23 in a patient with a groin mass^[14-16].

Histopathology

Historically, TIO-associated mesenchymal tumours were considered a heterogeneous population. Recently, however, it has been suggested that roughly 90% represent phosphaturic mesenchymal tumours of mixed connective tissue type^[17-19]. Other tumours, albeit much less common, associated with TIO include: hemangiopericytoma, sinonasal-type hemangiopericytoma, chondroblastoma, enchondroma, chondromyxoid fibroma^[19,20]. Rarely, TIO has been reported with other tumour types, including carcinoma and hematolymphoid neoplasms^[20].

Treatment of TIO

Surgical treatment with wide excision of the primary lesion can result in a cure and attempts should, therefore, be made to localize and remove the tumour.

Medical treatment of TIO includes phosphate supplements (15 to 60 mg of elemental phosphate per kg per day in 4 to 5 divided doses) and calcitriol (15 to 60 ng/kg per day in one to two doses); prescribed with the aim of keeping phosphate and PTH in the lower normal range. Note that in the doses needed to heal bone, phosphate is often poorly tolerated and the most common side effect is diarrhea. Patients should be monitored for hypercalciuria and nephrocalcinosis. A potential adjunct to phosphate and calcitriol is induction of hypoparathyroidism with cinacalcet - a calcium-sensing receptor agonist. This treatment is effective because the full phosphaturic effect of FGF23 is dependent on PTH^[21].

In conclusion, our patient had a clinical picture consistent with TIO. He complained of chronic L hip pain and while he denied symptoms of weakness or fatigue he was using a cane for ambulation. The patient's laboratory testing was consistent with tumour-induced osteomalacia. He had hypophosphatemia due to renal phosphate wasting (indicated by the persistently low levels of urinary phosphate reabsorption), a low serum 1,25(OH)₂D, and an increase in serum FGF23. Other possible causes of renal phosphate wasting with elevated FGF23 levels in-

clude x-linked hypophosphatemia, autosomal dominant hypophosphatemia and autosomal recessive hypophosphatemia. Typically, these conditions present in childhood or adolescence and may be associated with a family history of hypophosphatemia. The fact that our patient was well until age 52 with no family history of bone disease or hypophosphatemia made these conditions unlikely. Total body octreotide scanning demonstrated nonspecific uptake in the sinus region consistent with sinusitis and a CT of the sinus confirmed a tumour in the left nasal sinus. The mass was biopsied and histopathology demonstrated a probable variant of sinonasal hemangiopericytoma-like tumour. The patient underwent surgical resection of this lesion and after surgery there was a resolution of laboratory abnormalities, clinical symptoms and a dramatic improvement in BMD. Our patient's clinical course highlights both the difficulty in diagnosing TIO and the rapid clinical improvement when the tumour is removed.

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Low grade chondrosarcoma of the nasal septum

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Abstract

Chondrosarcoma of the nasal septum is extremely rare. In some cases, it may be difficult to preoperatively differentiate low grade chondrosarcoma from benign cartilaginous tumors such as chondroma. We report a case of low grade chondrosarcoma of the nasal septum with characteristic radiologic findings. Characteristic radiologic findings such as calcifications on computed tomography scan and a ring-and-arc pattern on enhanced T1 weighted image were useful in the preoperative diagnosis of low grade chondrosarcoma of the septum. Awareness of radiologic findings of low grade chondrosarcoma can help to make an accurate diagnosis and perform appropriate excision, leading to successful local control.

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Key words: Chondrosarcoma; Nasal septum; Endoscopic surgical procedure; Computed tomography; Radiology

Core tip: Characteristic radiologic findings such as calcifications on computed tomography scan and a ring-and-arc pattern on enhanced T1 weighted image were useful in the preoperative diagnosis of low grade chondrosarcoma of the septum. Awareness of radiologic findings of low grade chondrosarcoma can help to make an accurate diagnosis and perform appropriate excision, leading to successful local control.

Lee DH, Jung SH, Yoon TM, Lee JK, Joo YE, Lim SC. Low grade chondrosarcoma of the nasal septum. *World J Clin Cases* 2013; 1(1): 64-66 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/64.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.64>

INTRODUCTION

Chondrosarcoma constitutes approximately 15% of all primary malignant bone tumors. Chondrosarcomas occur most frequently in the long bones, pelvis, and ribs, but rarely occurs in the nasal cavity. Chondrosarcoma of the nasal septum is very rare and is sometimes difficult to suspect on physical examination. However, because differentiating low grade chondrosarcomas from chondromas is also difficult radiologically^[1] or histologically^[2], accurate diagnosis can be a challenge to physicians. Here, we present a case of low grade chondrosarcoma of the nasal septum with characteristic radiologic findings which was successfully treated with endoscopic surgery.

CASE REPORT

A 56-year-old woman presented with the left nasal obstruction which was present for 1 mo. On endoscopic examination, the patient was noted to have an obstructing mass in the posterior portion of the left nasal cavity which was originated from the posterior nasal septum (Figure 1). No abnormalities of facial sensation or vision were detected. A computed tomography (CT) scan revealed the presence of approximately a 3 cm sized soft-tissue mass with punc-

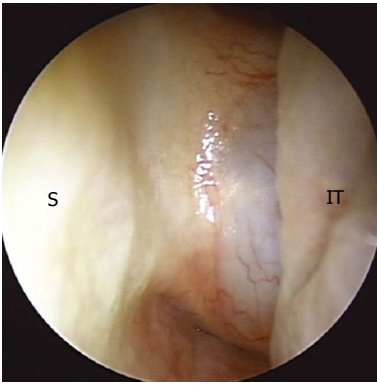


Figure 1 Endoscopic view shows a smooth surfaced mass on the posterior septum. S: Septum; IT: Inferior turbinate.



Figure 2 Computed tomography scan reveals an approximately 3 cm sized soft-tissue mass with focal septal destruction and calcifications (arrow) on the posterior septum.

tuates calcifications centered on the posterior septum. The mass bowed the medial wall of the left maxillary sinus and extended into the nasopharynx, but there was no bone erosion of the skull base (Figure 2). On magnetic resonance imaging (MRI), a septal mass showed low-intensity on T1-weighted images, high-intensity on T2-weighted images, and heterogeneous enhancement with ring-and-arc appearance on enhanced T1-weighted images, suggesting low grade chondrosarcoma (Figure 3). Following this, an intranasal endoscopic biopsy of the septal mass was performed. The histopathologic result showed benign cartilaginous tissue, suggestive of chondroma. With radiologic findings and histologic findings, low grade chondrosarcoma was strongly suspected. The mass was removed endoscopically. Final histopathology was consistent with low-grade chondrosarcoma and the histopathological surgical margin was tumor free. No adjuvant treatment was deemed necessary. The post-operative course was uneventful. At 2 years after the surgery, the patient showed no evidence of recurrence.

This report was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital.

DISCUSSION

The most common sites for chondrosarcoma of the head and neck have been variably reported as jawbones, paranasal



Figure 3 Magnetic resonance imaging findings. A: T2WI demonstrates a mass (arrow) with high-intensities, which corresponds to chondroid matrix; B: T1WI with gadolinium-enhanced shows heterogeneous enhancement with ring-and-arc appearance which corresponds to fibrovascular bundles (arrow) surrounding the cartilaginous nodules.

sinuses, nasal cavity, and the maxilla. Of the 56 patients in the Mayo series, 41.1% of chondrosarcomas were located in the nasal septum, ethmoid, and sphenoid, 25% in the maxillary sinus, 19.6% in the maxilla, 10.7% in the mandible and 3.6% in the tip of the nose^[3]. Among sinonasal involvements, chondrosarcoma of the nasal septum is extremely rare.

Presenting symptoms can vary depending on the involvement of adjacent structures by the tumor. Nasal obstruction is the common complaint of patients with chondrosarcoma of the nasal septum. Septal chondrosarcoma can involve the paranasal sinuses, skull base, palate, and/or orbit^[4-8].

Chondrosarcomas have a lobulated growth pattern, hypercellularity, and cytologic atypia. They are categorized into three grades, Grades 1, 2, and 3, on the basis of the degree of cellularity, nuclear size and atypia, and mitotic activity. Grade 1 (low grade) tumors display an abundant chondroid matrix with scattered clusters of chondrocytes with near-normal nuclei, no mitotic figures, and occasional binucleation; Grade 2 tumors have a higher degree of cellularity with a less-chondroid matrix, increased mitotic figures, multinucleation, and hyperchromatic vesicular nuclei; Grade 3 tumors are characterized by irregularly shaped chondrocytes in a myxoid matrix, more increased hypercellularity, nuclear pleomorphism, and mitosis than Grades 1 and 2 tumors^[9,10]. Histological differential diagnosis includes chondroid differentiation in osteosarcomas, enchondromas, and chondroid chordomas^[11]. One of the most difficult challenges involves the distinction between low

grade chondrosarcomas and enchondromas at radiology and histology, which often lead to initial misdiagnosis^[1,2]. In our case, low grade chondrosarcoma could not be differentiated from chondroma on punch biopsy specimen.

Because chondrosarcomas grow slowly with a lobular pattern of hyaline cartilage matrix and peripheral endochondral ossification and undergo myxoid degeneration and necrosis, these pathological features will produce the appearance of chondrosarcoma on imaging studies. Imaging study is complementary to histology and can be paramount in the diagnosis of low grade chondrosarcomas. Although plain X-ray of the paranasal sinus provides little information, CT and MRI are found to be very helpful. On CT, chondrosarcomas typically appear as lesions composed of hypodense matrix with typical calcifications which may vary from amorphous to punctuate to large. Associated bone erosion or destruction can also be seen in such cases^[12]. MRI findings of low grade chondrosarcoma have been shown to be characteristic. Low-grade chondrosarcomas are typically hypo- to isointense on T1WI. On T2WI, marked hyperintensity is shown, which represents the lobular architectures of hyaline cartilage with high water content and the cartilaginous lobules may be surrounded by low-signal-intensity septa which are related to mineralized matrix, marrow, and fibrosis^[13,14]. The contrast enhancement pattern after Gadolinium administration shows characteristic peripheral and septal pattern, as shown in our case^[12,13,15-17]. This ring-and-arc pattern corresponds to fibrovascular bundles surrounding the cartilaginous lobules and has been known to be suggestive of low grade chondrosarcoma^[16,17], although controversial^[13].

F-18 fluoro-2-deoxyglucose positron emission tomography (¹⁸F-FDG PET) has been reported to help in cartilaginous tumor grading and outcome prediction. When the maximum SUV cutoff of 2.0 was used to distinguish benign and malignant cartilage neoplasms in 26 operated cartilaginous tumors, the sensitivity of ¹⁸F-FDG PET was 90.9%, specificity 100%, and accuracy 96.6%^[18].

Mainstay of treatment for chondrosarcoma of the nasal septum is wide excision with a cuff of normal tissue. Chondrosarcomas are usually resistant to radiation and chemotherapy because of slow growth of tumors with a relatively low fraction of dividing cells^[6,19]. In general, 5-year survival rate ranges from 54% to 81%, when all grades of chondrosarcoma are included^[6]. Due to recurrences after long disease-free intervals, lifelong follow-up with imaging studies and endoscopic examination is recommended.

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Oral rehabilitation of a Parkinson's patient: A case report

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Author contributions: Singh Y fabricated the complete denture for the patient; Saini M assisted in the procedure and helped in writing the paper; Garg N helped in photography and other miscellaneous work regarding the case report; all authors contributed to the manuscript in writing and revision.

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Abstract

Parkinson's disease is an idiopathic disorder of the central nervous system, characterized by resting tremors, muscular rigidity, slow and decreased movements. Oral rehabilitation of these patients requires special care, especially in those cases where the patient's socioeconomic status is not good and patient cannot come several times for fabrication of a complete denture. This clinical report presents a case of a Parkinson's patient who was completely rehabilitated in 3 appointments using special techniques. Border molding, final impression and jaw relation procedures were done in one appointment by using a custom tray with detachable handles and occlusal rims.

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Key words: Parkinson's disease; Tich buttons; Detachable handles and occlusal rims; Monoplane teeth

Core tip: Parkinson's disease is a debilitating disease. Patients cannot visit the dentist frequently for procedures like complete denture, especially when the disease is at an advanced stage. The matter becomes worse when the patient is poor and unable to bear the

cost. This case report presents a solution to above mentioned problem in a simple and lucid manner, where patient has to visit the dentist only thrice, at no extra cost.

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INTRODUCTION

Parkinson's disease is a chronic, progressive, neurodegenerative disorder, characterized by resting tremor (in hands, arms, legs, jaw and face), rigidity and stiffness (limbs and trunk), and postural instability or impaired balance and coordination^[1-3].

It is the fourth most common neurodegenerative disorder^[2]. It is characterized by resting tremors, muscular rigidity, slow and decreased movement and postural instability. It is a major cause of disability, social isolation, loss of self esteem and depression. Oral rehabilitation of these patients requires a multidisciplinary approach^[3] and special care because, due to increased tremors, increased saliva, diminished adaptive skills and poor muscle control by the patient, prosthodontic procedures become difficult to perform and retention of dentures is compromised^[4]. Also, the patient finds it difficult to care for and maintain the denture. Therefore, prosthodontic procedures become difficult to perform and require special care and attention. Moreover, the patient cannot visit the dentist several times due to his medical condition^[5].

Previous studies^[6-10] have been done on the fabrication of complete denture for patients suffering from Parkinson's disease. The main drawback was its cost. The Parkinson's patient who belongs to a poor socio-economic status cannot afford such therapy. Here, tich buttons were used instead of metal styli to solve this problem. Tich buttons are cheap and more easily available than metal styli.

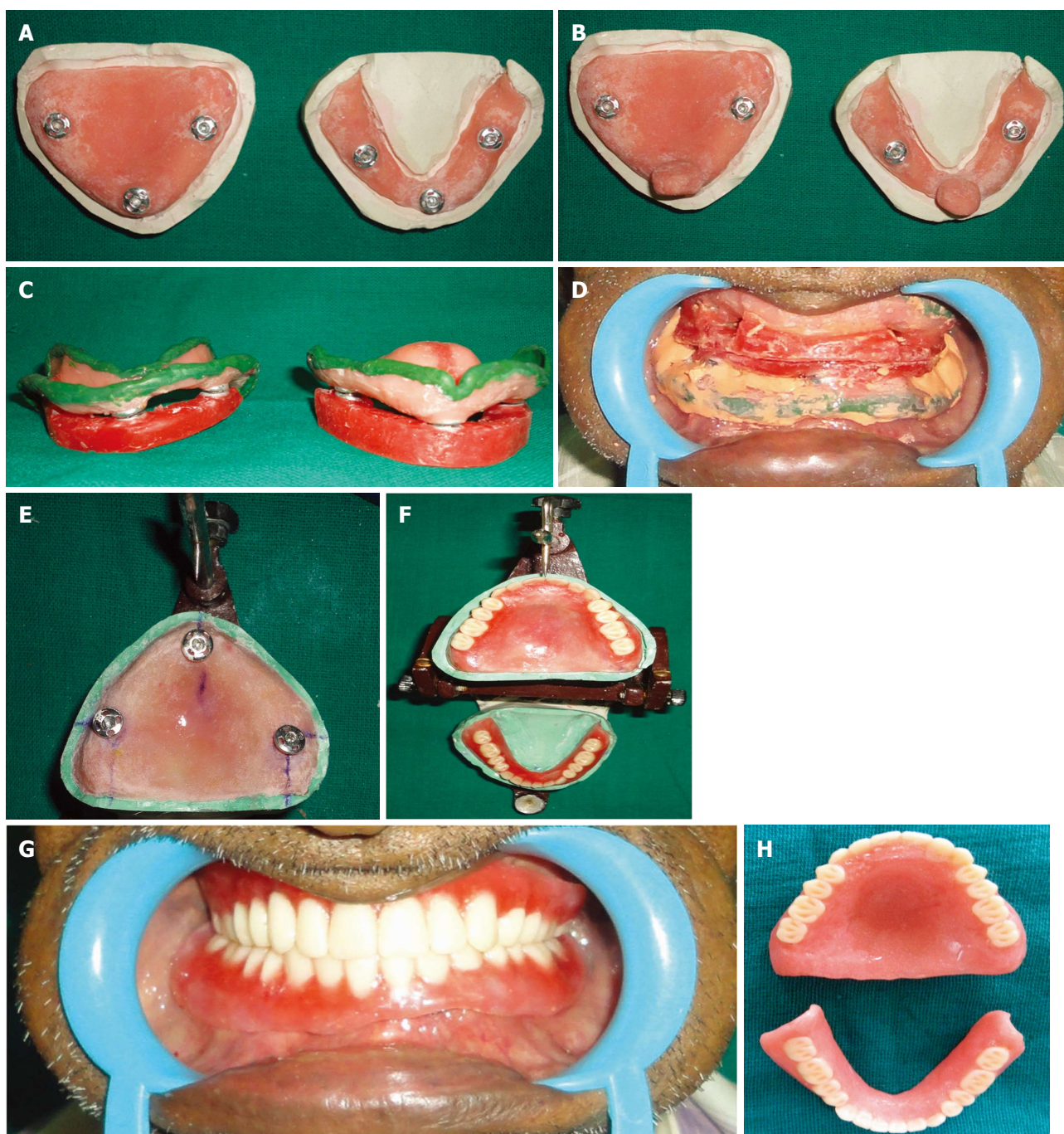


Figure 1 Denture procedure. A-C: Maxillary and mandibular special trays. A: Before the acrylic resin set, sleeve of one tich button was inserted in the anterior region and two in the posterior region; B: After setting, handles were separated from the tray and all tich buttons locked with its other part and occlusal rims were fabricated on it; C: Now the handles were removed and occlusal rims were attached, ready to record vertical and centric jaw relation in a conventional manner; D: Recording of jaw relation. Final impression was made with zinc oxide eugenol with handles reattached. After final impression, both occlusal rims were reattached and sealed at established vertical and centric relation; E: Articulation and mounting of casts on mean value articulator. Articulation and mounting of casts on mean value articulator; F: The rims reattached on the new sleeves and teeth arrangement was done using monoplane teeth; G: Trial dentures were checked in the patient's mouth for esthetics, phonetics, border extensions, midline and vertical dimension; H: Dentures cured and polished and delivered to the patient.

This clinical report describes the fabrication of complete denture for a patient suffering from Parkinson's disease by using certain modifications, like combining border molding, final impression and jaw relation procedures in one appointment^[1] by using a custom tray with detachable handles and occlusal rims with the help of tich buttons and use of non-anatomic or monoplane

teeth that helped in delivery of the denture in three appointments.

CASE REPORT

A 55-year-old male patient reported to the dental OPD, Subharti Dental College, Meerut for the fabrication of

complete denture. The patient had a 5-year medical history of Parkinson's disease and was on drug therapy. His physical and financial condition led to planning a denture with certain modifications.

Procedure

On the first day, primary impressions were made with an impression compound in the conventional manner and the primary cast was obtained and the acrylic resin was mixed and adapted on the primary cast to make a custom tray in the conventional manner. Before the acrylic resin set, the sleeve of one tich button was inserted in the anterior region and two in the posterior region (Figure 1A). Surveyor was used for this so as to make the long axis of all vertical and parallel to each other. Now the other part of the tich button was placed on the anterior and handles were made (Figure 1B). After setting, the handles were separated from the tray and all tich buttons locked with its other part and occlusal rims were fabricated on it. Now the maxillary and mandibular custom trays were ready for making impressions with the detachable handles and occlusal rims, depending on the procedure. On the second appointment, with the handles attached, border molding was completed. Now the handles were removed and occlusal rims were attached and vertical and centric jaw relation records were established in a conventional manner (Figure 1C). The final impression was made with zinc oxide eugenol with handles reattached. After the final impression, both occlusal rims were reattached and sealed at the established vertical and centric relation (Figure 1D). Custom tray and final impressions from occlusal rims were separated and handles reattached and impressions were poured after beading and boxing. Occlusal rims were reattached and measurements of the proper position of buttons and height of the rims noted to avoid any error in placing buttons on denture bases. Finally, mounting was done. Denture bases were fabricated in the conventional manner but at the same time placing sleeves of buttons on it before setting (Figure 1E). Position of the buttons can be verified by rims as well as measurements taken before. Now the rims reattached on the new sleeves and teeth arrangement was done using monoplane teeth (Figure 1F). On the third appointment, trial dentures were checked in the patient's mouth for esthetics, phonetics, border extensions, midline and vertical dimension (Figure 1G). To avoid a fourth visit, wax up and carving were done at the time of teeth arrangement. Dentures were cured and polished and delivered to the patient (Figure 1H).

DISCUSSION

Parkinson's disease is a chronic, progressive, neurodegenerative disorder, characterized by resting tremor (in hands, arms, legs, jaw and face), rigidity and stiffness (limbs and trunk), and postural instability or impaired balance and coordination. There are peculiar clinical fea-

tures of this disease, like resting tremors, muscular rigidity and hypokinesia, facial impassiveness and cogwheel type of rigidity^[12].

Dentists face many problems^[13,14] in fabrication of complete denture in such patients because increased tremors, increased saliva, diminished adaptive skills and poor muscle control make impression making and jaw relation recording difficult, causing compromised retention. When the center of gravity is displaced, there may be tendency to fall forward/backward. The tongue may dislodge the mandibular denture and facial muscles that are rigid or uncontrollable may prevent a maxillary denture from maintaining a retentive seal. Also, the patient finds it difficult to care for and maintain the denture.

The patient was not able to visit several times for the procedure. Therefore, border molding, final impression and jaw relation procedures were combined in one appointment by using a custom tray with detachable handles and occlusal rims with the help of tich buttons. In such cases, facebow transfer and Gothic arch tracings cannot be recorded due to the medical condition of the patient. This eliminated the use of a semi or fully adjustable articulator. Monoplane teeth were used to compensate for the variable centric relation.

The technique described here is relatively simple and a drastic departure from the conventional procedure. With this technique, complete denture was delivered in three visits and was also very economical for the patient. Although this technique increases laboratory time, it reduces the clinical visits to a greater extent without compromising the basic principles of complete denture fabrication.

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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World J Clin Cases 2013 May 16; 1(2): 71-95





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Isolated gastric Crohn's disease

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nuclear anti-neutrophil cytoplasmic antibody; Anti-*Saccharomyces cerevisiae* antibody

Core tip: Crohn's disease (CD) is a chronic idiopathic inflammatory disease of gastrointestinal tract characterized by segmental and transmural involvement of gastrointestinal tract. The stomach is rarely the sole or predominant site of CD accounting for less than 0.07% of all gastrointestinal CD. Serological testing and careful histopathological examination by excluding other causes of granulomatous gastritis can play a vital role to arrive at the diagnosis of atypical CD.

Abstract

Crohn's disease (CD) is a chronic idiopathic inflammatory disease of gastrointestinal tract characterized by segmental and transmural involvement of gastrointestinal tract. Ileocolonic and colonic/anorectal is a most common and account for 40% of cases and involvement of small intestine in about 30%. The stomach is rarely the sole or predominant site of CD. To date there are only a few documented case reports of adults with isolated gastric CD and no reports in the pediatric population. Isolated stomach involvement is very unusual presentation accounting for less than 0.07% of all gastrointestinal CD. The diagnosis is difficult to establish in cases of atypical presentation as in isolated gastroduodenal disease. In the absence of any other source of disease and in the presence of nonspecific upper GI endoscopy and histological findings, serological testing can play a vital role in the diagnosis of atypical CD. Recent studies have suggested that perinuclear anti-neutrophil cytoplasmic antibody and anti-*Saccharomyces cerevisiae* antibody may be used as additional diagnostic tools. The effectiveness of infliximab in isolated gastric CD is limited to only a few case reports of adult patients and the long-term outcome is unknown.

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Key words: Gastrointestinal tract; Crohn's disease; Peri-

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GASTRIC CROHN'S DISEASE

In common presentations, the diagnosis of Crohn's disease (CD) is usually based on a combination of typical clinical, laboratory, endoscopic and histopathological findings. However, the diagnosis is difficult to establish in cases of atypical presentation as in isolated gastric disease. In such a scenario other possible etiologies must be systematically ruled out in order to establish the correct diagnosis. These conditions may include *Helicobacter pylori* (*H. pylori*) infection, tuberculosis, non-steroidal anti-inflammatory drugs gastritis, Menetrier's disease, gastrinoma, collagen vascular disease and lymphoma. Additional diagnostic strategy in atypical cases of inflammatory bowel disease is the use of anti-*Saccharomyces cerevisiae* antibody (ASCA). This serological marker can be a helpful adjunctive tool in the diagnostic process despite the test's limitations.

Treatment regimens for gastric CD have been poorly studied. The routine treatment of inflammatory gastritis in CD includes the concomitant use of acid-suppressive drugs and immunomodulators such as ASCA products or

steroids. In recent years infliximab [anti-tumor necrosis factor- α (TNF- α)] has become an important addition to the therapeutic options in CD. The effectiveness of infliximab in isolated gastric CD is limited to only a few case reports of adult patients and the long-term outcome is unknown^[1-3].

In most cases of CD the presentation, workup and diagnosis run a familiar and substantiating course. The symptoms of gastric CD are nausea, vomiting, epigastric pain and weight loss^[2,4]. These symptoms arise from peptic ulcers and or obstruction in the outlet of the stomach^[5]. A clinically symptomatic disease, however, is seen in 4% of cases^[6]. Sometimes, however, this disease can manifest in an entirely non-specific and unusual manner. Uncommon presentations of CD may manifest as a single symptom or sign, such as impairment of linear growth, delayed puberty, perianal disease, mouth ulcers, clubbing, chronic iron deficiency anemia or extra-intestinal manifestations preceding the gastrointestinal symptoms, mainly arthritis or arthralgia, primary sclerosing cholangitis, pyoderma gangrenosum and rarely osteoporosis. In such cases, the diagnosis is challenging and can remain elusive for some time.

The stomach is rarely the sole or predominant site of CD. To date there are only a few documented case reports of adults with isolated gastric CD and no reports in the pediatric population. Normally, the diagnosis of CD is based on clinical presentation, radiological abnormalities of the small bowel, gastroscopy and colonoscopy findings and non-specific or typical pathological features.

Radiology studies in gastroduodenal Crohn's normally demonstrate similar features to those found in more distal CD, such as thickened folds, ulcers, nodularity, stenosis and distorted anatomy. Upper gastrointestinal endoscopy in gastric CD may be grossly normal or it may reveal various combinations of edema, erythema, ulcers, nodularity and cobblestone appearance. The antrum is most frequently involved, while the proximal stomach is often spared. Gastric biopsies have poor specificity and the changes of non-specific gastritis may be seen in other conditions such as *H. pylori* infection. Discovery of granulomatous gastritis (Figure 1) might help to narrow the differential diagnosis to CD, tuberculosis, malignancy and collagen vascular disease. Interestingly, however, granulomas are only identified in 3%-24% of the biopsies and repeat biopsies do not result in higher rates of granuloma discovery^[7]. However, the marked edematous, inflamed and ulcerated regions with cobblestone appearance and inflammatory pseudopolyps found mainly in the antrum on endoscopy are at least suggestive of CD.

In the absence of any other source of disease and in the presence of nonspecific upper endoscopy and histological findings, serological testing can play an important role in the diagnosis of atypical CD. Recent studies have suggested that perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and ASCA may be used as additional diagnostic tools for patients with suspected inflammatory bowel disease and help to differentiate between CD and

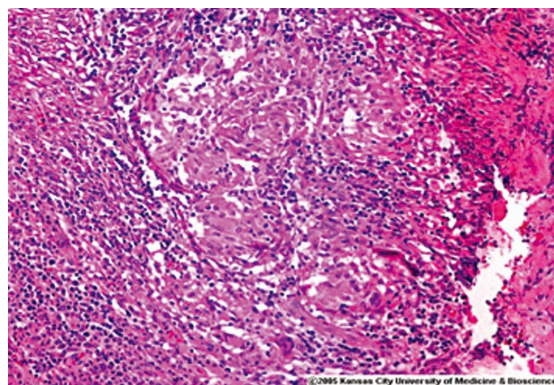


Figure 1 Section showing noncaseating granuloma (hematoxylin and eosin, $\times 10$).

ulcerative colitis. Indeed, ASCA is detected in 55%-60% of children and adults with CD and only 5%-10% of controls with other gastrointestinal disorders. This finding pANCA highlights the relatively good specificity but poor sensitivity of ASCA as a marker for CD. pANCA on the other hand is more specific to ulcerative colitis and the combination of a positive ASCA test with a negative pANCA test has a positive predictive value of 96% and a specificity of 97% for CD. In addition, some *NOD2/CARD15* gene polymorphisms, particularly *L1007P* homozygosity, were found to be associated with gastroduodenal CD and with younger age at diagnosis. It is possible that these genes might also help to support the diagnosis in the atypical presentation of CD in the future.

Infliximab, a monoclonal antibody to TNF- α , is often used in cases of steroid refractory CD. The role of infliximab in treating patients with gastric CD has scarcely been studied. In one case series, infliximab was effective in healing ulcers in two patients^[2], but the development of lung cancer in one and surgery in the other necessitated stopping the treatment. In another case study the symptoms in a patient with diffuse mucosal thickening and ulceration throughout the antrum and duodenum continued despite prednisone and a twice-daily dose of a proton pump inhibitor. Treatment with infliximab led to marked improvement within 1 wk^[2]. Surgical therapy in CD can be indicated for ulcers not responding to medical therapy, massive bleeding, in gastric outlet obstructions for which balloon dilatation is unsuccessful, or in cases where gastric fistulas have developed^[5]. Recurrence after surgical therapy is common, and re-operations are frequently required^[7,8].

In summary, atypical cases with non-conclusive clinical, endoscopic and pathological findings, the ASCA test could be helpful in the diagnostic process. Infliximab may be an effective treatment in cases of severe isolated gastropathy due to CD.

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Biological therapy for dermatological manifestations of inflammatory bowel disease

Maddalena Zippi, Roberta Pica, Daniela De Nitto, Paolo Paoluzi

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Abstract

Ulcerative colitis and Crohn's disease are the two forms of inflammatory bowel disease (IBD). The advent of biological drugs has significantly changed the management of these conditions. Skin manifestations are not uncommon in IBD. Among the reactive lesions (immune-mediated extraintestinal manifestations), erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major cutaneous ills associated with IBD, while psoriasis is the dermatological comorbidity disease observed more often. In particular, in the last few years, anti-tumor necrosis factor (TNF)- α agents have been successfully used to treat psoriasis, especially these kinds of lesions that may occur during the treatment with biological therapies. The entity of the paradoxical manifestations has been relatively under reported as most lesions are limited and a causal relationship with the treatment is often poorly understood. The reason for this apparent side-effect of the therapy still remains unclear. Although side effects may occur, their clinical benefits are undoubted. This article reviews the thera-

peutic effects of the two most widely used anti-TNF- α molecules, infliximab (a fusion protein dimer of the human TNF- α receptor) and adalimumab (a fully human monoclonal antibody to TNF- α), for the treatment of the major cutaneous manifestations associated with IBD (EN, PG and psoriasis).

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Key words: Biological therapies; Erythema nodosum; Inflammatory bowel disease; Psoriasis; Pyoderma gangrenosum

Core tip: Ulcerative colitis and Crohn's disease are the best known forms of inflammatory bowel disease (IBD) and are considered immune-mediated disorders of unknown etiology that primarily affect the gastrointestinal tract. In addition, other organ systems can be involved, such as skin. Erythema nodosum, pyoderma gangrenosum and psoriasis are the dermatological comorbidities often associated with it. The anti-tumor necrosis factor (TNF)- α drugs (infliximab and adalimumab) have significantly changed the management of these conditions. In this brief review, we provide an overview on the prevalence and clinical aspects of the more commonly reported skin manifestations of IBD and the role of TNF- α inhibitors in their treatment.

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INTRODUCTION

Extraintestinal manifestations (EIMs) are commonly seen in association with inflammatory bowel disease (IBD). The reported prevalence of EIMs in IBD ranges from

25% to 40%^[1]. EIMs can involve any organ or system, with the musculoskeletal and the dermatological ones being the most common. Major skin involvement has been described in 2% to 34% of patients with IBD^[2]. Erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major skin manifestations associated with IBD, defined as reactive lesions (immune-mediated EIMs), while psoriasis is the dermatological associated disease observed more frequently.

The advent of biological therapies [tumor necrosis factor (TNF)- α inhibitors] has changed the course of these EIMs. In particular, there are three TNF- α inhibitors commercially available: etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA), a fusion protein dimer of the human TNF- α receptor; infliximab (Remicade®, Centocor Incorporated, Horsham, PA), a chimeric mouse-human monoclonal antibody to TNF- α ; and adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL), a fully human monoclonal antibody to TNF- α . All these drugs specifically bind to TNF- α , blocking its biological activity^[3], with important effects on anergic regulatory T cells, restoring their capacity to inhibit cytokine production^[4]. The aim of this brief review is to investigate the role of biological therapy in these kind of dermatological manifestations associated with IBD.

EN

EN is the most common cutaneous lesion. It is usually easily recognized on account of its characteristic features; in fact, a biopsy is helpful only in atypical cases. EN lesions are frequently palpable and appear as raised, tender, red or violet subcutaneous nodules 1-5 cm in diameter. EN commonly affects the extensor surfaces of the extremities, particularly the anterior tibial areas, but the arms and the trunk can also be affected. The differential diagnosis of EN includes other types of panniculitis, like cutaneous infections and subcutaneous lymphomas^[5].

The prevalence of EN in IBD and Crohn's disease (CD), respectively, ranged from 4.2% to 7.5% and seems to be higher in CD than in ulcerative colitis (UC)^[6-8]. The occurrence of lesions is closely related to intestinal disease activity and their treatment is based on that of the underlying IBD. In a study of 792 patients affected by IBD, every case of EN (48 patients) responded to medical treatment of the IBD^[9].

Reading the literature, we have found only two cases of EN successfully treated with anti-TNF- α therapy; a case of a child with CD refractory to treatment with corticosteroids and immunomodulators had a rapid and sustained response to the anti-TNF- α antibody infliximab^[10] and a case of a refractory chronic EN successfully treated with adalimumab^[11]. On the other hand, a case of an EN as paradoxical occurrence has been reported after infliximab infusion given for ankylosing spondylitis in a patient without IBD^[12].

PG

PG typically presents with ulcerated lesions with viola-

ceous undetermined borders that are covered with pus or necrotic debris^[13]. These ulcers can be solitary or multiple, unilateral or bilateral, and can range in size from several centimeters to an entire limb^[14]. PG usually occurs on the extensor surface of the legs but can appear anywhere on the skin, like on the abdominal wall adjacent to a post-surgical stoma^[15]. While EN usually correlates with IBD activity, PG correlation with IBD activity is controversial. In fact, PG does not always respond to treatment of underlying bowel disease and response to bowel resection is unpredictable^[16]. In recent publications, PG is reported in 0.6%-2.1% of UC and CD patients^[6,7], even though it seems more prevalent in UC.

Rapid healing of these lesions should be the therapeutic aim because PG can be a debilitating skin disorder. Usually, systemic corticosteroids and cyclosporin are the most commonly drugs used. Biological therapy is reserved only for specific cases. In fact, infliximab has been reported to be successful in treating severe or refractory lesions^[5]. A multicenter retrospective study of medically refractory PG patients reports a positive response to infliximab^[17]. The mechanism of action is in line with the putative involvement of immune-mediated factors in the pathogenesis of PG concerning suppression of inflammatory processes. In the study by Tan *et al*^[18], two patients with refractory Crohn's fistula and PG had a rapid improvement shortly after the first infusion with infliximab. Sapienza *et al*^[19] also reported a good response of PG lesions in four patients with CD treated with infliximab.

The authors supposed that the rapid response to infliximab in these patients was the result of blunted T cell activation early in the inflammatory cascade leading to a decrease in neutrophil infiltration^[19]. The largest study on the treatment of PG with IFX was published by Brooklyn *et al*^[20]. This was a multicenter, randomized, placebo-controlled trial of 30 patients, including 19 patients with IBD. IFX 5 mg/kg or placebo was given at week 0. At week 2 (the primary end point), significantly more patients in the IFX group had improved compared to placebo (46% *vs* 6%, $P = 0.025$); the response was based upon reduction on size, depth and degree of the lesions. At week 2, subjects in both arms were then offered an open-label for IFX. Overall, 29 patients received IFX with the majority of them showing a beneficial clinical response at week 6 (response 69%, remission 31%). The response rate was over 90% in patients with short duration of PG (< 12 wk) and less than 50% in those with disease present for more than 3 mo. In addition, there was no difference in response between PG patients with IBD and those without^[20].

In the literature there is a case of a young women with CD and PG who was successfully treated with Adalimumab^[21]. She was a 38-year-old woman with fistulizing CD (enterogastric fistula) that manifested as diffuse abdominal pain and bloody diarrhea, accompanied by arthralgia and PG. The patient was treated with high doses of parenteral methylprednisolone, methotrexate and IFX without any improvement. A positive response to adalimumab therapy was observed: after 2 mo of therapy, the ulcerative skin

lesion healed completely and after 5 mo the enterogastric fistula was closed^[21].

On the other hand, three cases of PG as a paradoxical occurrence have been reported after infliximab infusion^[22-24]. A 38-year-old woman developed severe PG while receiving treatment with infliximab and azathioprine for active lymphocytic ileitis, in whom the ulcer was finally resolved when treatment with adalimumab was initiated^[22]. A 40-year-old woman with UC, developed PG following the second infusion of IFX. In this case, infliximab was discontinued and cyclosporine was initiated with remission of the skin lesion^[23]. Finally, a case of a PG has been reported during infliximab infusion given for rheumatoid arthritis in a patient without IBD^[24].

Psoriasis

Psoriasis is a chronic skin condition characterized by erythematous papules and plaques. Psoriasis seems to be more common in CD patients than in the general population^[25]. Danese *et al.*^[26] found that psoriasis occurs in 7%-11% of the IBD population, compared to 1%-2% of the general population. Yates *et al.*^[27] in their study found that psoriasis was more prevalent in CD (11.2%) than in UC (5.7%). Psoriatic lesions have a high concentration of TNF- α , similar to lesions seen in CD, suggesting some immunological overlap. In fact, the association of IBD with psoriasis is believed to be both genetically and immunologically related^[28].

Evidence in favor of infliximab and adalimumab for psoriasis has been derived from clinical studies managed by dermatologists. Gottlieb *et al.*^[29] analyze the efficacy and safety of infliximab as induction therapy for patients with severe plaque psoriasis. In this multicenter, double-blind, placebo-controlled trial, 249 patients with severe plaque psoriasis were randomly assigned to receive intravenous infusions of either 3 or 5 mg/kg of infliximab or placebo given at weeks 0, 2 and 6. The primary end-point was the proportion of patients who achieved at least 75% improvement in the psoriasis area and severity index score from baseline at week 10. Infliximab treatment resulted in a rapid and significant improvement in the signs and symptoms of psoriasis. At week 10, 72% of patients treated with infliximab (3 mg/kg) and 88% of patients treated with infliximab (5 mg/kg) achieved a 75% or greater improvement from baseline in the psoriasis area and severity index score compared with 6% of patients treated with placebo ($P < 0.001$)^[29]. A subsequent follow-up study by Reich *et al.*^[30], conducted on 378 patients with moderate to severe plaque psoriasis, demonstrated that 1 year of IFX was effective in both induction and maintenance regimens^[30]. In the literature, six cases of patients with plaque psoriasis unresponsive to previous therapies, including infliximab and etanercept, in whom adalimumab (given at 40 mg/wk for 20 wk) resulted in clinical improvement are also described^[31].

In the last years, paradoxical cases of psoriatic lesions induced or exacerbated by anti-TNF- α therapy have been reported more frequently, an observation that does not

seem to relate to the age of the patient or to the duration of treatment^[32-34]. Psoriasiform eczema, eczema and xerosis were the most commonly observed type of skin paradoxical inflammation^[35].

The role played by the cytokine network in psoriasis is crucial in understanding the complex mechanisms that underlie the paradox anti-TNF- α -induced psoriasis. Recently, in the pathogenesis of this condition, interferon (IFN)- γ has been called into question^[36,37]. This cytokine (IFN- γ), in combination with molecules such as TGF- β , IL-15 and IL-20, can enhance the proliferation of keratinocytes and inhibit their apoptosis^[38]. For these kinds of reactions topical therapy with corticosteroids, keratolytics (salicylic acid, urea), emollients, vitamin D analogues and ultraviolet (UV) therapy (UVA or narrow band UVB) are usually used. A class effect is suggested in patients with psoriatic lesions that do not improve with topical therapy and develop recurrent lesions after being switched to anti-TNF- α therapies. Uncontrolled skin lesions led to discontinuation of anti TNF agents in about 34% of patients^[39].

We herein report two recent systematic reviews. Denadai *et al.*^[40] included thirty-four studies in their first study. Sixty-nine patients with IBD were analyzed. Most patients had CD (89.86%), were female (47.83%), had an average age of 27.11 years and no reported history of psoriasis (84.05%). The most common type of psoriatic lesion that developed was plaque-type psoriasis (40.58%). There was a complete remission of psoriatic lesions in 86.96% of IBD patients despite differences in the therapeutic approaches: cessation of infliximab therapy led to resolution in 47.83% of cases and 43.48% of patients were able to continue infliximab therapy^[40].

Subsequently, in another systematic review, Denadai *et al.*^[41] included 47 studies (222 IBD patients). Of the 222 patients, 78.38% were diagnosed with CD and 48.20% were female. The mean patient age was 26.5 years and 70.72% of patients had no history of psoriasis. Patients developed psoriasiform lesions (55.86%) and infliximab was the anti-TNF- α therapy that caused the cutaneous reaction in most of them (69.37%). The majority of patients were managed conservatively without discontinuing anti-TNF- α therapy and complete remission of cutaneous lesions was observed in 63.96% of cases^[41].

CONCLUSION

Early recognition of dermatological manifestations associated with IBD is very important for their treatment. The advent of biological response modifiers (anti-TNF- α inhibitors) represents a new and efficacious approach that is able to modify the clinical course of such patients. The diagnosis of the cutaneous manifestations of IBD generally is based on their characteristic features and biopsy is reserved only for atypical cases.

Treatment of EN is usually based on the underlying IBD (CD or UC) and is performed using systemic steroids. PG is initially treated with systemic steroids, oral

calcineurin inhibitors and then with infliximab or adalimumab.

The anti-TNF treatment can induce paradoxical inflammation of the skin which is generally considered a class-drug effect and it is usually reversible upon drug switching or discontinuation. In most cases, psoriatic lesions are the more commonly seen paradoxical inflammation of the skin. In fact, in recent years, an increasing number of cases of onset psoriasis related to anti-TNF therapy in IBD patients has been reported. Psoriasis appearing during anti-TNF- α therapy is considered a class effect of TNF- α blocking agents rather than a drug-specific adverse event^[42]. Plaque psoriasis on the extremities and the trunk were the most frequent presentations. The mechanism underlying this paradoxical phenomenon is controversial but it is well known that the increased production of IFN- γ , a key element in the induction of psoriasis, after TNF- α blockage might play a major role^[42]. Reading the literature, we found that actually there is no consensus as to whether to continue or discontinue the anti-TNF- α therapy in these cases. In our opinion, the decision should be individualized. Topical steroid treatment is often effective in most patients. Anti-TNF discontinuance may be reserved for patients with severe psoriasis or for the ones that do not respond to topical therapy.

In conclusion, since the introduction of the biological agents, antibodies to cytokine TNF- α , the treatment of IBD and their EIMs such as cutaneous ones has changed dramatically. Although side effects may occur, their clinical benefit remains undoubted.

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Globalised world, globalised diseases: A case report on an amoebiasis-associated colon perforation

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Author contributions: All authors conceived the case report, had read the manuscript in its final version and had checked it and provided it with critical remarks; Redaelli M and Schencking M took on the data analysis, the literature review and preparation of the manuscript; all authors have read the manuscript in its final version and have checked it and provided it with critical remarks.

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Key words: Amoebiasis; *Entamoeba histolytica*; Colon perforation; Surgical treatment

Core tip: This case shows how important it is that medicine providers expected rare diseases from other regions from the globalised world. The clinical signs of this patient have been wrongly interpreted. Itself the operation was not targeted. The histopathological examination of resected intestine had a surprising result, but not the source of the clinical signs. Only the use of the polymerase chain reaction (PCR) identified the causal link between the clinical signs and the trigger. So the PCR should be the central feature in the diagnostic of unclear or undefined clinical signs.

Redaelli M, Mahmoodzad J, Lang R, Schencking M. Globalised world, globalised diseases: A case report on an amoebiasis-associated colon perforation. *World J Clin Cases* 2013; 1(2): 79-81 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i2/79.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i2.79>

Abstract

In 2010 the World Health Organisation estimated the number of infections with *Entamoeba histolytica* at about 50 million cases including 100000 fatal courses. In most cases this infection is a subclinical event with few or none symptoms noticeable for the patient. Courses of this disease and incidence of this parasite in industrialised nations are not yet fully investigated. Our case reports about a 68-year-old male patient from Turkey who lives for more than 30 years in Germany and had not been abroad during the past 2 years. Resistant asymptomatic amoebic dormant bodies caused an emergency-laparoscopy and revealed the seldom complication of a colon perforation. In the age of globalisation all providers in the health care systems are urged to acquaint themselves also with non-typical syndromes for the countries they work in order to reduce preventable morbidity respectively mortality rates.

INTRODUCTION

Infection with *Entamoeba histolytica* (*E. histolytica*) usually occurs by ingestion of contaminated water, unwashed fruits or vegetables. Faecal-oral transmission has also been described. An amoebiasis with bloody, mucousy stools with a frequency up to 40-50/d can result with intestinal pain, spasms and high fever^[1].

As a resistant dormant body the amoebas can develop cysts and remain asymptomatic in the colon for years. For yet unknown reasons it can amount to a mutation of the amoebas' DNA leading to a change of the enzymatic pattern^[2,3]. These enzymes may allow penetration of the amoeba into the intestinal mucous membrane sometimes with fatal outcome. A possible intestinal finding is a perfo-

ration of the colon. Furthermore dissemination of amoebas to other organ-systems is possible due to the entrance of amoebas into the bloodstream. Most frequently liver and heart as well as the central nervous system and the urinary system are affected^[4,5].

Perforation of the colon as a result of an amoebic colitis is a seldom complication but typically carries a high morbidity and mortality^[6-8]. On the European continent the incidence of this illness is extremely rare, yet the increasing globalisation of trade and services as well as migration result also in a globalisation of infectious diseases and therefore an increasing number of amoebic colitis in Europe.

The worldwide relevance of infections with *E. histolytica* can be evaluated by the numbers estimated by the World Health Organisation of yearly 50 million with about 100000 fatal courses.

CASE REPORT

Medical history and non-invasive diagnostic testing

A 65-year-old Turkish man presented to the emergency department with spasmodic abdominal pain that had increased over several days and was therefore hospitalized. At the time of admission his body mass index was 33.6 (height: 185 cm, weight: 115 kg). He had been living in Germany for 30 years and had not travelled to any other country during the past 2 years. The patient did not suffer from diarrhoea or fever and had no pre-existing conditions. There were no visits to the general practitioner during the past 6 mo.

Physical examination revealed the patient's general condition to be compromised with diffuse pain located throughout the abdomen and described as pressure. There were also peritoneal signs and muscular rigidity. The point of maximum tenderness was located in the right lower quadrant and midline. Peristalsis was reduced significantly; the rectal examination was without pathological findings.

The complete blood count was significant for leucocytosis (11000/L), the C-reactive protein was within the normal range with 0.7 mg/dL, and all other routine laboratory parameters were also without pathological findings.

Abdominal sonography revealed a narrow perihepatic margin of fluid. Abdominal X-rays in two planes did not show signs of free air or any typical findings of an ileus with the right colon stool-filled. Because of the clinical situation it was decided to utilize invasive diagnostics and invasive therapy if necessary.

Invasive diagnostic testing and therapeutic procedure

An emergency-laparoscopy was carried out on the day of the admission because of suspected perforated appendicitis. The intraoperative findings included a long-segment, covered perforation of the cecum and the right hemicolon accompanied by a 2 quadrant-peritonitis. Because of the seriousness of the intraoperative findings a switch to an open laparotomy became necessary.

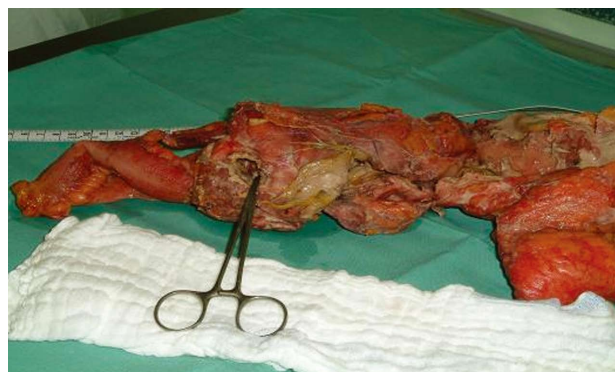


Figure 1 A right hemicolectomy with a R0-resection.

Following a median laparotomy the full extent of the patient's findings became evident: a massive necrotising inflammation of the hemicolon including perforation, plus a "wooden phlegmon" of the mesocolon reaching up to the retroperitoneum. Because of suspected sarcoma of the mesocolon, a right hemicolectomy with a R0-resection was performed accomplished after extensive mobilisation of the right colon and the colon transversum (Figure 1). This procedure was followed by an ileotransversotomy, an end-to-end anastomosis with Vicryl-single button suture seromuscular, extra mucous and in a single row.

Initial histopathological examination of formalin fixed colon dissection samples showed the characteristics of a low malignant Non-Hodgkin-lymphoma. Following further pathological examination could ascertain that the perforation was caused by a severe amoebic colitis followed by a granulomatous inflammation of the mesocolon. A diagnosis of malignant lymphoma was ruled out.

Postoperative course

The amoebic colitis was treated with metronidazole followed by paromomycin resulting in successful eradication of the amoebae. In addition methicillin resistant *Staphylococcus aureus* was cultured from intraoperative specimens. The patient was placed in contact isolation after the surgical intervention and provided with rehabilitation services. Repeated stool samples during the patient's stay in hospital were all negative for amoebic infection.

During the postoperative course the patient developed an infection of the laparotomy wound accompanied by symptoms of an ileus and had to undergo another laparotomy on the 5th postoperative day. This surgery revealed an abdominal wall abscess without intra-abdominal findings. The subsequent postoperative course was uncomplicated. After 63 d of stay in hospital the patient could be discharged fit and healthy.

DISCUSSION

The mechanism of infection in this case is not apparent. With amoebic infections being very uncommon in Germany one can speculate that the patient's occupation

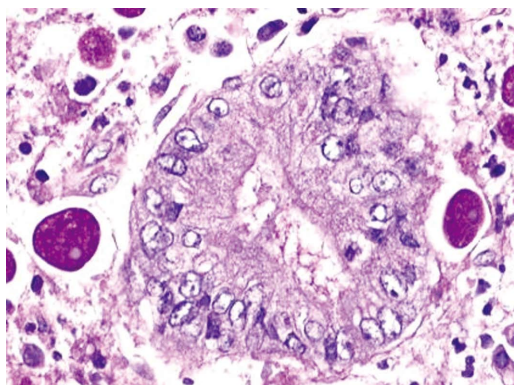


Figure 2 The intracellular phagocytosed erythrocytes, which are pathognomonic for this kind of amoeba.

as a storekeeper for an airport company could have led to contact with contaminated materials or surfaces. In addition there is the possibility of this case representing a relapse. The patient could have been asymptotically infected before his emigration to Germany or during visits to his home country (prevalence in Turkey: 15%)^[9].

During laparotomy the intraoperative findings mimicked a sarcoma of the mesocolon. The diagnosis could not be assured until the final histopathological results were available: perforation because of a preexisting amoebic colitis. A granulomatous infection appearing as a “wood phlegmone” of the mesocolon has been described as a rare manifestation of infection with *E. histolytica*, which is the only pathogenic amoeba for humans. Figure 2 shows the intracellular phagocytosed erythrocytes, which are pathognomonic for this kind of amoeba.

Antibiotic therapy with metronidazole was recommended as first-line therapy in Germany at the time of hospital admission^[10]. A Cochrane Review from 2009 suggests that tinidazole may be more effective^[11]. If amoebas are found in the stool of asymptomatic individuals they are considered chronic carriers. Only patients, who are chronic carriers and near contact persons are considered notifiable cases in Germany.

Only a rare amount of case reports describing the *E. histolytica* induced symptoms of colitis or intestinal perforations due to wide necrosis of the intestine are existing in current scientific literature; in comparison to these cases our patient didn't suffer of fever or diarrhoea and underwent a successful inpatient treatment^[1,12].

An ulcerous colitis can originate from an amoebic infection. Therefore stool samples for this pathogen should always be sent for microscopy and, in addition, if available for molecular diagnostic tests such as testing by polymerase chain reaction. Diagnostic imaging can not provide

a sufficient contribution to the causality amoebic infection and colitis.

In the age of globalisation all providers in the health care systems are urged to acquaint themselves also with non-typical syndromes for the countries they work in order to reduce preventable morbidity respectively mortality rates.

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A vaginal drain of a pelvic abscess due to colonic diverticulitis

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Core tip: Large diverticular abscesses (> 3 cm) should be treated by antibiotics and percutaneous drain. Abscess deep in the pelvis pose a unique problem because numerous intervening structures create obstacles to safe percutaneous access. Transvaginal drain of pelvic abscess could be an useful alternative, when percutaneous approach is not feasible.

Milone M, Sosa Fernandez ME, Venetucci P, Maietta P, Sosa Fernandez LM, Taffuri C, Milone F. A vaginal drain of a pelvic abscess due to colonic diverticulitis. *World J Clin Cases* 2013; 1(2): 82-83 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i2/82.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i2.82>

Abstract

Although well recognized for tubo-ovarian abscesses, we report, in our best knowledge, the first case of a vaginal drain of a pelvic abscess due to colonic diverticulitis. A 78-year-old patient presented with abdominal and pelvic pain, fever (39.3 °C) and an elevated white blood cell count (18500/mL). After abdominopelvic computed tomography the patient was presumed to have a pelvic abscess, which developed as a complication of the sigmoid diverticulitis. Due to the numerous intervening structures that create obstacles to safe percutaneous access, we planned a trans-vaginal drain. A rapid recovery was obtained within 2 d from the procedure and, at present, the follow-up was uneventful after 18 mo. We believe that transvaginal drain of pelvic abscess could be a useful alternative, when percutaneous approach is not feasible.

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Key words: Vaginal; Drain; Diverticulitis; Pelvic abscess; Echography

INTRODUCTION

Although well recognized for tubo-ovarian abscesses^[1,2], we report, in our best knowledge, the first case of a vaginal drain of a pelvic abscess due to colonic diverticulitis.

CASE REPORT

A 78-year-old patient presented with abdominal and pelvic pain. Physical examination demonstrated fever (39.3 °C) and mild tachycardia (120/min) with bilateral lower abdominal quadrant tenderness. Blood analysis revealed an elevated white blood cell count (18500/mL). The abdominopelvic computed tomography scan revealed a left sided collection with a prominent air-fluid level suggesting pelvic abscess, measuring 8 cm × 6 cm, close to the vagina. Multiple diverticula were identified and the sigmoid colon was lying around the collection with its borders that could not be distinguished from the abscess. The mesentery of the sigmoid colon was also found to be thickened due to inflammation (Figure 1).

The patient was presumed to have a pelvic abscess, which developed as a complication of the sigmoid di-

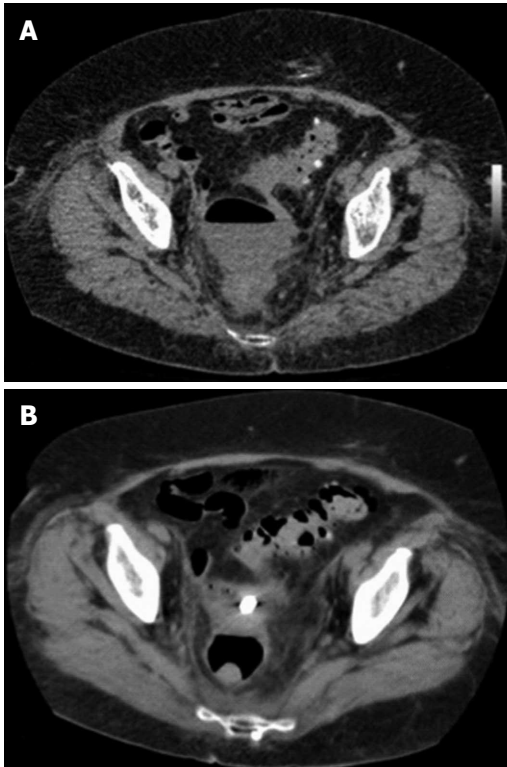


Figure 1 Abdominopelvic computed tomography. A: Before the procedure; B: After the procedure.

diverticulitis, and, according to guidelines, we planned the drainage of the lesion^[3]. However, due to the numerous intervening structures that create obstacles to safe percutaneous access, we planned a trans-vaginal drain.

The endovaginal ultrasound sonography (US) examination was performed using an end-fire endovaginal US probe with an attached needle guide. A puncture needle was introduced into the fluid collection under continuous US guidance and fluid from the cavity was aspirated with a syringe. A guidewire was introduced into the cavity *via* the puncture needle. Then a self-retaining pigtail catheter with a string lock was introduced over the guide wire into the cavity (Seldinger technique). The catheter was left *in situ* and irrigated three times per day.

A rapid recovery (normal temperature and leukocyte levels) was obtained within 2 d from the procedure (Figure 1). The catheter was removed after 2 wk, when the spontaneous output was clear and was less than 10 mL per day.

The short-term follow-up consisted of outpatient visits 7 to 10 d and 3 to 4 wk after operation. For long-term follow-up, a visit was scheduled and included an endovagi-

nal US every 3 mo. At present the follow-up was uneventful after 18 mo.

DISCUSSION

Large diverticular abscesses (> 3 cm) should be treated by antibiotics and percutaneous drain. Percutaneous drain is the standard therapy in the absence of indications for immediate surgery^[3]. However, abscess deep in the pelvis pose a unique problem because numerous intervening structures create obstacles for safe percutaneous access. These include pelvic bones, bowel, bladder, iliac vessels, and female reproductive organs. Alternative approaches to deep pelvic abscess include transvaginal, transrectal, transperineal and transgluteal punctures^[4,5]. Transvaginal drainage has been described in several reports^[1,2], but there has been no previous documentation of a vaginal drain of a pelvic abscess due to colonic diverticulitis.

In this case, rapid recovery was obtained with long-term disease-free survival, which is encouraging for its future use as an alternative drain of abscess due to diverticulitis.

Although further prospective studies evaluating the clinical usefulness of transvaginal drain of pelvic abscesses due to colonic diverticulitis are needed to give a definitive conclusion, we believe that transvaginal drain of pelvic abscess could be a useful alternative, when percutaneous approach is not feasible.

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A rare case of acute compartment syndrome after saphenectomy

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Abstract

Saphenectomy is one of the most validated criteria to treat varicose veins of the lower legs. Although many complications were well described, little is known about compartment syndrome due to muscle ischemia caused by constrictive bandages applied after stripping of varicose veins. We presented a case of successful conservative treatment of compartment syndrome after saphenectomy. Rehabilitation was found effective in improving fatigue, stiffness and tenderness showing the effectiveness of the combined conservative-rehabilitative treatment. However conservative treatment could not be considered the treatment of choice in daily practice. A severity score assessment of compartment syndrome should be useful to assess to which patients is allowed to not perform fasciotomy.

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Key words: Compartment; Saphenectomy; Varicose veins; Muscle ischemia; Rehabilitation

Core tip: A case of successful conservative treatment

of compartment syndrome after saphenectomy. Rehabilitation was found effective in improving fatigue, stiffness and tenderness showing the effectiveness of the combined conservative-rehabilitative treatment.

Milone M, Venetucci P, Iervolino S, Taffuri C, Salvatore G, Milone F. A rare case of acute compartment syndrome after saphenectomy. *World J Clin Cases* 2013; 1(2): 84-86 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i2/84.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i2.84>

INTRODUCTION

Saphenectomy is one of the most validated criteria to treat varicose veins of the lower legs.

Although many complications were well described^[1], little is known about compartment syndrome due to muscle ischemia caused by constrictive bandages applied after stripping of varicose veins^[2]. We presented, in our best knowledge, the first case of a successful conservative treatment of compartment syndrome after saphenectomy.

CASE REPORT

A 51-year-old man underwent saphenectomy because of chronic varicose veins of the lower right leg. His past medical history was unremarkable. The stripping technique involved the interruption of the femoral-saphenous junction, stripping of the great saphenous vein, multiple removals of the tributary veins of the saphena and ligation of the extrafascial perforating veins. No intra-operative complications occurred.

In the immediate post-operative period (6 h from the surgery), pain and tension in the operated leg appeared. Moreover, a complete function impairment of the leg was evident. The dressing was removed when the patients started complaining of these symptoms.

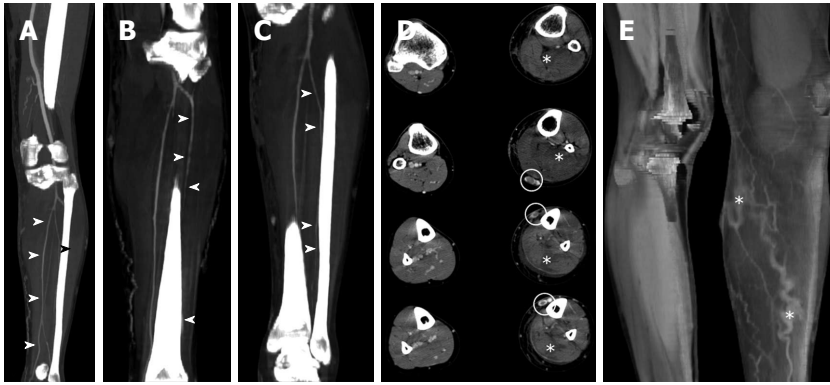


Figure 1 A computed tomography of the lower leg revealed a swollen compartment without vascular lesions and hypertension at the venous end of the capillary beds. A, B, C: The reconstruction MIP/3D that showed the viability of posterior tibial (A), anterior tibial (B) and interosseal artery (C) (marked by headarrows); D: The swollen muscle compartment (marked by *); E: The presence of hypertension at the venous end of the capillary beds (marked by *).

In the first post-operative day the physical examination demonstrated in the operated leg pain on passive stretching of the muscle, tense, swelling, sensory loss and paralysis. His blood analysis revealed a very elevated creatin kinase activity (50200 U/mL).

A computed tomography of the lower leg revealed a swollen compartment without vascular lesions and hypertension at the venous end of the capillary beds (Figure 1). The color-duplex sonography confirmed the absence of artery or vein thrombosis.

The patient was presumed to a compartment syndrome and the measurement of intracompartmental pressure was not performed for the clinical evidence according to validated criteria^[3]. Decompression by fasciotomy was indicated as the primary treatment but the patient denied his consent to the procedure. Elevation of the limb was used in an attempt to reduce pressure. Two weeks later, a conservative rehabilitative treatment was started.

The patient underwent a 2 mo-lasting twice/daily comprehensive rehabilitation, defined as systematic multidisciplinary treatment given by physician, occupational therapist and exercise physiologists. The rehabilitation program included physical therapy with exercise aiming at improves aerobic fitness, muscle strength and mobility and occupational therapy. This 2-mo treatment brought to a satisfactory functional recovery. Outpatient rehabilitation program continued for 3 mo thereafter. Complete function recovery was obtained after 6 mo.

DISCUSSION

Varicose veins in the lower extremities are a sign of chronic venous disorder due to valvular incompetence of the superficial venous system. This problem has a high prevalence (a third of the population) and generates an important number of surgical interventions (one of the most frequently performed operation in the world), as shown in the Edinburgh Study^[4,5]. Surgical treatment provides symptomatic relief and significant improvements in quality of life in patients with uncomplicated varicose veins. Stripping is one of the validated methods to treat varicose veins. It is a good procedure in terms of

simplicity, speed safety, and because the technique is well standardized^[6-9].

Although many complications were well described after stripping including the most frequently wound infection, nerve injury, vascular injury and venous thromboembolism^[1], little is known about compartment syndrome due to muscle ischemia caused by constrictive bandages applied after stripping of varicose veins^[2].

Acute compartment syndrome is a condition in which raised pressure within a closed fascial space reduces capillary perfusion below a level necessary for tissue viability. The initial injury leads to swelling within a compartment. This causes an increase in intracompartmental pressure with compressive closure of the thin-walled venules resulting in hypertension at the venous end of the capillary beds. Eventually arteriolar compression occurs, leading to muscle and nerve ischaemia with muscle infarction and nerve damage. Measuring intracompartmental pressure is only necessary when the clinical signs of compartment syndrome are unclear, in an unconsciousness or uncooperative patient, in a young child or when the clinical symptoms and signs are equivocal. The primary treatment should be decompression by fasciotomy as soon as possible. Elevation of the limb is sometimes used as a temporary measure in an attempt to reduce pressure^[3].

Danner *et al*^[2] describe four patients suffering from lower limb compartment syndromes, which were caused by constrictive bandages applied after stripping of varicose veins. The dressing was erroneously only partially removed, when the patients started complaining of severe pain and tension in the operated legs. The damages varied from extended irreversible neuromuscular defects to lesser functional handicaps. Three patients had corrective surgery. The clinical follow up over several years showed little improvement and secondary complaints were frequent.

At variance with this previous experience we have described the first case of conservative treatment without secondary complaints and a complete recovery.

Although, in our report, rehabilitation was found effective in improving fatigue, stiffness and tenderness showing the effectiveness of the combined conservative-

rehabilitative treatment, further studies are needed to evaluate the role of rehabilitation program in such disease.

However conservative treatment could not be considered the treatment of choice in daily practice. A severity score assessment of compartment syndrome should be useful to assess to which patients is allowed to not perform fasciotomy. More in details it would be important to know when a conservative treatment could be performed safely. Further more representative research are needed to assess this issue.

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Synchronous rectal and esophageal cancer treated with chemotherapy followed by two-stage resection

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Abstract

We report a case of 61-year-old male who had synchronous advanced rectal cancer involving the urinary bladder massively associated with multiple liver metastases, and esophageal cancer successfully treated by neoadjuvant chemotherapy followed by two-stage resection. Although complete resection of each of the lesions was considered possible by performing anterior pelvic exenteration, liver resection, and esophagectomy, it might be impossible for the patient to endure the stress of all of these operative procedures at once. Therefore, we planned to perform staged treatment with prioritizing consideration. First, we instituted chemotherapy with the FOLFOX (oxaliplatin + fluorouracil + leucovorin) plus cetuximab regimen, which could adequately con-

trol both rectal and esophageal cancer. After 6 cycles of chemotherapy, high anterior resection combined with cystoprostatectomy and lateral segmentectomy plus partial hepatectomy was performed followed by staged esophagectomy with three-field lymph node dissection. It was possible to use oxaliplatin and cetuximab safely as neoadjuvant therapy not only for advanced rectal cancer but for esophageal cancer, and it was effective.

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Key words: Rectal cancer; Esophageal cancer; Neoadjuvant chemotherapy; Cetuximab; Oxaliplatin

Core tip: In case with synchronous multiple cancers, it is sometimes difficult to identify the origin especially when liver and/or pulmonary lesions have a possibility of metastases, or to decide on a course or priority of the treatment. FOLFOX + cetuximab (Cet) therapy could provide a favorable control of not only rectal origin accompanied by liver metastases but also esophageal cancer, which made possible to undergo two-stage curative resection. FOLFOX + Cet regimen might be a useful option for such refractory rectal and esophageal cancer.

Utsunomiya S, Uehara K, Kurimoto T, Hirose K, Fukaya M, Takahashi Y, Taguchi Y, Itatsu K, Nagino M. Synchronous rectal and esophageal cancer treated with chemotherapy followed by two-stage resection. *World J Clin Cases* 2013; 1(2): 87-91 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i2/87.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i2.87>

INTRODUCTION

In the last decade, remarkable advances have been achieved in chemotherapy for colorectal cancer as a result of the

advent of the novel anticancer drugs such as irinotecan and oxaliplatin (L-OHP), and the molecularly targeted drugs such as vascular endothelial growth factor inhibitors and epidermal growth factor receptor (EGFR) inhibitors. Cetuximab (Cet), one of the EGFR inhibitors, has a strong cytoreductive effect and survival benefit in *KRAS* wild-type colorectal cancer, and it has not only been incorporated in treatment strategies together with L-OHP as palliative therapy for unresectable metastatic colorectal cancer, but as perioperative chemotherapy for resectable advanced cancer or conversion chemotherapy for unresectable metastatic diseases^[1,2].

Although, more than 50% of esophageal cancers are adenocarcinoma in Western countries, approximately 90% of esophageal cancers are squamous cell carcinoma (SCC) and the half of them are located in the mid-thoracic esophagus in Japan^[3]. The gold standard of treatment for esophageal cancer in Japan is radical esophagectomy with three-field lymph node dissection, and neoadjuvant chemotherapy with a 5-fluorouracil (5-FU) plus cisplatin regimen (FP) is recommended for clinical stage II/III patients^[4]. In Western countries, some regimens including L-OHP or Cet have been reported to be safe and effective for advanced esophageal cancer^[5-8].

We report a case of synchronous advanced cancers of the rectum and the esophagus, successfully treated by neoadjuvant chemotherapy with a FOLFOX (L-OHP + 5-FU + leucovorin) plus Cet regimen followed by two-stage surgical resection.

CASE REPORT

A 61-year-old male patient was admitted for a urinary tract infection. An abdominopelvic computed tomography (CT) revealed an intrapelvic mass that had invaded the bladder and multiple hepatic lesions with weak contrast enhancement (Figure 1). On colonoscopy, a circumferential ulcerative lesion was seen in the upper rectum (Figure 2). Biopsy revealed a moderately differentiated adenocarcinoma, and *KRAS* genotyping showed that it was the wild type. On esophagogastroscope, a depressed lesion with a little surrounding elevation was observed in the mid-thoracic esophagus, and biopsy resulted in a diagnosis of SCC (Figure 3). Based on the results of these examinations, a diagnosis of synchronous advanced cancers consisting of a rectal cancer involving the urinary bladder associated with multiple liver metastases (cT4b, cN0, cM1, Stage IV), and an esophageal cancer (cT2, cN0, cM0, Stage I B) were made.

First, after creating a loop colostomy with the sigmoid colon in order to control the urinary tract infection, which had developed as a result of a bladder fistula, and to remove the rectal obstruction, we instituted neoadjuvant chemotherapy with the FOLFOX + Cet regimen. An abdominopelvic CT after 6 cycles of chemotherapy showed marked regression of both the primary lesion in the rectum and the liver metastases (Figure 4). Although no marked change in the size of the esophageal cancer

was observed during esophagogastroscope, flattening of the lesion was noted. Five months after diagnosis, high anterior resection combined with cystoprostatectomy, diverting ileostomy, neobladder reconstruction, and lateral segmentectomy plus partial hepatectomy were performed with 6-wk completion of chemotherapy. The operative time was 981 min, and blood loss was 1555 mL. The pathological diagnosis of the both lesions was moderately differentiated adenocarcinoma with invasion of the urinary bladder (ypT4b, ypN0, ypM1, Stage IV). There was moderate vascular invasion, but the surgical margins were negative. According to the Japanese Classification of Colorectal Carcinoma, the histological effect of the chemotherapy was Grade 1b at the primary site and Grade 2 at the site of the liver metastases. Although wound infection and urinary tract infection occurred as postoperative complications, they treated conservatively, and the patient was discharged on postoperative day 15.

Because recovery of the patient's general condition was delayed due to postoperative watery diarrhea, ileostomy closure was performed. Even though 5 mo had passed since the completion of chemotherapy, esophagogastroscope showed no evidence of an increase in size of the esophageal cancer, and it was concluded that the disease had been adequately controlled (Figure 3B). Esophagectomy with three-field lymph node dissection and anterosternal reconstruction with gastric tube were performed 4 mo after rectal resection. The operative time was 584 min, and blood loss was 1027 mL. The pathological diagnosis was poorly differentiated SCC (ypT1b, ypN1, cM0, Stage II B). The histological effect of chemotherapy was minimal with slight cancer cell degeneration or necrosis. Postoperatively, anastomotic leakage occurred, but it was improved by conservative management, and the patient was discharged on postoperative day 70.

Eleven months after rectal resection, pulmonary node with elevation of carcinoembryonic antigen (CEA) was pointed out and right lower lobectomy was performed. Pathological findings showed it metastasis from rectal adenocarcinoma. The patient is alive without cancer 15 mo after pulmonary resection.

DISCUSSION

In case with synchronous multiple cancers, it is sometimes difficult to identify the origin especially when liver and/or pulmonary lesions have a possibility of metastases, or to decide on a course or priority of the treatment. When the origin of liver or pulmonary lesions is unclear, there are several solution strategies. Biopsy is the most reliable method for a definite diagnosis. However, biopsy occasionally causes a future disseminated diseases, therefore it might be avoided in cases having possibility of curative resection. The increasing level of tumor markers is sometimes helps us to diagnosis. Another promising option is chemosensitivity. The good response to chemotherapy is helpful to make diagnosis. In this case, if the liver tumor came from the esophageal cancer, FOLFOX and Cet

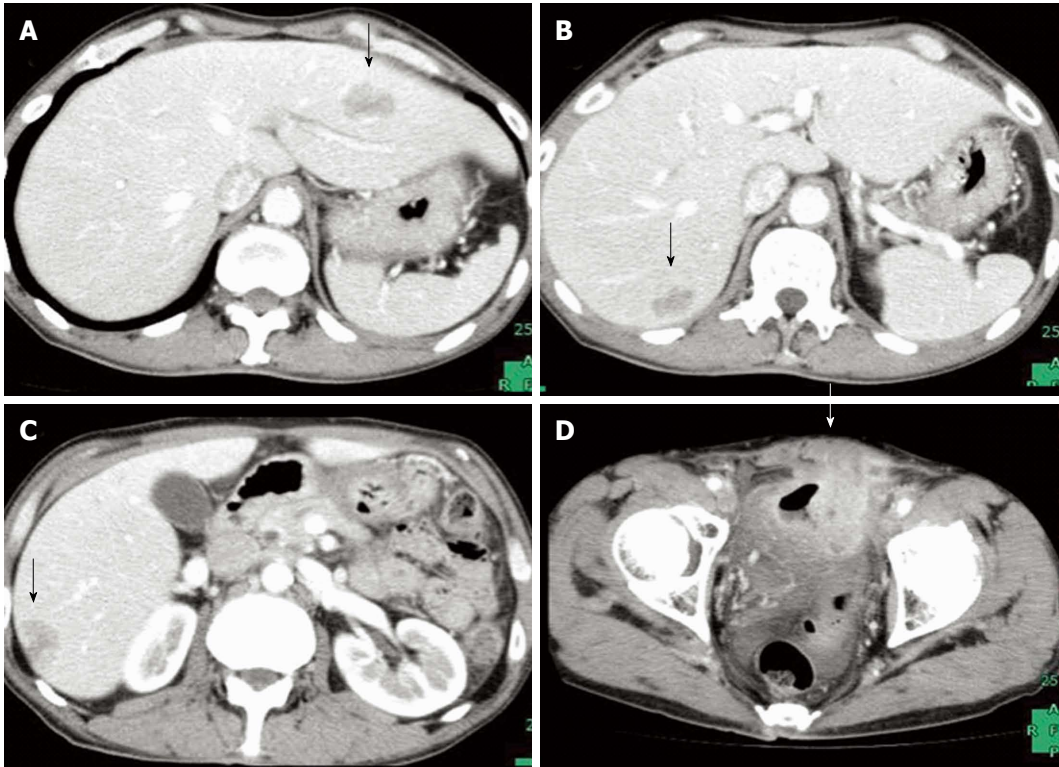


Figure 1 Computed tomography before treatment showed multiple liver metastases (arrows) and a primary upper rectal tumor that had invaded the urinary bladder. A, B: Multiple liver metastases; C, D: A primary upper rectal tumor.

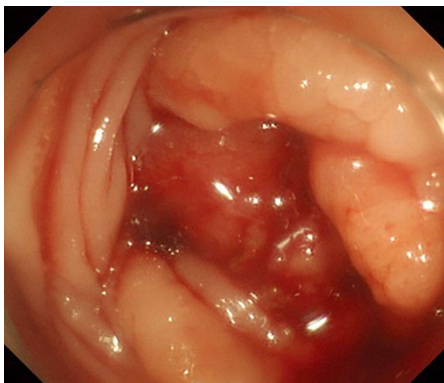


Figure 2 Colonoscopy revealed a circumferential lesion in the upper rectum and the lumen was almost completely obstructed.

might be invalid. However, in general, surgical treatment in curative intent has not indicated for the patients with liver metastases from esophageal squamous carcinoma or with colorectal liver metastases which progress in spite of aggressive chemotherapy. As a result, shrinkage of the liver tumor enabled us to perform curative resection and to confirm the origin to be the rectum. In case of progression in any tumor, palliative treatment should be one of the options. The pulmonary recurrence is also considered to come from the rectal cancer, because of increasing level of CEA. If the level of CEA was within normal range, initial chemotherapy or biopsy might be selected.

R0 resection of each of the lesions in this patient with two cancers was considered possible by performing

anterior pelvic exenteration, liver resection, and esophagectomy. However, it might be impossible for the patient to endure the stress of all of these operative procedures at once. Therefore, we planned to perform staged treatment with prioritizing consideration. A 5-year overall survival (OS) rate of approximately 45% had been reported after surgical resection of liver metastases from colorectal cancer^[9], as opposed to a rate of 60% after initial surgical treatment of clinical T1/2 SCC of the thoracic esophagus^[10]. Additionally, the patient's complaints are another important part. In this case, the patient had repeated urinary tract infection and no esophageal obstructions. Therefore, we decided to treat the colorectal cancer and liver metastases preferentially.

The only potentially curative treatment for patients with liver metastases from colorectal cancer is surgical resection, but the postoperative recurrence rate has been reported to be approximately 75%, which is too high. To improve the survival rate or reduce the recurrence rate, new surgical strategies combined with developed systemic anticancer agents have recently been evaluated. As a result of EORTC40983 study, reported by Nordlinger *et al.*^[11], curative surgery combined with 6-mo perioperative chemotherapy is now generally recommended for patients with resectable liver metastasis, especially for chemotherapy naïve patients. However, the optimal chemotherapy regimen remains uncertain. A phase II trial of the efficacy of Cet in combination with either the FOLFOX regimen or FOLFIRI regimen (CELIM study) was conducted in patients with unresectable liver metas-

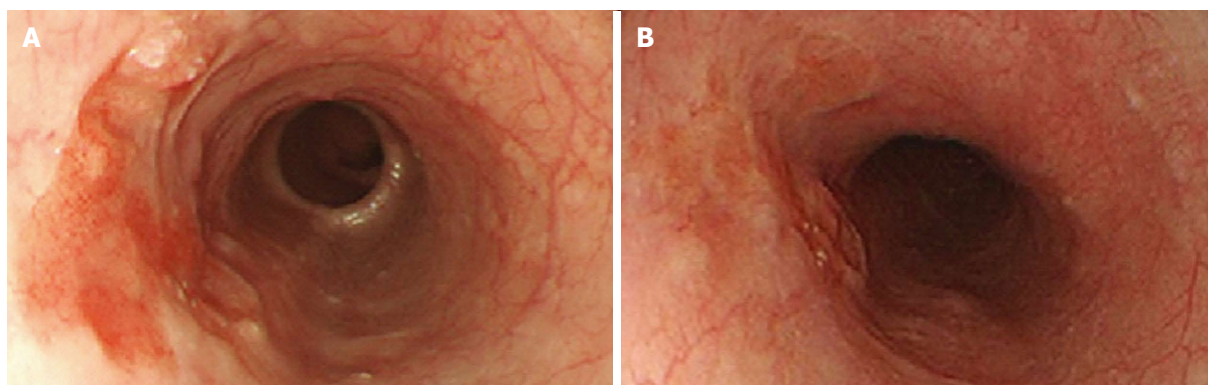


Figure 3 On esophagogastroscopy, a depressed lesion with a little surrounding elevation was observed in the mid-thoracic esophagus, and biopsy resulted in a diagnosis of squamous cell carcinoma. A: Esophagogastroscopy before treatment revealed a shallow depressed area in the middle third of the thoracic esophagus; B: After 6 cycles of chemotherapy, the esophageal lesion had flattened slightly, and there was good disease control.

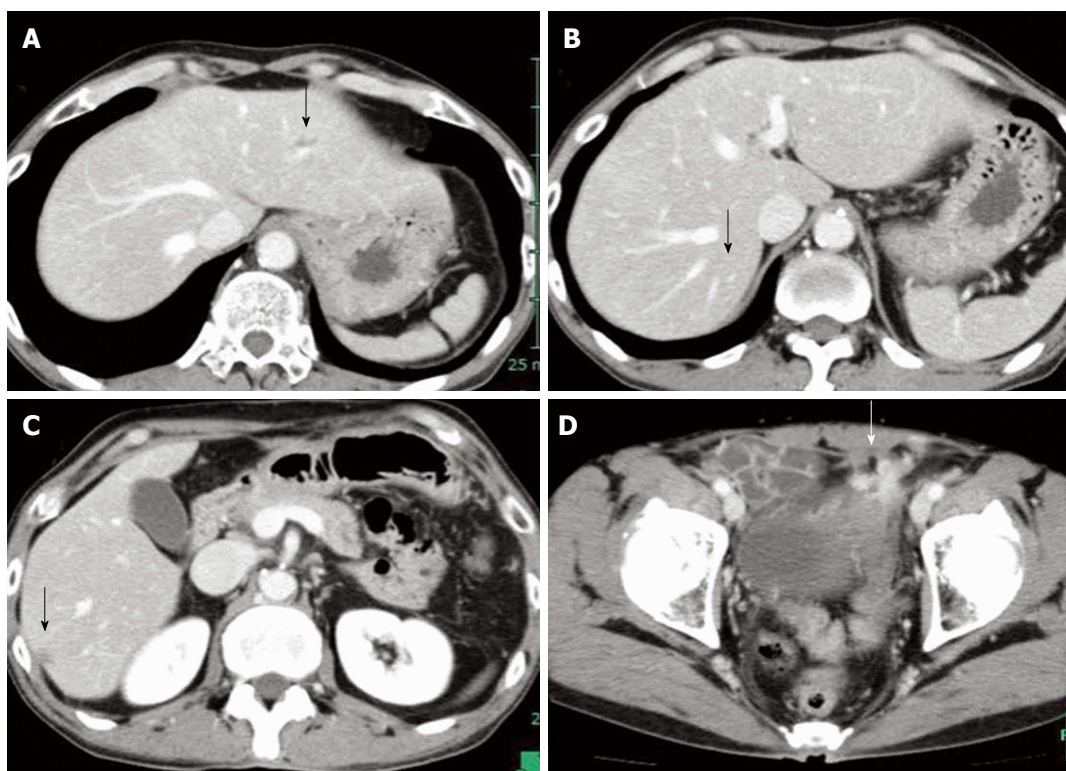


Figure 4 The computed tomography findings after 6 cycles of mFOLFOX6 plus cetuximab chemotherapy showed a good response in both the liver metastases (arrows) and primary lesion. A, B: Liver metastases; C, D: Primary lesion.

tasis. Since the overall response rate (68%) and R0 resection rate (38%) in the Cet plus FOLFOX regimen group were superior to those (57% and 30%, respectively) in the Cet plus FOLFIRI regimen group^[2], we treated our patient with the mFOLFOX6 + Cet regimen in anticipation of obtaining the maximum tumor regression effect and survival benefit.

The greatest concern with this treatment strategy was rapid progression of the esophageal cancer as a result of the decreased immune capacity associated with the highly invasive operation, which consist of extended pelvic surgery and liver resection. Therefore, controlling the esophageal disease during this period for rectal cancer

treatment was extremely important. A Japanese randomized phase III trial (JCOG 9907) compared preoperative chemotherapy to postoperative chemotherapy for patients with clinical stage II/III SCC of the esophagus, and the results showed that the 5-year OS of the preoperative chemotherapy group was significantly superior to that in the postoperative chemotherapy group (55% *vs* 43%, $P = 0.04$)^[4]. Based on the results of this trial, the standard treatment for advanced thoracic esophageal cancer has changed from surgery followed by postoperative chemotherapy to preoperative chemotherapy followed by surgery in Japan. In Western countries, modern cytotoxic agents and targeted drugs have been reported to be effec-

tive and safe in patients with advanced esophageal cancer. L-OHP is a promising antineoplastic platinum derivative with a more favorable toxicity profile than cisplatin. Response rates of to the FOLFOX regimen and CapeOx (capecitabine + LOHP) regimen have been reported to be 39%-44%, suggesting be that they might be equivalent to the current standard FP regimen^[5-7]. Lorenzen *et al*^[8] conducted a randomized phase II trial that investigated the activity and safety of adding Cet to the standard FP regimen (FP + Cet). The overall response rate and disease control rate were 19% and 75%, respectively, in the FP + Cet group, and superior to the rates in the FP alone group (13% and 57%, respectively). Moreover, there was no evidence that L-OHP or Cet aggravated the known toxicities.

In our patient, objective clinical and pathological response was stable disease, which indicated FOLFOX + Cet was not necessarily effective. However, rapid progression of esophageal cancer could be avoided, although it was untreated for 6 mo between the last administration of the chemotherapy and the esophageal cancer surgery. FOLFOX + Cet might suppress the growth of esophageal cancer.

In conclusion, we have reported the case of synchronous advanced rectal cancer involving the urinary bladder massively associated with multiple liver metastases, and esophageal cancer. FOLFOX + Cet therapy could provide a favorable control of not only rectal origin accompanied by liver metastases but also esophageal cancer, which made possible to undergo two-stage curative resection. FOLFOX + Cet regimen might be a useful option for such refractory rectal and esophageal cancer.

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Squamous papilloma in the external auditory canal: A common lesion in an uncommon site

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Author contributions: Chang NC drafted the article; Chien CY was the attending physician of the presented patient; Wu CC and Chai CY were the pathologists who reviewed the specimen and provided the pathological photographs.

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Key words: Squamous papilloma; External auditory canal; Human papilloma virus; Koilocytosis; Review

Core tip: Squamous papillomas (SPs) are common benign neoplastic lesions. However, SPs of the external auditory canal (EAC) are rarely reported in the English literature. A case of EAC SPs is presented here with a discussion and brief review of the literature.

Chang NC, Chien CY, Wu CC, Chai CY. Squamous papilloma in the external auditory canal: A common lesion in an uncommon site. *World J Clin Cases* 2013; 1(2): 92-95 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i2/92.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i2.92>

INTRODUCTION

Squamous papillomas (SPs) are benign neoplastic lesions usually affecting the skin, oral mucosa, upper aerodigestive tract and genital organs. It is believed that the human papilloma virus (HPV) is an etiological factor of papillomas; thus, they are also called viral warts. Cutaneous SPs are a very common skin condition; however, SPs of the external auditory canal (EAC) are rarely reported in the English literature although they commonly occur in the southern Chinese population. This indicates that SPs of EAC might be an ethnically specific disease. There are several cutaneous neoplastic lesions similar to SPs in appearance. The definitive diagnosis of SPs relies on histopathological examination. Here, we present a clinical case and briefly review the literature concerning the etiology, natural course, diagnosis and management of EAC papillomas.

CASE REPORT

The presented case is a 19-year-old young Taiwanese fe-

Abstract

Squamous papillomas (SPs) are common benign neoplastic lesions, usually affecting the skin, oral mucosa, upper aerodigestive tract and genital organs. However, SPs of the external auditory canal (EAC) are rarely reported in the English literature. In this report, we present a 19-year-old female with left EAC SP. The etiology, natural course, diagnosis and management of this disease are discussed, with a brief review of the literature.

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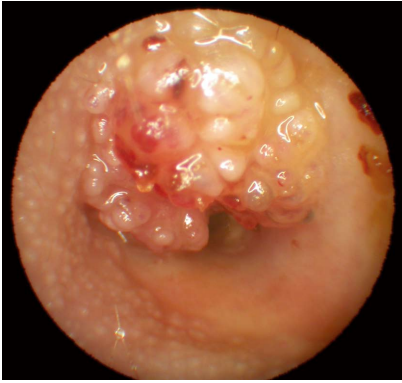


Figure 1 Pre-operative findings of the left external auditory canal. A multiple granular mulberry-like neoplastic lesion located on the superior aspect of left external auditory canal.

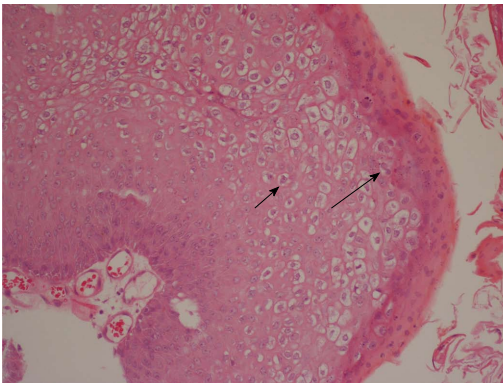


Figure 2 Histopathological findings (hematoxylin and eosin, × 200). Histopathological examinations revealed the characteristic features of hyperkeratosis, papillomatosis, parakeratosis, acanthosis and koilocytosis. Koilocytosis indicates diseased cells caused by human papilloma virus infection. Characteristic squamous cells containing peri-nuclear clearing with condensation of peripheral cytoplasm are the typical pictures of koilocytic cells. Irregular, raisin-shaped nucleus (short arrow) and bi-nuclei cells (long arrow) may be present.

male who visited our office with a history of left external ear canal blockage for several months. Surgical intervention for bilateral external ear canal tumors had been performed in another institute about 2 mo previously. Unfortunately, not long after the surgical procedure, left ear auditory canal fullness recurred and she visited our clinic for evaluation and management. She did not bring the report of the pathological examinations in the previous institute when she came to our office and merely described that they were benign lesions, as related by the previous surgeon.

Under otoscopic examination, an irregular, granular, mulberry-like neoplastic lesion was found, located at the cartilaginous part of the left EAC (Figure 1), and non-specific findings were noted in the contralateral ear. A surgical removal with ordinary instruments under microscope was arranged and performed.

The histopathological examination showed hyperkeratosis, papillomatosis, parakeratosis, acanthosis, koilocytosis and inflammatory infiltrates in the upper dermis, characteristic features of SPs (Figure 2). The wound healed well



Figure 3 Post-operative follow up conditions. One month after the surgical removal was performed. The wound healed well without scar contracture or recurrence.

without specific complications during the post-operative follow-up (Figure 3).

DISCUSSION

Etiology

SPs are very common skin lesions. There is a high prevalence of SPs in the EAC. Papillomas, accounting for up to 78.9% of benign ear tumors, have been reported, with 95.2% of ear papillomas located in the EAC^[1]. However, SPs of the external ear have been reported infrequently in the English literature, although they occur commonly in the southern Chinese population. This is probably secondary to the cultural ritual of mechanical cleansing with unsterilized re-used instruments by which infectious agent inoculation may take place^[1-3]. Surgical procedures of the ear may also be a route for the dissemination of SP^[4]. It is generally assumed that SPs are caused by HPV infections and SP is considered to be a viral wart^[5]. Cutaneous SPs are caused most frequently by HPV types 1, 2, 3, 4, 27 and 57^[6,7]. However, HPV types 6 and 11 were found to be the main causative agents for SPs of the EAC^[1,8]. HPV types 6 and 11 are the most common pathogens for oral papillomas, recurrent respiratory papillomatosis and anogenital warts^[7]. Like the disseminations of HPV types 6 and 11 in the aerodigestive tract and genital papillomas, vertical infection of HPV from the mother at delivery might be the primary route of the virus acquisition. The hair follicles have been suggested as possible reservoirs^[7]. SPs are rare in children younger than 5 years of age; however, EAC SP in a 3-year-old patient has been reported^[9].

Natural course

EAC SP is a benign lesion which is generally solitary and has a low risk of bony destruction. It grows slowly and may cause a mechanical obstruction of the EAC, leading to pressure necrosis of the adjacent bone or conductive hearing impairments^[10]. Involvement of the tympanic membrane is seldom reported^[3,4]. Viral warts of the skin are not harmful and usually go away without any treat-

ment^[6]; however, the possibility of spontaneous resolution of EAC SPs is still unclear. The common causative HPV types are quite different in skin warts (types 1, 2, 3, 4, 27 and 57) from that in EAC SPs (types 6 and 11); the behaviors may be different with distinct HPV types. Although EAC SPs are generally believed to be mainly caused by the “low-risk” HPV types 6 and 11, malignant transformation has been reported^[11].

Diagnosis

Most neoplastic lesions of the EAC are benign and up to 80% of these lesions are papillomas^[1]. Grossly, SPs commonly appear as a round or oval, flat papule with a broad base on the skin or mucous membranes. Histologically, they arise from stratified squamous epithelium and are characterized by the growth of multiple papillary fronds (papillomatosis), hyperkeratosis, parakeratosis, acanthosis, infrequent mitosis and rare nuclear atypia^[1,11]. Squamous cells with clear cytoplasm, dense dark nuclei and occasionally bi-nuclei are called koilocytic cells, which indicate an infection of the cells by HPV^[8].

Inverted papilloma (IP) in the EAC is similar to SP in gross appearance. However, IP has a distinct behavior from SP and should be carefully differentially diagnosed. IP, or Schneiderian papilloma inverted type, is an aggressive benign neoplastic lesion with a tendency for local recurrence and association with carcinoma. Microscopically, IP is characterized by the digitiform proliferation of squamous epithelium into the underlying connective tissue stroma^[12]. HPV types 6, 11, 16 and 18 are the most common causative agents associated with IP and types 16 and 18 are more commonly associated with malignancy^[9,12,13].

Treatments

Surgical removal of the lesion remains the most effective method in the treatment of EAC SPs. Several methods, including cryosurgery, electrodesiccation with/without curettage and carbon dioxide laser, have been described and are believed to be effective^[5]. The major complication of surgical treatment is possible scarring and subsequent stenosis of the EAC. Insertion of a silastic tube in the canal as a stent and meticulous postoperative care to prevent wound infection may provide uncomplicated healing^[9].

Some agents are reported to be effective in topical treatments for viral warts. Salicylic acid and cryotherapy have shown significant effects in the clearance of cutaneous warts, especially in the hand and foot areas. Dinitrochlorobenzene, 5-fluorouracil, intralesional bleomycin, intralesional interferon, photodynamic therapy and intralesional antigen have been tried in previous studies but without much evidence for their effectiveness^[6]. The effects of the above topical treatments for SPs in the EAC are not clear; hence, topical methods are not recommended as primary management for EAC SPs.

Radiotherapy for SPs in the EAC was tried in an earlier report^[3]. The authors reported an excellent result for

the treatment of recurrent SP in the EAC, middle ear and the mastoid cavity by radiotherapy. However, radiotherapy carries potential risks for malignant transformation of the cells and other complications, such as hearing impairment, EAC stenosis and vestibular, trigeminal and facial nerve neuropathies^[14,15], so it is not recommended as the primary treatment method.

There are HPV vaccinations to prevent anogenital warts and cancers^[16]. These vaccines mainly protect against HPV types 6, 11, 16 and 18, the major types causing cervical cancer, anogenital wart/cancer, recurrent respiratory papillomatosis and EAC SP. These vaccines have been approved for use of prevention of genital cancers by the United States Food and Drug Administration since 2006^[16,17]. The vaccines are not indicated to prevent cutaneous and oral mucosal SPs; however, along with increasing HPV vaccination rates, the decrease of SP prevalence would be expected.

SP in the EAC is a common benign neoplastic lesion located in an uncommonly reported site. It may be caused by the infection of HPV. Surgical removal remains the treatment of choice for EAC SPs.

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Monitoring photodynamic therapy of head and neck malignancies with optical spectroscopies

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Abstract

In recent years there has been significant developments in photosensitizers (PSs), light sources and light delivery systems that have allowed decreasing the treatment time and skin phototoxicity resulting in more frequent use of photodynamic therapy (PDT) in the clinical settings. Compared to standard treatment approaches such as chemo-radiation and surgery, PDT has much reduced morbidity for head and neck malignancies and is becoming an alternative treatment option. It can be used as an adjunct therapy to other treatment modalities without any additive cumulative side effects. Surface illumination can be an option for pre-malignant and early-stage malignancies while interstitial treatment is for debulking of thick tumors in the head and neck region. PDT can achieve equivalent or greater efficacy in treating head and neck malignancies, suggesting that it may be considered as a first line therapy in the future. Despite progressive development, clinical PDT needs improvement in several topics for wider acceptance including standardization of protocols that involve the same administrated light and PS doses and establishing quantitative tools for PDT dosimetry planning and response monitoring. Quantitative measures such as optical parameters, PS concentration, tissue

oxygenation and blood flow are essential for accurate PDT dosimetry as well as PDT response monitoring and assessing therapy outcome. Unlike conventional imaging modalities like magnetic resonance imaging, novel optical imaging techniques can quantify PDT-related parameters without any contrast agent administration and enable real-time assessment during PDT for providing fast feedback to clinicians. Ongoing developments in optical imaging offer the promise of optimization of PDT protocols with improved outcomes.

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Key words: Head and neck cancer; Photodynamic therapy; Monitoring and predicting response; Blood flow; Oxygenation; Oxygen metabolism; Diffuse optical imaging

Core tip: Most treatment approaches including chemo-radiation and surgery can induce prolonged morbidity and functional loss resulting in severe impairment of patients' quality of life. Photodynamic therapy (PDT) is an emerging alternative treatment option without any significant accumulative side effects due to targeted light illumination and preferential accumulation of photosensitizers (PSs). However, PDT has not found widespread applications at the clinic mainly due to variable responses that originated from unstandardized treatment protocols such as different light and PS doses. Novel optical imaging techniques can quantify PDT-dosimetry related parameters such as local light and PS dose in tissue and PDT response related parameters such as tissue oxygenation and blood flow noninvasively without any contrast agent administration, thereby providing real-time feedback about the treatment efficacy for optimizing and standardizing PDT.

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INTRODUCTION

Head and neck malignancies refer to malignancies arising from the oral cavity, pharynx, nasal cavity and sinuses^[1-3]. Head and neck squamous cell carcinoma (HNSCC), constituting approximately 90% of malignancies in the head and neck region, remains the fifth most common form of cancer worldwide with an incidence of approximately 800000 new cases per year^[4]. Most of these tumors may be attributed to risk factors such as tobacco and alcohol consumption. HNSCC is a heterogeneous disease with different stages ranging from benign squamous hyperplasia, dysplasia, carcinoma *in situ* (CIS) to invasive carcinoma^[5]. Early stage diagnosis and treatment of HNSCC increases the likelihood of successful treatment and improves patients' quality of life, lowers risk of mortality and health costs^[5,6].

Substantial efforts concentrate on early detection with fair success, but still many patients present with clinically evident tumors that require effective treatment^[7]. Several treatment options are available including surgery, chemotherapy, radiation therapy or combinations thereof^[8]. In spite of improvements in these treatment modalities, they have their own limitations. For example, surgery may require resection of vital tissue such as part of the tongue resulting in functional loss. On the other hand, organ-preserving surgery can result in high recurrence rates. Nonsurgical management with chemo and radiation therapies to improve local-regional disease results in only modest or suboptimal improvements in survival but with significantly high cost side effects including speech and swallow function^[9]. These conventional therapies may induce permanent vasculature dysfunction and necrosis, severe toxicities and irreversible injuries to non-tumor tissue such as the oral mucosa and the salivary glands, often resulting in morbidity and severe impairment of patients' quality of life. Further, normal tissue toxicity such as mucositis, bleeding and inflammation may lead to changes in applied dose quantity, and treatment re-schedule, which may affect treatment efficacy and outcome. For these reasons, an alternative treatment modality that is effective, safe, repeatable, minimally invasive and non-surgical is desired for the management of head and neck malignancies.

Photodynamic therapy (PDT) uses light to activate a photosensitizer (PS) in the presence of oxygen for local tissue destruction, has potential in these respects and is particularly attractive due to its significant level of normal tissue preservation and its repeatability without cumulative side effects^[10]. It has potential impact particularly for cases with multiple lesions and wide-spread early stage head and neck diseases (e.g., leukoplakia, invasive carcinoma) in the oral cavity^[11]. However, PDT has not found widespread applications at the clinic mainly due to variable responses that originated from unstandardized treatment protocols such as different light and PS doses. Optical imaging can quantify local light and PS dose in tissue and monitor PDT; and therefore can provide feedback about the treatment efficacy. Thus, we expect optical im-

aging modalities will help in optimizing and standardizing PDT. Below we will detail PDT treatment and optical imaging for monitoring and ultimately predicting PDT response.

CLINICAL PDT

PDT is an emerging treatment option for many malignancies including head and neck. It is minimally invasive with much less side effects compared to conventional therapies. Since it does not have any significant accumulative side effects, it can be repeated many times and be applied before or after chemotherapy, radiation therapy. It can also be used as an adjuvant therapy to these therapies and surgery to eliminate residual microscopic tumor cells. PDT light can be delivered at the surface for wide and superficial malignancies and pre-malignancies such as mucosal dysplasia and CIS in the oral cavity. Interstitial light delivery is applied in treating thick and deep tumors for the aim of debulking tumors as an adjuvant to surgery.

Basics of PDT

PDT efficacy depends on three main elements: a sufficient amount of light, photosensitizing drug (also called PS) and available oxygen in tissue. The PS is activated during light illumination and the active PS reacts with molecular oxygen to produce singlet oxygen that induces direct cell killing, vascular destruction and immune response^[12,13]. Most PSs are administered systemically but some can be applied topically for head and neck lesions in the oral cavity and nonmelanoma skin tumors. After a specific time, depending on the PS itself, PS accumulates specifically more in the diseased site compared to normal and surrounding periphery sites. Tumor to normal tissue contrast is generally 2-3 fold with a passive targeting mechanism, but even 10-fold contrast has been reported^[14]. At the optimal time point of accumulation, a specific wavelength of light depending on the optical absorption properties of the PS is shined at a predetermined power to activate the PS to create a photodynamic reaction. Due to specific accumulation of the PS and localized light illumination, PDT is a local therapy rather than a systemic therapy like chemotherapy. The treatment volume depends on both PS and light penetration depth. For example, for the cases of Photofrin[®], which is the first FDA-approved PS that was developed here at Roswell Park Cancer Institute, light illumination is at approximately 630 nm with a penetration depth of 5 mm or less. Thus, Photofrin[®] has been in use worldwide to treat early stage carcinomas in many organs including the head and neck.

Superficial and interstitial PDT approaches for head and neck diseases

Previous studies have shown that PDT is safe and effective in the treatment of early carcinomas of the head and neck^[2,10,11,13,14-35]. PDT is an excellent choice for early-stage malignancies since local treatment and limited light

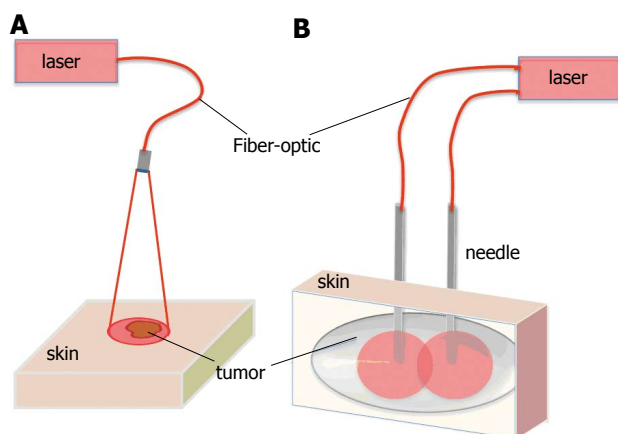


Figure 1 Representation for light delivery during surface and interstitial photodynamic therapy. A: Surface illumination photodynamic therapy (PDT) for treating superficial malignancies. Laser light is directed to tissue surface via micro-lens fiber. Tumor is located superficially; B: Interstitial PDT treatment for deeper and thicker malignancies. Individual fibers are placed inside 19-gauge needles and inserted into tissue. Number of fibers is selected according to treated volume.

penetration eliminates the side effects that can occur in the sensitive areas of the oral cavity such as soft palate. Lasers are the choice for the light sources and laser light is delivered *via* surface illumination by using a micro-lens as shown in Figure 1A. For deeper and thicker tumors, however, superficial illumination is not suitable. In this case, light is delivered by feeding laser fibers through needles placed directly into the tumor (Figure 1B). This approach is very similar to brachytherapy or interstitial radiotherapy^[36,37].

CHALLENGES

One of the main challenges of PDT is treating deeper and thicker tissues. However, this is not an issue for superficial malignancies. Pain management is a frequently reported challenge^[38]. Another common side effect of PDT is the long-term skin photosensitivity, especially for the cases of systemic administration of PSs such as Photofrin® (porfimer sodium). ALA-PDT is another widely used treatment option for early stage malignancies with much reduced skin photosensitization, but with the drawback of severe pain during treatment, often necessitating anesthesia. Therefore, the development of PSs that do not induce long-term photosensitivity, produce durable results and are patient friendly is of significant clinical benefit. In this respect the second generation PSs, such as Photoclor (HPPH) used in our clinical trials, have shown clinical promise with their improved efficacy, higher penetration depths and significantly less skin photosensitivity.

Variable outcomes are the main roadblock to wider use of PDT. The lack of standardized protocols with the same light and PS type and doses, as well as imprecise dosimetry drives the variable PDT responses^[36,37]. There is strong evidence that variations in clinical response are a direct result of dosimetry that does not take into account

individual differences^[39]. In order to bring PDT to a full realization of its potential benefits, quantitative tools are likely to play an essential role. They can provide standardization of site-specific individualized protocols by assessing light and PS doses.

Another challenge for clinical PDT of the head and neck is the difficulty in predicting the responders and non-responders^[36]. Quantitative optical imaging tools can play a crucial role in filling this niche. These tools are currently in primitive stages and not widely used in clinical settings for monitoring PDT mainly because optical measurements may require extra clinical time and extra fiber replacements during PDT. The techniques are limited to pre- and post-PDT measurements but with the advent of new technologies they can be adapted for monitoring during PDT, which would have three-fold benefits: (1) reduced required clinical time, (2) no interruptions of treatment light for the optical measurements, and (3) more accurate quantification of kinetics of PDT-related parameters such as photobleaching and blood flow kinetics, which have been shown to be predictors of PDT response^[36,40-50].

CLINICAL OPTICAL IMAGING FOR PDT MONITORING

Tissue oxygen level is crucial for effective PDT since the PS initiates chemical reactions that result in cellular and vascular damage in targeted tissue in the presence of oxygen. Tissue oxygenation is highly affected by vascular parameters such as blood flow and blood oxygenation. During the PDT process, PS is consumed continuously. Thus, the efficacy of PDT is dependent on the vascular parameters and PS level and consumption (photobleaching)^[50,51]. Vascular parameters and PS level change during PDT and these changes may be useful early markers for therapy response^[36,44,52-54].

Optical imaging is a wide topic that includes many different imaging approaches. Here we will focus on a subdivision called diffuse optical spectroscopies (DOS) for probing millimeter to centimeter deep tissue^[55-61]. In this context, DOS includes diffuse reflectance spectroscopy (DRS)^[62-67], diffuse fluorescence spectroscopy (DFS)^[40,67-70] and diffuse correlation spectroscopy (DCS)^[71,72]. We have recently developed a multi-modal optical imaging technique that combines DRS, DFS and DCS in a single instrument and showed the feasibility of quantification of optical parameters (absorption and scattering), drug concentration and vascular parameters such as blood flow and oxygenation in a clinical setting^[44,73].

Multi-modal optical instrument

The technical details of our multi-modal optical system can be found elsewhere^[44,73], but here we briefly mention the basic working principles. The instrument performs measurements sequentially in the order of blood flow (DCS), optical parameters, blood oxygenation and volume (DRS), and fluorescence (DFS). Figure 2A and B

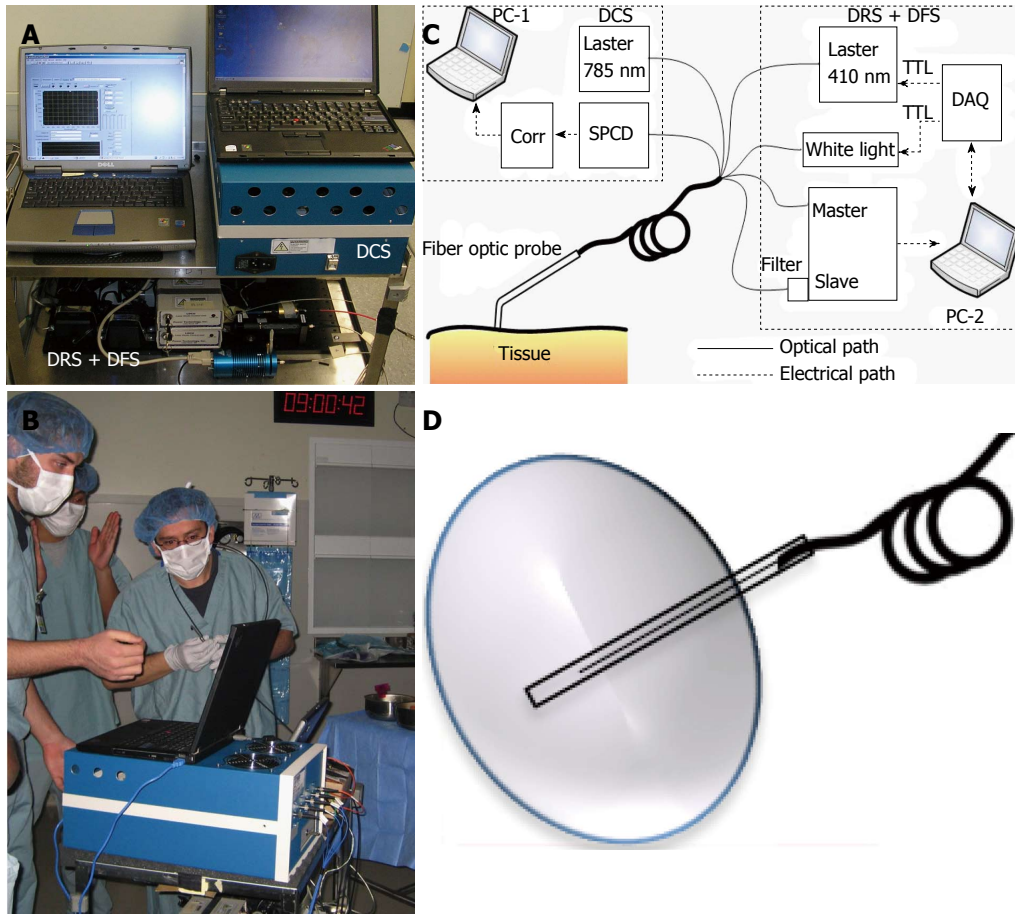


Figure 2 Clinical multi-modal optical instrument for photodynamic therapy dosimetry and response monitoring. A: Picture of multi-modal clinical optical instrument; B: During the measurements at the operating room; C: Diagram of multi-modal clinical optical instrument; D: Interstitial optical probe for measurements in deep and thick tumors. Adapted from the reference^[45] with the permission.

shows the picture and schematic diagram of the instrument, respectively. The DCS instrument has a 785 nm, long coherence length laser (Crysta Laser), four single photon-counting detectors (SPCD, Perkin-Elmer), and a custom-built autocorrelator board (Correlator.com). Photodetector outputs were fed into a correlator board and intensity autocorrelation functions and photon arrival times were recorded by a computer. After blood flow measurements, the second laptop initiates fluorescence (DFS) and reflectance (DRS) data acquisition by utilizing TTL switching via a data acquisition card (DAQ, National Instruments). In absorption (DRS) mode, broadband diffuse reflectance measurements were taken by exciting the tissue with tungsten halogen lamp (Ocean Optics) and collecting the light with the Master channel of a two-channel spectrometer (Ocean Optics). In fluorescence (DFS) mode, a 410 nm laser diode (Power Technology) excites the PS in Soret band and the slave channel of the spectrometer collects the fluorescence spectra.

A hand-held “surface” probe that holds the light source and detector fibers can be used for measuring superficial malignancies by directly placing the tip of the probe on the tissue surface (Figure 2C). Although the instrument stays the same, the hand-held surface probe is ill-suited for interstitial light delivery and noninvasive mea-

surements and the probe-tissue interface must be changed accordingly. For an “interstitial” probe, source and detector fibers are placed inside a catheter (Figure 2D).

Optical parameters and local light dose distribution by DRS

Currently the standard PDT light dosimetry at the clinics is based on the prescribed incident dose, which does not take into account reflected and scattered light in the lesion. Head and neck malignancies can exhibit a multifocal, wide-field nature of invasion and they may occur at diverse sites (*e.g.*, tongue, lip, palate, *etc.*). Therefore, they can have different optical parameters resulting in considerable inter- and intra-patient variations in the deposited local dose^[11]. It has been shown that the measured effective local dose can be more than 5-fold greater than the incident administered dose, illustrating the need for *in situ* dose monitoring on an individual basis^[39]. Dosimetry systems using isotropic light detectors to measure both incident and scattered light are becoming more available in clinical systems^[36,37]. Multi-channel systems that can measure light dose at multiple points of interest in real time can provide on-line feedback to clinicians during treatment planning.

Tissue absorption and tissue scattering parameters

modify light attenuation and thus affect the true light dose delivered to the whole three-dimensional tissue volume. Thus, direct light dose measurements may not be sufficient to quantify volumetric light distribution. Since malignancies can be highly heterogeneous, three dimensional optical parameter mapping can show heterogeneity of local light dose to the whole lesion volume. Several techniques are available for mapping of optical parameters (optical absorption and scattering) *in vivo*. Most of them are based on the photon diffusion equation with multi source-detector separations. Photon fluence (rate) is measured as a function of source-detector distance and measured data is fit to the diffusion model to extract optical parameters.

Local PS dose distribution by DFS and DRS

It has been demonstrated that PSs demonstrate significant inter- and intra-patient heterogeneity in distribution, leading to variations in the accumulated PDT dose and treatment failures^[36,74,75]. It has been also suggested that the variation of the treatment outcome can be reduced by adjusting the light dose based on the pretreatment PS distribution so that PDT dose is uniform in the whole disease^[36,75-78]. Although DRS can be used to quantify PS concentration by using the absorption peak of PSs, DFS is the preferred choice for this aim, since the fluorescence contrast is usually higher than the absorption contrast *in vivo*. However, fluorescence signal is affected by the tissue optical properties, and thus is not directly related to PS concentration. Ratiometric methods (with respect to optical attenuation and autofluorescence) may correct this signal distortion significantly^[79,80]. Moreover, short source-detector separation (or single source-detector) based optical probes and empirical calibration techniques that calibrate the system with respect to reference optical phantoms may allow quantification of drug concentration. For quantifying PS concentration using DFS data, background subtracted fluorescence signal is usually normalized with the reflectance data obtained by DRS^[65,66,70,81]. Fluorescence signal is assumed to be a linear combination of contributing components (*i.e.*, PS fluorescence, tissue autofluorescence, *etc.*). The normalized tissue fluorescence is fit to the modeled tissue fluorescence to extract PS concentration^[44,73].

Tissue response monitoring by DRS and DCS

Tissue oxygen is crucial for effective PDT^[36,82-84]. Tissue oxygen, in turn, is affected by vascular parameters such as blood oxygenation, blood volume and blood flow^[50,52]. Most PSs have significant vascular disrupting effects, and can create substantial vascular changes. All these parameters are inter-dependent to each other and can change continuously during PDT^[4,36]. Blood flow changes during PDT correlated strongly with tumor growth delay, and blood oxygenation and volume changes were correlated with PDT outcome^[50,52,85]. Moreover, PS photobleaching has been shown to be a surrogate marker of PDT response^[40,86-90]. Therefore, continuous monitoring of

these parameters could be useful for providing real-time treatment feedback, and may serve as quantitative *in vivo* markers for assessing treatment response^[4,36,63].

For quantifying vascular parameters such as blood oxygenation and blood volume, an analytic diffuse reflectance model can be utilized to fit the diffusion model to experimental diffuse reflectance data obtained by DRS. We assume tissue absorption is composed of a linear contribution from oxy-hemoglobin and deoxyhemoglobin in blood, and PS absorption. Blood volume is related to total hemoglobin concentration and is defined as the sum of oxy-hemoglobin and deoxy-hemoglobin concentrations, and blood oxygen saturation is defined as the ratio of oxy-hemoglobin concentration to total hemoglobin concentration. Tissue scattering is usually modeled as Mie type behavior that is related to scatterer size and concentration^[91]. A multi-wavelength fitting algorithm is usually used to directly extract the hemoglobin concentrations or blood oxygen saturation and blood volume^[63,92,93]. Blood oxygen saturation is related to tissue oxygen and hypoxia^[52,94] and blood volume is related to microvessel density^[95].

Tissue blood flow is measured using a previously described and validated DCS instrument, which measures rapid light intensity temporal fluctuations in tissue and then uses the autocorrelation functions associated with these fluctuations to extract information about the speed of moving tissue scatterers, in this case red blood cells^[44,49,96-101]. The decay rate of the autocorrelation function is related to blood flow^[99-101]. DCS is advantageous compared to conventional imaging modalities in that it measures directly blood cell movements and does not need any contrast agent administration and pharmacokinetic models to quantify blood flow.

A surrogate molecular marker for PDT efficacy

It is often desired to correlate noninvasive parameters with other techniques such as molecular biomarkers of a treatment response. We have shown previously in preclinical models and clinical biopsy samples that the cross-linking of the signal transducer and activator of transcription 3 (STAT3) correlates with the accumulated PDT dose and can be a quantitative biomarker of cellular killing^[102,103]. The crosslinking is identified by immunoblot analysis for STAT3 protein in the extracts from tumor tissue sections calculated as homodimeric complex I relative to total STAT3 signal^[102,103]. We compared our measured indices with the STAT3 crosslinking as showcased below.

A clinical case report

In our previous work we demonstrated the assessment of PDT response-related multi-parameters of blood flow, oxygenation, blood volume, PS concentration in the same clinical setting of Photoclor (HPPH)-mediated PDT in head and neck lesions in the oral cavity^[44]. We reported an interesting case where two patients had lesions treated with

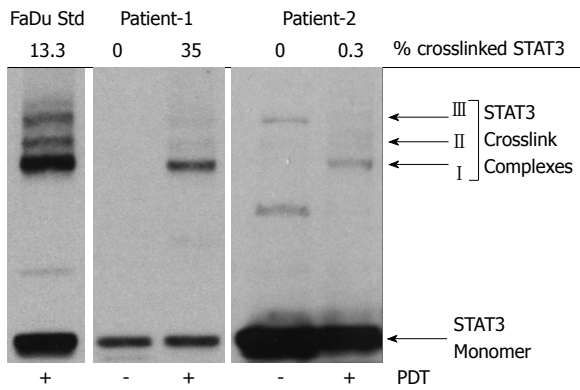


Figure 3 Signal transducer and activator of transcription 3 crosslinking as a molecular marker for local photodynamic therapy dose. Signal transducer and activator of transcription 3 (STAT3) crosslinking for Patient-1 and Patient-2 with a human hypopharyngeal carcinoma cell line (FaDu) shown as a control. Adapted from the reference^[74] with the permission. PDT: Photodynamic therapy.

the same administered PS dose (HPPH, 4.0 mg/m²) and a similar delivered light dose (approximately 125 J/cm²), but the accumulated local doses were more than 100-fold different as determined by the STAT3 crosslinking (Table 1). The first patient had a large CIS of the hard palate on the roof of the mouth and PDT induced photoreaction with 35% STAT3 crosslinking, and the second patient had high-grade dysplasia in a papilloma of the buccal mucosa with only 0.3% STAT3 crosslinking (Figure 3). We quantified local PDT-related parameters with diffuse optical methods to investigate whether this substantial difference could be detected noninvasively since these parameters can affect accumulated local dose.

As Table 1 summarizes, PDT-induced changes in the quantified optical parameters were significantly different between these lesions. Changes in PS concentration (Δ cHPPH), blood flow index (Δ BFI) and blood volume fraction (Δ BVf) were significantly higher in Patient-1 (P1) than in Patient-2 (P2), but the changes in blood oxygen saturation were similar for both patients, though the trend was different: P1 had an increase and P2 showed a decrease trend.

We further investigated whether this difference could be observed before therapy by quantifying pre-PDT contrasts (mean \pm SE) by noninvasive methods. All parameters except blood volume fraction were significantly different between the lesions (Table 2). The lesion of P1 had more favorable properties related to accumulated local PDT dose, since its PS content as well as blood flow, blood volume and blood oxygen saturation were higher than P2.

Our results indicated that parameters quantified with DOS at pre-PDT as well as PDT-induced changes may be indicative of local PDT reaction and may be *in vivo* predictors of PDT outcome. Since each parameter showed different contrast and therapy-induced changes, one parameter alone may not be a strong indicator of PDT response and multi-parameters assessed by optical methods may provide accurate measure of PDT response^[44].

Table 1 Photodynamic therapy-induced changes in photodynamic therapy-related parameters for two patients

	Lesion type	STAT3	Δ BFI	Δ BVf	Δ StO ₂	Δ cHPPH
P1	CIS	35%	83.4%	23%	+15.2%	51.8%
P2	Dysplasia	0.3%	59.2%	7.5%	-17%	38.6%

Changes in BFI was significant for both patients while changes in cHPPH were only significant for patient-1. Adapted from the reference^[74] with the permission. Δ represents changes in parameters. STAT3: Signal transducer and activator of transcription 3; cHPPH: photosensitizer concentration; BFI: Blood flow index; BVf: Blood volume fraction; StO₂: Saturation; P1: Patient-1; P2: Patient-2; CIS: Carcinoma *in situ*.

Table 2 Pretreatment contrasts in photodynamic therapy-related parameters between two patients (mean \pm SE)

	Lesion type	BFI (a.u.)	BVf (%)	StO ₂ (%)	cHPPH (μ mol/L)
P1	CIS	6.7 \pm 2.8	2.5 \pm 0.7	74 \pm 2	0.34 \pm 0.02
P2	Dysplasia	1.8 \pm 0.5	1.3 \pm 0.2	64 \pm 3	0.10 \pm 0.03

All parameters except blood volume fraction showed a significant difference between two patients. Adapted from the reference^[74] with the permission. cHPPH: photosensitizer concentration; BFI: Blood flow index; BVf: Blood volume fraction; StO₂: Saturation; P1: Patient-1; P2: Patient-2; CIS: Carcinoma *in situ*.

CONCLUSION

In summary, PDT is regarded as an emerging treatment option for the head and neck malignancies. PDT can be applied repetitively if the previous treatment fails. With the advent of newly developed PSs, specificity and penetration depth can be improved. The simplicity of the PDT treatment and reduced cost of technology such as light sources and light delivery devices can help wide usage at the clinical settings. Moreover, there is a need for standardization of clinical protocols by using the same light and drug types and doses. Novel optical methods can provide PDT-dose related parameters such as optical parameters and PS concentration in the whole lesion, as well as can quantify blood flow, oxygenation and PS photobleaching for assessing the PDT response and providing feedback to clinicians for optimization and standardization of PDT in clinics.

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Hepatitis C treatment with triple therapy in a patient with hemophilia A

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Telaprevir; Factor VIII inhibitor; Protease inhibitor

Core tip: This is a case of a patient who has Hemophilia A with factor VIII inhibitor and chronic hepatitis C. After successfully treating the patient's hepatitis C with protease-inhibitor based triple therapy and achieving response-guided therapy with negative hepatitis C virus RNA after week 4, the patient's need for recombinant factor VIII decreased significantly.

Singh G, Sass R, Alamiry R, Zein N, Alkhouri N. Hepatitis C treatment with triple therapy in a patient with hemophilia A. *World J Clin Cases* 2013; 1(3): 106-107 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i3/106.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i3.106>

Abstract

We report a case of successful treatment of chronic hepatitis C infection with telaprevir-based triple therapy in a patient with hemophilia A complicated by factor VIII inhibitor. A twenty-two years old male with hereditary hemophilia A and high-titer factor VIII inhibitor was taking maintenance doses of recombinant factor VIII. He visited our clinic for treatment of his chronic hepatitis C with the newly instituted protease inhibitor based therapy. He was diagnosed with hepatitis C genotype 1a at one year of age. He was initiated on telaprevir, ribavirin and peg-interferon for treatment of hepatitis C and qualified for response-guided therapy. He completed treatment at 24 wk with minimal adverse effects. Notably, after 4 wk of hepatitis C treatment, his factor VIII inhibitor screen was negative and the dose for recombinant factor VIII decreased by half of the initial dosing before he was treated for hepatitis C. We suspect that suppressing hepatitis C may help decrease factor VIII inhibitor level and the need for recombinant factor VIII.

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Key words: Hepatitis C virus; Hemophilia; Factor VIII;

INTRODUCTION

Chronic hepatitis C virus (HCV) infection has been a heavy burden to patients with hemophilia^[1]. Patients with hemophilia A frequently receive transfusion of factor VIII as part of their management which can lead to development of antibodies that can neutralize factor VIII^[2]. HCV infection by itself and its treatment with interferon can lead to the development of auto-antibodies including acquired factor VIII inhibitor^[3,4]. Therefore, treating HCV in hemophiliacs with factor VIII inhibitor remains challenging.

CASE REPORT

A 22-year-old male with a history significant for hereditary hemophilia A complicated by refractory high-titer factor VIII inhibitors and hepatitis C genotype 1a infection diagnosed at the age of 1 year was referred to our clinic regarding hepatitis C treatment. The patient has been treated with recombinant human factor VIII 6000 IU Bid to maintain his factor level at around 20%. He was also receiving rituximab (to help decrease his factor VIII auto-

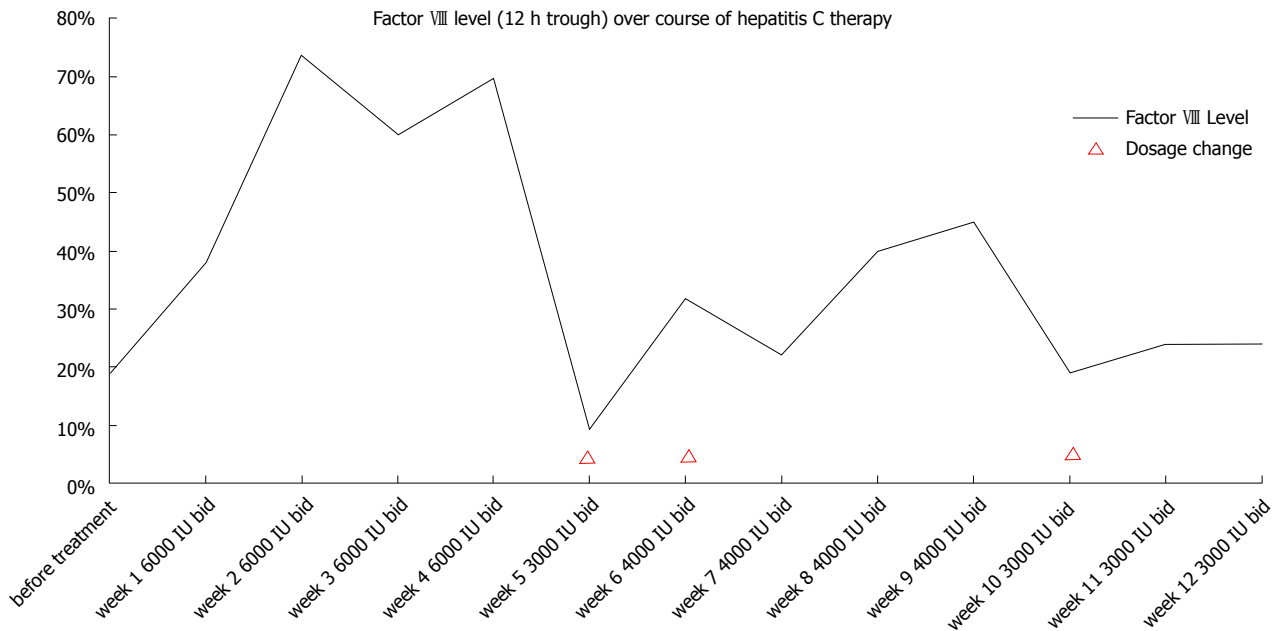


Figure 1 A graph demonstrating factor VIII levels and dosage while on telaprevir-based triple therapy.

antibodies) every 4–6 mo for 3 years. Liver biopsy was not performed prior to starting HCV treatment due to concerns about bleeding and the patient was HCV treatment naïve. Patient was started on hepatitis C telaprevir-based triple therapy (telaprevir 750 mg *tid*, weight based ribavirin, and peg-interferon alpha-2a) with good virologic response (HCV RNA was undetectable at treatment weeks 4, 12 and 24). He qualified for response-guided therapy and completed his treatment at 24 wk. He tolerated therapy relatively well without the need to dose reduce his ribavirin or peg-interferon alpha-2a. Interestingly, within a few days after starting telaprevir therapy his factor VIII level started to increase significantly and after four wk of hepatitis C treatment, his factor VIII inhibitor screen was negative and his need for recombinant factor VIII decreased by 50% as shown in Figure 1. His HCV RNA remained negative at 24 wk after he completed telaprevir-based therapy and the patient achieved a sustained virologic response.

DISCUSSION

To our knowledge, this is the first case report on using telaprevir-based triple therapy in a hemophilia patient with factor VIII inhibitor. Acquiring factor VIII inhibitor after HCV infection has been described in previous literature^[5]. In our patient, we speculate that the HCV infection itself was inducing production of a factor VIII

inhibitor. Consequently, the production of factor VIII inhibitor was suppressed once the virus was cleared with appropriate therapy. This case demonstrates that HCV therapy was safe and that suppressing HCV may help decrease factor VIII inhibitor level and the need for recombinant factor VIII. We hope that our report will encourage other practicing clinicians to treat this challenging patient population.

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Paradoxical embolus straddling patent foramen ovale demonstrated by computed tomographic pulmonary angiography

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Abstract

An elderly gentleman presented to the emergency department with a recent history of dyspnoea, collapse and transient neurological symptoms. He was noted to be hypoxic with a significantly elevated D Dimer. A computer tomography pulmonary angiogram demonstrated a large embolus with a further filling defects within the left and the right atria, abutting the interatrial septum. Suspicion of a paradoxical pulmonary embolus was raised and the patient subsequently underwent echocardiography which confirmed a patent foramen ovale (PFO). He was commenced on warfarin therapy. In patients with elevated right heart pressure, a PFO can be unmasked and give rise to cerebral emboli. Clinical suspicion should be raised in patients with pulmonary emboli or deep venous thrombosis if there is a concomitant history of focal neurological symptoms.

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Key words: Pulmonary embolus; Paradoxical embolus; Computer tomography pulmonary angiogram; Patent

foramen ovale; Stroke

Core tip: Patent foramen ovale (PFO) are common but usually closed and asymptomatic due to the greater pressure in the left heart. They however pose a particular risk for patients with large pulmonary emboli (PE) where they can open providing a right to left shunt when the right heart pressure rises due to pulmonary arterial obstruction by PE. In these circumstances thrombus can transit the PFO paradoxically embolising systemically. We report a case of a patient with a large PE who had a cerebral embolus where thrombus is imaged straddling the PFO at computer tomography pulmonary angiography.

Cormack L, Murchison JT. Paradoxical embolus straddling patent foramen ovale demonstrated by computed tomographic pulmonary angiography. *World J Clin Cases* 2013; 1(3): 108-110 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i3/108.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i3.108>

INTRODUCTION

Patent foramen ovale (PFO) is estimated to be present in approximately 27% of the population^[1]. Under normal physiological conditions where left-sided heart pressure exceeds right-sided pressure, the foramen remains closed. However, in circumstances where right-sided pressure is elevated, for example in pregnancy, cor pulmonale or in the presence of pulmonary thromboembolic disease, the foramen can be opened which may result in paradoxical emboli entering the left-heart and systemic circulation. The presence of thrombo-embolic disease and a PFO thus increases the risk of stroke.

This case highlights the value of computer tomography (CT) pulmonary angiogram, for example when

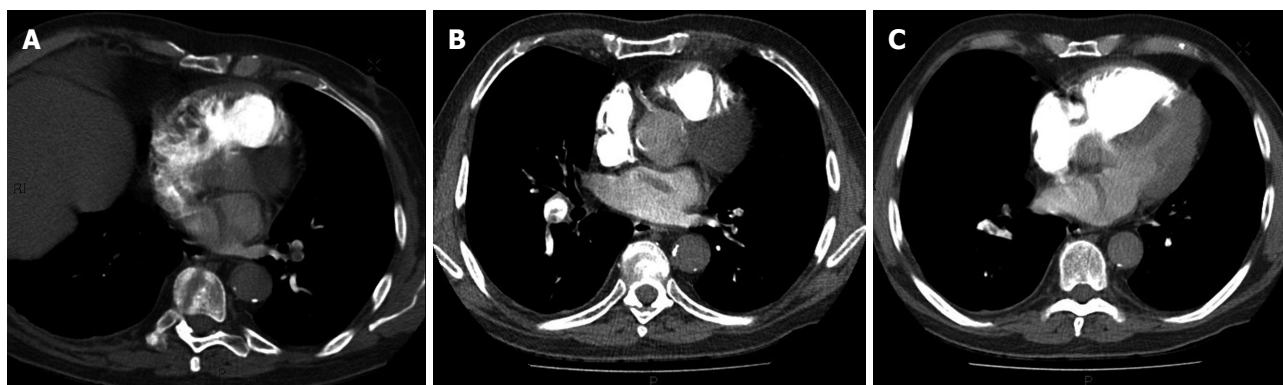


Figure 1 Findings at computed tomographic pulmonary angiography. A: Computer tomography pulmonary angiogram (CTPA) demonstrating a serpiginous low attenuation filling defect in the left atrium which extends across into the right atrium through a patent foramen ovale representing a paradoxical embolus (oblique axial view). There are also filling defects in the left lower lobe pulmonary artery due to pulmonary emboli; B: Demonstrating a filling defect in the left atrium filling defects in the right lower lobe pulmonary artery due to pulmonary emboli (axial view); C: CTPA demonstrating a filling defect in the left atrium, abutting the intra-atrial septum and bowing of the intra-ventricular septum due to raised right heart pressure (axial view).

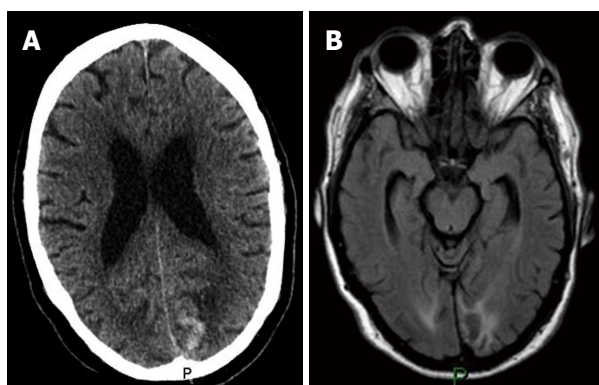


Figure 2 Neurological imaging. A: Unenhanced computer tomography brain examination (axial view) demonstrating left occipital high attenuation with surrounding low attenuation; B: Magnetic resonance imaging brain examination (axial view, FLAIR sequence) demonstrating left occipital lobe infarct with haemorrhagic transformation.

compared to perfusion scanning, in assessing right heart strain as a result of pulmonary embolus, in addition to the possibility of detecting paradoxical embolus when present.

CASE REPORT

Case presentation

An 80-year-old gentleman with history of type 2 diabetes, chronic renal impairment and hypertension presented to the emergency department with marked dyspnoea, dizziness and collapse but without loss of consciousness. There were no features to suggest underlying infection. He also described transient left-sided paraesthesia and weakness, which had largely resolved by the time he was assessed. He was noted to be hypoxic and tachycardic with a markedly raised D Dimer (34704 µg/L). CT pulmonary angiography was requested which confirmed the presence of large pulmonary emboli, but also a further filling defects within the left and right atria (see investi-

gations below). Bubble contrast echocardiography confirmed the presence of a PFO.

Investigations

CT pulmonary angiogram: Large bilateral pulmonary artery emboli with a further serpiginous filling defect visible within the left atrium, abutting the inter-atrial septum and extending into the left atrium. Appearances represent a paradoxical embolus caught in a PFO (Figure 1).

Unenhanced CT brain examination (performed the day after computed tomographic pulmonary angiography): High attenuation within the medial aspect of the left occipital lobe, in keeping with acute haemorrhage due to haemorrhagic transformation of an infarct/embolic infarct (Figure 2A).

Magnetic resonance imaging brain examination, without contrast: Performed 19 d after CT brain examination to rule out multiple emboli to the brain in order to help decide whether to surgically close the PFO. This showed bilateral occipital increased FLAIR signal with restricted diffusion in keeping with infarction. High T1 signal in the left occipital lobe consistent with a degree of haemorrhagic transformation (Figure 2B).

Echocardiography: With bubble contrast, confirmed the presence of a PFO.

Treatment

The patient was commenced on warfarin therapy to treat pulmonary embolus. He was not considered for surgical closure of the PFO.

Outcome and follow-up

The patient made a good recovery initially. A follow-up CT brain performed because of a fall and head injury sustained at home eighteen months following initial presentation did not show any further ischaemic events.

DISCUSSION

Previous case reports of paradoxical pulmonary emboli have been able to demonstrate thrombus within a patent septal defect on echocardiography^[2,3], however this finding has not been previously reported on CT pulmonary angiography. Further cases have shown a PFO only (without thrombus)^[4], or have failed to demonstrate the source of the right-to-left shunt^[5].

CT pulmonary angiography is the gold standard for detecting acute pulmonary embolus^[6]. It has a high sensitivity (83%-100%) and specificity (89%-97%)^[7,8]. An additional advantage of computed tomographic pulmonary angiography is the assessment of right ventricular/left ventricular (RV/LV) ratio as an indicator of severity in acute pulmonary embolism. Transverse RV/LV diameter ratio has been shown to be significantly higher in patients who die in hospital than amongst those who survive acute pulmonary embolus^[9].

Visualisation of thrombus within the atria or ventricles is an unusual finding which should prompt further investigation of a septal defect and right-to-left shunt. Whilst the clinical history alone in this particular case may have been sufficient to provoke investigation of a PFO, the finding of thrombus within the left atrium made the presence of a PFO almost certain and may therefore have expedited echocardiography and neuro-imaging.

According to National Institute for Clinical Excellence guidelines, the optimal treatment of patients with a PFO who have had a thromboembolic event remains undefined^[10]. Medical management with antiplatelet or anticoagulation therapy is frequently used to reduce the risk of further paradoxical thrombi. Closure of the PFO may be performed in patients who have further embolic events despite medical management, or in cases where anticoagulant therapy is contraindicated. Percutaneous procedures allow closure of the PFO without the need for major surgery. In this case the presence of acute haemorrhage, presumed to be haemorrhagic transformation of an embolic infarct, further complicated management, however the decision was made that it was in the patient's best interest to proceed with anticoagulation.

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Syringomyelia associated with cervical spondylosis: A rare condition

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Abstract

Spinal spondylosis is an extremely common condition that has only rarely been described as a cause of syringomyelia. We describe a case of syringomyelia associated with cervical spondylosis admitted at our division and treated by our institute. It is the case of a 66-year-old woman. At our observation she was affected by moderate-severe spastic tetraparesis. T2-weighted magnetic resonance imaging (MRI) showed an hyperintense signal within spinal cord from C3 to T1 with a more sharply defined process in the inferior cervical spinal cord. At the same level bulging discs, facets and ligamenta flava hypertrophy determined a compression towards subarachnoid space and spinal cord. Spinal cord compression was more evident in hyperextension rather than flexion. A 4-level laminectomy and subsequent posterior stabilization with intra-articular screws was executed. At 3-mo follow up there was a regression of tetraparesis but motor deficits of the lower limbs residuated. At the same follow up postoperative MRI was executed. It suggested enlargement of the

syrinx. Perhaps hyperintensity within spinal cord appeared "bounded" from C3 to C7 with clearer margins. At the level of surgical decompression, subarachnoid space and spinal cord enlargement were also evident. A review of the literature was executed using PubMed database. The objective of the research was to find an etiopathological theory able to relate syringomyelia with cervical spondylosis. Only 6 articles have been found. At the origin of syringomyelia the mechanisms of compression and instability are proposed. Perhaps other studies assert the importance of subarachnoid space regard cerebrospinal fluid (CSF) dynamic. We postulate that cervical spine instability may be the cause of multiple microtrauma towards spinal cord and consequently may damage spinal cord parenchyma generating myelomalacia and consequently syrinx. Otherwise the hemorrhage within spinal cord central canal can cause an obstruction of CSF outflow, finally generating the syrinx. On the other hand in cervical spondylosis the stenotic elements can affect subarachnoid space. These elements rubbing towards spinal cord during movements of the neck can generate arachnoiditis, subarachnoid hemorrhages and arachnoid adhesions. Analyzing the literature these "complications" of cervical spondylosis are described at the origin of syringomyelia. So surgical decompression, enlarging medullary canal prevents rubbings and contacts between the bone-ligament structures of the spine towards spinal cord and subarachnoid space therefore syringomyelia. Perhaps stabilization is also necessary to prevent instability of the cervical spine at the base of central cord syndrome or syringomyelia. Finally although patients affected by central cord syndrome are usually managed conservatively we advocate, also for them, surgical treatment in cases affected by advanced state of the symptoms and MRI.

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Key words: Syringomyelia; Cervical spondylosis; Syringomyelia surgery; Syringomyelia etiology; Syringomy-

elia physiopathology

Core tip: Our study assume that central cord syndrome can result in syringomyelia. We postulate that cervical spine instability may be the cause of myelomalacia and consequently syrinx. In cervical spondylosis with related central cord syndrome or syringomyelia we underline the importance of surgical decompression and stabilization. Surgical decompression prevents “complications of cervical spondylosis” at the base of syringomyelia. Stabilization is also necessary to prevent instability of the cervical spine at the base of central cord syndrome or syringomyelia. Finally we propose the surgical treatment also for patients affected by central cord syndrome showing advanced state of the symptoms and magnetic resonance imaging.

Landi A, Nigro L, Marotta N, Mancarella C, Donnarumma P, Delfini R. Syringomyelia associated with cervical spondylosis: A rare condition. *World J Clin Cases* 2013; 1(3): 111-115 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i3/111.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i3.111>

INTRODUCTION

Syringomyelia (Gr. Syrinx = tunnel) is a disease characterized by the presence of a cystic tubular cavity within the spinal cord, containing fluid that might be either cerebrospinal fluid (CSF) or indistinguishable from it. It is a very complex disorder with multiple etiologies and a variety of proposed mechanisms of cyst formation. No single theory will cover all instances^[1]. It may develop by various factors. It is most commonly associated with complex hindbrain malformations, such as Chiari malformations, encephalocele and Dandy-Walker cysts. Other causes include postmeningitic and posthemorrhagic hydrocephalus, basilar invagination, spinal arachnoiditis, extramedullary compressions, tethered cord, acquired tonsillar herniation, intramedullary spinal tumours. Acute traumatic cervical spinal stenosis due to fracture or acute severe disc prolapse may result in secondary syrinx formation. Spinal spondylosis is an extremely common condition that has only rarely been described as a cause of syringomyelia^[2-5]. We analyzed the pertinent literature trying to show a possible etiopathogenetic mechanism.

CASE REPORT

We describe a case of syringomyelia associated with cervical spondylosis admitted at our division and treated by our institute. Moreover a review of the literature was executed using PubMed database. Objective of the research was to find an etiopathological theory able to relate syringomyelia with cervical spondylosis. We included only case reports about syringomyelia associated with cervical spondylosis. The simultaneous presence of another etiopathological factor at the origin of syringomyelia was

Table 1 Review of the literature

Author	Age (yr) and sex	Spondylosis level	Proposed mechanism
Kaar <i>et al</i> ^[2]	71, F	C3-C4	Instability of the spine
Kimura <i>et al</i> ^[3]	64, F	C4-C5, C6-C7	Intermittent spinal cord compression
Rebai <i>et al</i> ^[5]	70, M	Not specified	A purely extradural decompression could be sufficient to induce regression of the medullary cavitation.
Lucci <i>et al</i> ^[6]	56, M	C4	The bony prominence produces ischemia and thus causes the degeneration of ascending and descending nervous fibers
Butteriss <i>et al</i> ^[7]	70, M	C5-C6	Improvement of related symptoms after decompressive surgery
Kameyama <i>et al</i> ^[8]	59, M	C3-C4 at C6-C7	The symptoms of the upper limbs improved after immobilization of the neck

The table exposes case reports about syringomyelia associated with cervical spondylosis reported in literature. Author, age and sex of the patient, spondylosis level and the proposed mechanism at the base of syringomyelia are mentioned. F: Female; M: Male.

considered an exclusion criterion.

Only 6 articles have been found (Table 1). Lucci *et al*^[6] reported 3 cases in their work. In all of them a relation between neurogenic osteoarthropathies of the upper limbs and intramedullary cavity at spinal computed tomography scan is described but only the third one denotes a relation between “essential” syringomyelia and cervical spondylosis. Lucci admits at the origin of syringomyelia the bony prominence that probably produces ischemia and thus causes the degeneration of the ascending and descending nervous fibers. Kimura *et al*^[3] present the case of a 64-year-old woman. Dynamic magnetic resonance imaging (MRI) revealed instability at C4-C5, spondylosis at C5-C6 and the syrinx extended from C2 to T3 level. It was reduced remarkably after anterior decompression and stabilization. Towards Kimura syringomyelia was caused by intermittent spinal cord compression. Butteriss *et al*^[7] report a case of a 70-year-old man with severe degenerative changes at C5/C6 with a large right paracentral disc-osteophyte complex. An unexpected cord syrinx was noted extending from C6/C7 inferiorly to T6. The patient declined decompressive surgery. Butteriss advocates surgery directed towards relieving the compressive lesion, rather than primary drainage of the syrinx. Kaar *et al*^[2] describe a case of cervical spondylotic myelopathy with instability at C3/C4 and cervicothoracic syrinx at MR imaging. In Kaar’s article the decompression and stabilization, without drainage of the syrinx were considered adequate surgical treatment. Rebai *et al*^[5] describe a case of a 70-year-old patient whose brain and cervical MRI showed syringomyelobulbia with cervical spondylotic myelopathy. Rebai *et al*^[5] proposes a decompressive surgery since extensive cervical laminectomy induced mild clinical improvement and furthermore a second MRI performed

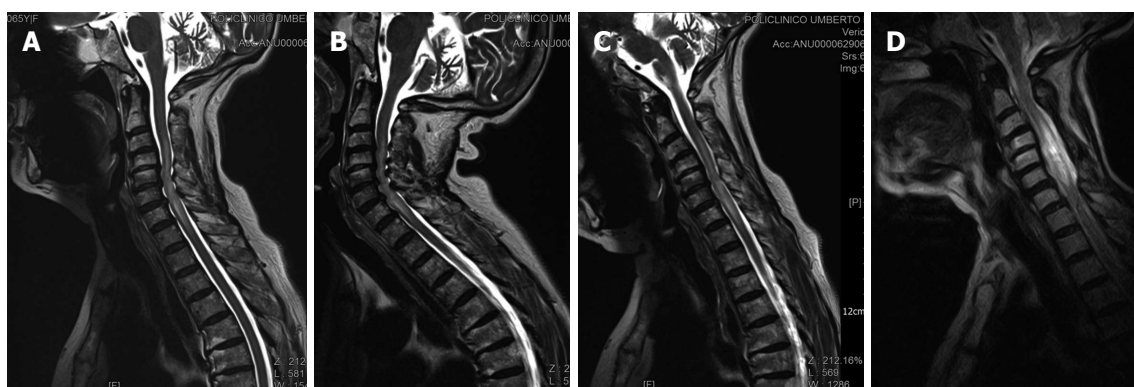


Figure 1 Preoperative magnetic resonance imaging. A: T2-weighted magnetic resonance imaging revealed hyperintensity of the central spinal cord extended from C3 to T1 without clear borders. In the inferior cervical spinal cord hyperintensity appeared more evident suggesting syrinx; B and C: At the same level cervical spinal cord compression was determined by bulging discs, facets and ligamenta flava hypertrophy, more evident in hyperextension (B) rather than flexion (C); D: It revealed enlargement of the syrinx, but decreased longitudinal extension of “central cord syndrome” bounded from C3-C4 to C7 with clearer borders. At the level of surgical decompression also spinal cord and subarachnoid space appeared expanded.

6 mo after surgery depicted a complete disappearance of the bulbo-medullar cavitation with secondary atrophy. Kameyama *et al*^[8] presents the case of a 59-year-old man with spondylosis at multiple levels from C3/C4 to C6/C7, and an intramedullary high signal intensity area from the level of C1 to C3/C4.

We report the case of a 66-year-old woman, whose presenting symptoms were gait disturbances and loss of balance. These disorders appeared about 9 mo before our observation. At our observation she was affected by moderate-severe spastic tetraparesis. Cervical dynamic-MRI was executed. T2-weighted MRI showed an hyperintense signal within spinal cord from C3 to T1. This process in the central cord resembled “central cord syndrome” with a more sharply defined process in the inferior cervical spinal cord that suggested syrinx (Figure 1). In hyperextension (Figure 1B) bulging discs were evident at the levels C3-C4, C4-C5, C5-C6, C6-C7 and C7-D1. At the same level facets and ligamenta flava hypertrophy determined a compression towards subarachnoid space and spinal cord. Spinal cord compression is more evident in hyperextension rather than flexion. We decided to undergo the patient at the surgical treatment. A 4-level laminectomy and subsequent posterior stabilization with intra-articular screws was executed. In the early post-operative days the patient underwent neuromotor rehabilitation and slight improvement of tetraparesis was evident. At 3-mo follow up there was regression of tetraparesis but motor deficits of the lower limbs residuated. At the same follow up postoperative MRI was executed. It (Figure 1D) suggested enlargement of the syrinx. Perhaps “central cord syndrome” appeared “bounded” from C3 to C7. At the level of surgical decompression, subarachnoid space and spinal cord enlargement were also evident.

DISCUSSION

Already in the 1950's some authors found a relationship between these two pathological entities. Stern *et al*^[9] recognized that cervical spondylosis can present sensory and

motor symptoms quite similar to the syringomyelic ones. Brain *et al*^[10] found radiographic lesions of the cervical spine in about 50% of the syringomyelic cases identical to those noted in spondylosis. The possible coexistence of the two diseases was claimed by Smith^[11] too. The results of the literature review revealed that compressive mechanism is the major theory at the origin of syringomyelia associated with cervical spondylosis. Al-Mefty *et al*^[12] proposed that compression causes cystic necrosis (myelomalacia). In a second period as the myelomalacia progresses, the necrotic tissue is phagocytized leaving a secondary cavity (syrinx) within the atrophied spinal cord. Also Uchida *et al*^[13] conducting a study on a twy/twy mouse, a unique animal that develops spontaneous spinal cord compression without any other reported genetic difference in the anatomy or physiology of the spinal cord, showed that spinal cord mechanical compression is characterized by the loss and exfoliation of anterior horn neurons with progressive spongy degeneration and demyelination in the white matter. Perhaps the extent of demyelination and Wallerian degeneration in the white matter increases proportionately with the magnitude of spinal cord compression. On the other hand, most of the apoptotic cells observed were oligodendrocyte. Though insignificant if compared to acute spinal cord injury, the longitudinally diffuse and extensive pattern of oligodendrocyte apoptosis in twy/twy mouse may be similar to the secondary damage process observed after acute trauma. In Levine's study at the origin of syringomyelia is described a subarachnoid obstruction. It may result in increasing CSF pressure above the block, compared with below generating a transmural hydrostatic effect with the collapse of vessels within the subarachnoid space above the block, and their dilatation below it. This mechanical stress on the cord parenchyma causes disruption of the blood-brain barrier, which in concert with raised intravascular pressure results in ultrafiltration of crystalloids and accumulation of fluid^[14]. Goel^[15] state that the fluid may dissect along planes of weakness within the cord resulting in the pathological appearance of a syrinx. It has been postulated that the development

of high fluid pressure and syrinx formation within the cord may act to counteract the local effect of the primary compressive lesion and as such may be a protective phenomenon. Several authors^[16-21] observing syringomyelia in spinal arachnoiditis, stated that intramedullary cystic degeneration is caused by ischemia due to circulatory disturbance in the subarachnoid space. Also the blockage of CSF pathways around the spinal cord, contribute to formation of cystic cavities^[22]. It is often believed that in syringomyelia with spinal arachnoiditis the CSF enters transmurally into the syrinx from the blocked subarachnoid space^[23].

Brierley^[24] first demonstrated movement of CSF tracers from the subarachnoid space into the spinal cord perivascular spaces. Then Rennels *et al*^[25], Wagner *et al*^[26] and Borison *et al*^[27] have shown that horseradish peroxidase injected into the subarachnoid space rapidly labels the perivascular spaces of the brain and spinal cord. Rennels *et al*^[25] proposed that a "paravascular" fluid circulation exists in the nervous system, with an active flow of CSF from the subarachnoid space into the perivascular spaces around arterioles and continuing through the basal lamina around capillaries. Without direct evidence, they suggested that fluid return to the basal lamina around venules or into the perivascular space of emerging veins. Milhorat *et al*^[4,28,29] and Cifuentes *et al*^[30] demonstrated that fluid is capable of moving from the spinal cord interstitial space into the central canal. Milhorat *et al*^[4,28] suggested that this mechanism constitutes the "lymphatic" function of the spinal cord. Cho *et al*^[31] reported that injection of kaolin solution into the spinal subarachnoid space enhanced the extension of intramedullary cavitations in a rabbit model of posttraumatic syringomyelia. Josephson *et al*^[32] demonstrated spinal cord edema and intramedullary cyst formation after spinal thecal sac constriction in rats. Klekamp *et al*^[33] produced an interstitial type of edema in the spinal cord by placement of a kaolin-soaked fibrin sponge on the posterior surface of the cat spinal cord at C1 to C2. Kimura *et al*^[3] reported about a patient affected by pain in the right arm, MRI showed instability at C4-C5 and compression of the spinal cord since a central spinal cord hyperintensity was evident in hyperextension. All these characteristics can be found in "central cord syndrome". He admitted that the longstanding static and dynamic intermittent compression of the spinal cord caused by C4 instability produce disorders of CSF dynamics in the spinal subarachnoid space and associated pooling of an abnormal amount of CSF in the spinal cord parenchyma. Perhaps the sloshing effect of the pulsatile CSF pressure, could make the cavity extend into a rostral and ventral direction. Also Kaar *et al*^[2] described a case of central cord syndrome since the patient was affected by dissociated sensory loss in the left upper limb, instability at C3-C4 on plains radiographs and T2-weighted MRI showing forward-bulging ligamenta flava and hyperintensity of the central spinal cord in T2-weighted MRI. He attributed the origin of the syrinx to cervical spine instability. Our case presents a more sharply defined process in the inferior cervical spinal cord. We postulate that cervical spine

instability may be the cause of multiple microtrauma towards spinal cord and consequently may damage spinal cord parenchyma generating myelomalacia and consequently the syrinx. Another possible theory may supports the hemorrhage within spinal cord central canal as the cause of CSF outflow obstruction, finally generating the syrinx. On the other hand we can assert the importance of subarachnoid space regard CSF dynamic. Several studies show that syringomyelia may be caused by tethered cord, arachnoiditis, arachnoid adhesions or subarachnoid hemorrhages. In cervical spondylosis the stenotic elements can affect this space. Rubbing towards spinal cord during movements of the neck can generate these "complications". On the other hand cervical spondylosis can generate a block of CSF hydrodynamic within subarachnoid space determining a vascular occlusion of the vessels above the block and consequently a spinal cord ischemic injury. Perhaps cervical spondylosis can directly damage spinal parenchyma like acute spinal trauma. This damage may be proportionally related to the grade of stenosis. So surgical decompression, enlarging medullary canal prevents rubbings and contacts between the bone-ligament structures of the spine towards spinal cord and subarachnoid space.

In conclusion, we can assert that syringomyelia is so rarely associated with cervical spondylosis because there are many compensating mechanisms (arterial, venous, CSF ones), like that of "lymphatic" circulation, so mild and intermittent compression like that found in cervical spondylosis hardly can be associated with syringomyelia unless there are other associated conditions like arachnoid adhesions, post-traumatic arachnoiditis, subarachnoid hemorrhages, Chiari malformations that determine an alteration towards the subarachnoid space. On the other hand, cervical spine instability can generate central cord syndrome or syringomyelia. Although patients affected by central cord syndrome are usually managed conservatively we advocate, also for them, surgical treatment in cases affected by advanced state of the symptoms and MRI.

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Trans-sacral screw fixation in the treatment of high dysplastic developmental spondylolisthesis

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Key words: High-dysplastic developmental spondylolisthesis; Spondylolisthesis; Trans-sacral screw; Pelvic balance; Spinopelvic imbalance

Core tip: The choice of treatment in L5-S1 ontogenetic spondylolisthesis is related to a correct clinical and diagnostic planning (X-ray, computer tomography, magnetic resonance imaging, measurement). In particular, the severity index and the square of unstable zone, and the standard measurements already described in the literature, are important to understand and to plane the correct surgical strategy, that require, in most of the times, fusion and interbody arthrodesis.

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Abstract

We describe the case of a 67-year-old woman with L5-S1 ontogenetic spondylolisthesis treated with pedicle fixation associated with interbody arthrodesis performed with S1-L5 trans-sacral screwing according to the technique of Bartolozzi. The procedure was followed by a wide decompressive laminectomy. The patient had a progressive improvement of the symptoms which gradually disappeared in 12 mo. The radiograph at 6 and 12 mo showed complete fusion system. The choice of treatment in L5-S1 ontogenetic spondylolisthesis is related to a correct clinical and diagnostic planning (X-ray, computer tomography magnetic resonance imaging, Measurement). In particular, the severity index and the square of unstable zone, and the standard measurements already described in the literature, are important to understand and to plane the correct surgical strategy, that require, in most of the times, fusion and interbody arthrodesis.

INTRODUCTION

Marchetti and Bartolozzi's classification^[1,2] is the most complete one regarding the prognosis and treatment of ontogenetic spondylolisthesis, including the description of the high or low dysplastic forms. Unfortunately, however, does not provide specific criteria to differentiate these two subgroups. In particular, it is accepted that the treatment of choice for both high-dysplastic developmental spondylolisthesis (HDDS) is surgical procedure, but it is unclear which is the best surgical strategy. A correct preoperative planning based on meticulous radiological examinations is crucial for the choice of the correct surgical treatment to be undertaken which is, when possible, a stabilization with interbody fusion.



Figure 1 Seriated radiological exams showing the progression of the spondylolisthesis from grade I in 1963, to grade III in 2010.

CASE REPORT

We describe the case of a 67-year-old woman with L5-S1 ontogenetic spondylolisthesis known since 30 years before. The patients complained recurrence of 15-d lumbar back pain episodes that improved after medical therapy. She referred difficulty in walking and in the upright position because of the presence of low back pain and right sciatica from 2 years. The patient brought seriated radiological examinations. The first one performed 30 years earlier showing a progression of the spondylolisthesis that from Meyerding grade I currently has become Meyerding grade III, with development of an important sacral dysmorphism giving a profile of an high dysplastic spondylolisthesis HDDS (Figure 1). Neurologically the patient presents a sacral kyphosis attitude, semi flexion of knees and hips in an upright position to compensate the pelvic imbalance, moderate weakness to the right lower limb at the dorsal flexion of the foot, sensitive disturbances in L5 territory to the right lower limb, neurogenic claudication at 100 m. According to the literature it was performed an orthostatic X-ray to visualizes the femoral heads and to calculate the dysplasia indexes in order to plan a correct surgical strategy. We have calculated: slip percentage (63%), the sacro-lumbar indexes (lumbar index 45%, pelvic incidence 86.2°, sagittal pelvic tilt index 0.52), the pelvic nutation indexes (sacral slope 39.9°, pelvic tilt 40.6°, sacral inclination 45°) and the sacro-lumbar ratio (77.3° slip angle, sacral kyphosis angle 25.8°). In relation to the measurements, the diagnosis of HDDS was confirmed

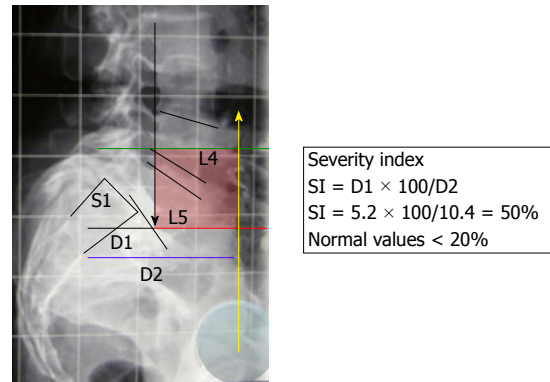


Figure 2 Analysis of the severity index and of the square of unstable zone. It's described by Lamartina^[14]. SI: Severity index.

Table 1 Measurements and indexes performed for the operative planning

Test		Our case	NR
Slipping		63%	
Sacro lumbar indexes	Lumbar index	45%	> 50%
	Pelvic incidence	86.2°	50°-60°
	Sagittal pelvic tilt index	0.52	> 0.70
Pelvic nutation indexes	Sacral slope	39.9°	32°-49°
	Pelvic tilt	40.6°	7.2°-7.9°
	Sacral inclination	45°	
Sacro-lumbar ratio	Slip angle	77.3°	
	Sacral kyphosis angle	25.8°	

(Table 1). The surgical planning requested the evaluation of the severity index and of the square of unstable zone (Figure 2)^[3,4]. All the indexes suggested us the indication for L4-L5-S1 fusion and L5-S1 interbody fusion to be executed with an anterior support. It was decided to proceed with pedicle screw fixation associated with interbody fusion performed with S1-L5 trans-sacral screwing according to the Bartolozzi's technique^[1,2]. The procedure was followed by a wide decompressive laminectomy (Figure 3). The patient had a progressive improvement of the symptoms which gradually disappeared in 12 mo. The radiograph at 6 and 12 mo showed a complete bone fusion (Figure 4).

DISCUSSION

The HDDS (Meyerding grade III° and IV°), caused by isthmus lysis, are characterized by a specific aspect, the pelvic retroversion, which generates an L5 dimorphism with trapezoidal shape and a consequent S1 dysplasia and round shape of the sacral promontory. The combination of these deformities causes L5-S1 kyphosis and increases the incidence of the slipping of L5 on S1. Such deformities cause alteration of the posture of the subject; in particular the pelvic retroversion causes a compensatory flexion of the hips and knees, in an attempt to realign the sagittal balance, and the lumbosacral kyphosis causes compensatory hyperlordosis of the adjacent lumbar segment. This process cause a considerable torsional force

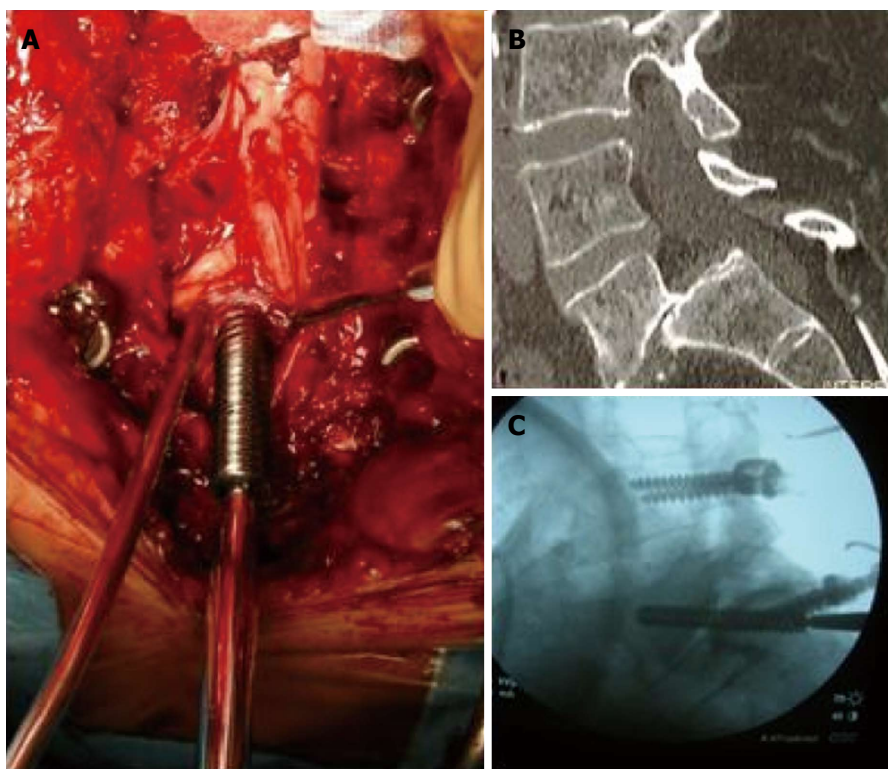


Figure 3 Intraoperative picture that showed the insertion of the trans sacral screw.

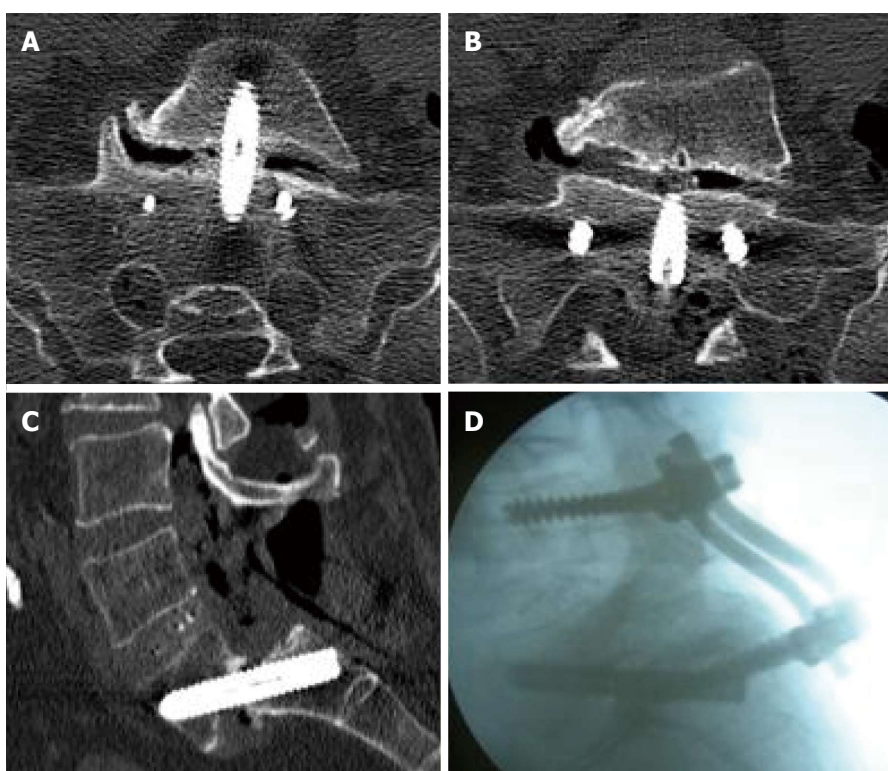


Figure 4 Computer tomography scan at 12 mo follow-up that showed the correct positioning and fusion of the system.

on the pelvis burdened by the L5-S1 disc orientation, which tends to be perpendicularly to the ground, in relation to the sacral inclination. This type of biomechanical

alterations affects significantly the sagittal balance, generating shear forces that allows the vertebral body to slide ventrally causing a framework of spondyloptosis^[5-11]. In

such cases, treatment of choice is surgical, and should be aimed to correct the sagittal loading, to decompress the interested tract and to fuse the mobile segment. In particular high dysplastic forms need anterior support before fusion in order to ensure a longer stability, since the only posterolateral or posterior interbody fusion (PLIF, TLIF) do not contract enough the foreword slipping of L5 on S1^[1,10,12-14]. Pelvic indexes and severity index evaluation allow us to identify which HDDS have such shear forces that do not permit a L5-S1 short fixation, so that has to be involved L4 too. The extension to L4 vertebral body is essential in order to reduce the cutting forces and to avoid the breaking the system^[3,4].

Low-grade HDDS (Meyerding I and II) are treated *via* posterior approach with interbody fusion (PLIF, TLIF), or when this is not executable, with PLF, providing good results in terms of long term fusion. From a technical point of view, the interbody fusion with anterior approach is the key point for the choice of treatment; the technique of choice for anterior interbody fusion is certainly the ALIF, performed with retroperitoneal anterior approach^[11]. The advantages of this approach are: the direct visualization of the L5-S1 disc, the possibility of insertion of the cage very anteriorly favoring arthrodesis, and the possibility of releasing the disc, increasing the mobility of L5 to S1 and favoring the maneuvers of reduction of the lysis that will be performed *via* posterior approach. The risks associated with the anterior approach are: peritoneal perforation, visceral lesions (ureters, bladder, intestines, *etc.*), vascular lesions (arteries and iliac veins), lesions of the hypogastric plexus (vaginal dryness in women and retrograde ejaculation in men) and the morbidity linked to the autologous bone graft donor site. In addition, the lack of familiarity to this approach puts the spinal surgeon in the position of having to have a general surgeon or a vascular surgeon to perform anterior approach. In the light of this, we decided to perform anterior arthrodesis with trans-sacral screw fixation described by Bartolozzi *et al.*^[1,2]. In our opinion, this technique has some advantages over ALIF. First of all, the risks related to the anterior approach and to the bone donor site morbidity are eliminated. The insertion of the screw is possible with the same surgical exposure of the *via* posterior approach, exposing the L5-S1 disc, the S1 back wall and the S1 lower limiting; this is achieved with a simple laminectomy. The exposure of the screw entry point is obtained by a slight pull of the dural sac medially, without any risk of neurological damage. Furthermore, as described in the literature, the possibility to insert two screws, one on the right site and one on the left site, reduces the manipulation on the dural sac. The inclination of the screw has to be almost perpendicular to the operating table, so there are no particular needs of inclination of the instrumentation. The screw are auto tapping and can be filled within autologous bone, allowing a good interbody fusion that offers excellent fusion. From a biomechanical point of view, the angle assumed by the screw respect the stabilization system, pointing

from the bottom upwards, provides adequate support to L5 that in this way counteracts the forces of sliding downward arresting the progression of the slipping out of the HDDS. The choice of treatment in L5-S1 ontogenetic spondylolisthesis is related to a correct clinical and diagnostic planning (X-ray, computer tomography, magnetic resonance imaging, measurement). In particular, the severity index and the square of unstable zone, and the standard measurements already described in the literature, are important to understand and to plane the correct surgical strategy that require, in most of the times, stabilization and interbody fusion. The choice of the technique depends on the surgeon and on the grade of fusion he wants to obtain: PLIF < TLIF < ALIF^[11,12,14]. HDDS require anterior support (ALIF or trans-sacral fusion) since posterior fusion in long term stabilization have an high risk of failure. The choice to extend the fusion at L4-L5 cannot be left to chance, but has be carefully planned on the basis of the preoperative exams (square of unstable zone), since in cases where it is necessary, its contribution to the stability of the system is essential.

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Lymph node non-Hodgkin's lymphoma incidentally discovered during a nephrectomy for renal cell carcinoma

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INTRODUCTION

The association between kidney cancer and lymph node lymphoma is infrequent. The biggest series reported with the two coexisting tumors included no more than twenty patients^[1,2]. Nevertheless, many authors have studied this relationship and suggest that it might be a statistical statement rather than sporadic.

We report a case of a nephroureterectomy for a renal mass incidentally discovered by imaging techniques. One of the lymph nodes of the renal hilum was diagnosed as non-Hodgkin's lymphoma B type. With the patient being asymptomatic, chemotherapy was not started and extension studies were requested.

We review the medical literature about the relationship between kidney cancer and non-Hodgkin's lymphoma.

CASE REPORT

We report a 64-year-old man with the incidental ultrasound discovery of a left kidney mass in the context of image studies for elevated blood pressure.

Medical history included ankylosing spondylitis with no other pathologies. Blood analysis showed low platelets with the rest of parameters within normal limits. One of the three urine cytologies showed urothelial atypia.

Abdominal computed tomography (CT) was requested and revealed a solid mass at the lower pole of the left kidney, in touch with the lower calyceal group, and with contrast enhancement, a permeable renal vein and one

Abstract

We report the case of a left laparoscopic nephroureterectomy with the incidental discovery of a non-Hodgkin's lymphoma in one of the lymph nodes of the renal hilum. A laparoscopic nephroureterectomy was decided on for a 64-year-old man. Renal cell carcinoma in the kidney and one lymph node of the renal hilum with non-Hodgkin's lymphoma was found. Chemotherapy was not started for the lymphoma discovery. There are no signs of relapse after two years of follow up. Coexistence in the same patient is an extremely rare condition. We review the literature about this issue to clarify this association.

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Key words: Renal cell carcinoma; Lymphoma; Nephrectomy

Core tip: This is a case of a nephroureterectomy for a renal mass incidentally discovered by imaging techniques. One of the lymph nodes of the renal hilum was diagnosed as non-Hodgkin's lymphoma B type, the patient being asymptomatic at that moment. Chemotherapy was not started and extension studies were requested.



Figure 1 Abdominal contrast enhanced tomography with left kidney mass.



Figure 2 Yellow kidney tumor in touch with rose node, located at hilum, 4 cm in diameter.

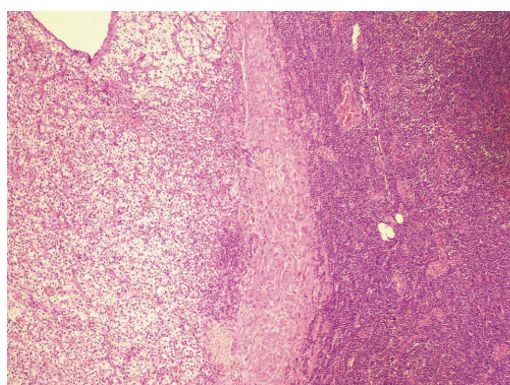


Figure 3 A microscopic view of the tumors. In the left, renal conventional clear cell carcinoma. In the right, a lymph node with small B cell lymphoma.

hilum adenopathy (Figure 1).

Exploration of the ureter with an ureterorenoscopy was performed to exclude ureteral lesions.

After discussion about the case with the contrast enhanced computed tomographic images, we performed a left laparoscopic nephrectomy and ureterectomy. We argued that the laparoscopic nephroureterectomy would not add more morbidity post surgery and it would give us information about the complete upper left urinary system (Figure 2).

The pathology report described a renal clear cell carcinoma, 3.8 cm in diameter and II Fuhrman cell grade. Additionally, lymphoid spreading was reported at one of the lymph nodes of the left renal hilum with pathology stage pT1N0. These findings and the immunochemistry studies (which were positive for CD20, bcl-2 and bcl-6 and negative for CD10) were in concordance with follicular non-Hodgkin's lymphoma B type and cell grade 2, with extension out of the node capsule and peripheral fat (Figure 3).

The post operative course was uneventful and the patient was discharged on the fifth day.

The patient was followed up by urology and hematology. Extension studies were requested and a neck-thorax-abdominal CT showed no special radiological findings.

Bone marrow biopsy was negative for lymph proliferative disease. Chemotherapy was not started and after two years of follow up, the patient is asymptomatic with no imaging signs of relapse in the control studies that were requested.

DISCUSSION

The American Cancer Society has reported that one of five Americans will develop cancer in their lifetime. For those patients who develop a tumor, the chance of developing a second tumor during their lifetime is one in three^[1].

Renal cell carcinoma (RCC) and non-Hodgkin's lymphoma are relatively common neoplasms that have dramatically different natural histories and management strategies. These neoplasms are considered curable in the early stages but the ability to treat the advanced disease is much more limited in renal cell carcinoma^[3].

Second malignancies reported to be associated with renal cell carcinoma include bladder^[4], prostate, rectum^[5], lung^[6], non-Hodgkin's lymphoma and melanoma. In general, 27.4% of the cases were related previously, 44.5% were synchronous and 39.2% were subsequent. Rabbani *et al*^[7] reported the specific association between non-Hodgkin's lymphoma and RCC from the whole sample of patients with RCC (763 patients) with a second primary malignancy (209 patients). They described 19 cases of non-Hodgkin's lymphoma, 8 as an antecedent, 8 synchronous and 3 metachronous^[7].

Many authors have reported the association between non-Hodgkin's lymphoma and kidney cancer but there are contradictory results^[8]. However, in one of the biggest series with patients affected by the two kinds of tumors (1425 patients), the standardized incidence of ratios (SIR) were used to estimate the risk of later primary cancer in patients diagnosed with renal cancer, calculated as the ratio of observed numbers (ONo) and expected numbers (ENo) of cases. The SIR for a second primary cancer in patients with RCC was significantly higher for bladder cancer, melanoma and non-Hodgkin's lymphoma. Addi-

tionally, non-Hodgkin's lymphoma was reported to occur with a much stronger rate after renal transplantation^[9].

In 1996, Tihan *et al*^[2] studied the coexistence of RCC and lymphoma, with 1252 renal cancer patients and 1660 non-Hodgkin's lymphoma patients reported. Two neoplasms coexisted in 15 patients, 11 females and 4 males. The average age was 62 years. The clinical presentation of patients with coexisting RCC and non-Hodgkin's lymphoma showed three patterns. In the most common pattern, patients developed lymphoma and staging work up revealed a low grade renal cancer. The second pattern was a renal mass and incidental diagnosis of low grade lymphoma located at the retroperitoneum or spleen. In the third pattern, there were 9 years between the occurrence of renal neoplasm and lymphoma. Most of the renal masses were managed by nephrectomy and the lymphoma with chemotherapy. Complete remission was reported in 50% of cases. Consequently, there was a statistical association and the possible etiology could be immune deficiencies or genetic/familial predisposition^[2].

In conclusion, we report the case of a patient that, after an intervention for a kidney tumor, a follicular non-Hodgkin's lymphoma was discovered in one of the lymph nodes of the renal hilum. The coexistence of RCC and non-Hodgkin's lymphoma is infrequent. However, many reports have investigated if this association is sporadic or statistical. In spite of the existence of papers in both directions, the most important studies with a significant number of patients suggest that the relationship between these two neoplasms is stronger than other kinds of tumors.

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Colonic lipoma covered by hyperplastic epithelium: Case report

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Abstract

Colonic lipomas are submucosal nonepithelial tumors covered by intact or eroded mucosa. In rare cases, alterations in the mucosa covering a lipoma include hyperplasia, adenoma, atrophy, ulceration, and necrosis. Here, we report a case of a colonic lipoma covered by hyperplastic epithelium in a 68-year-old woman. Based on the colonoscopy findings, a snare polypectomy was performed for a presumptive diagnosis of an epithelial lesion; however, the histological examination revealed a colonic submucosal lipoma with overlying hyperplastic epithelium.

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Key words: Lipoma; Colonic lipomas; Hyperplastic; Colonoscopy

Core tip: we report a rare case of a colonic lipoma with

overlying hyperplastic epithelium. Removing an asymptomatic colonic lipoma is not necessary, as it may have no clinical significance. However, treatment plans for colonic lipomas might be reconsidered as transformation of the mucosa lining of a lipoma could occur in small and asymptomatic lesions.

Yeom JO, Kim SY, Jang EC, Yu JY, Chang ED, Cho YS. Colonic lipoma covered by hyperplastic epithelium: Case report. *World J Clin Cases* 2013; 1(3): 124-127 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i3/124.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i3.124>

INTRODUCTION

Lipomas are generally rare, but are the most common nonepithelial benign tumors of the gastrointestinal tract. Colonic lipomas are uncommon mesenchymal neoplasms, with a reported incidence of 0.2%-4.4%^[1]. Colonic lipomas are usually asymptomatic and detected incidentally at colonoscopy, radiological investigation, surgery, or autopsy. The most common colonoscopic finding is a smooth, slightly yellow, spherical polyp, that is usually sessile and rarely pedunculated, with intact overlying mucosa^[2]. In rare cases, the mucosa covering a lipoma shows alterations such as hyperplasia^[3,4], atrophy^[5], adenomatous changes^[6,7], and necrosis and/or ulcerations^[8-10]. We herein report a case of colonic lipoma covered with hyperplastic epithelium in a 68-year-old woman and review the literature pertaining to this condition.

CASE REPORT

A 68-year-old woman with abdominal discomfort for several weeks was referred to our department by a private internist for further investigation of a 9 mm polyp in the ascending colon that was revealed during a barium enema for the evaluation of symptom. She denied constipation,

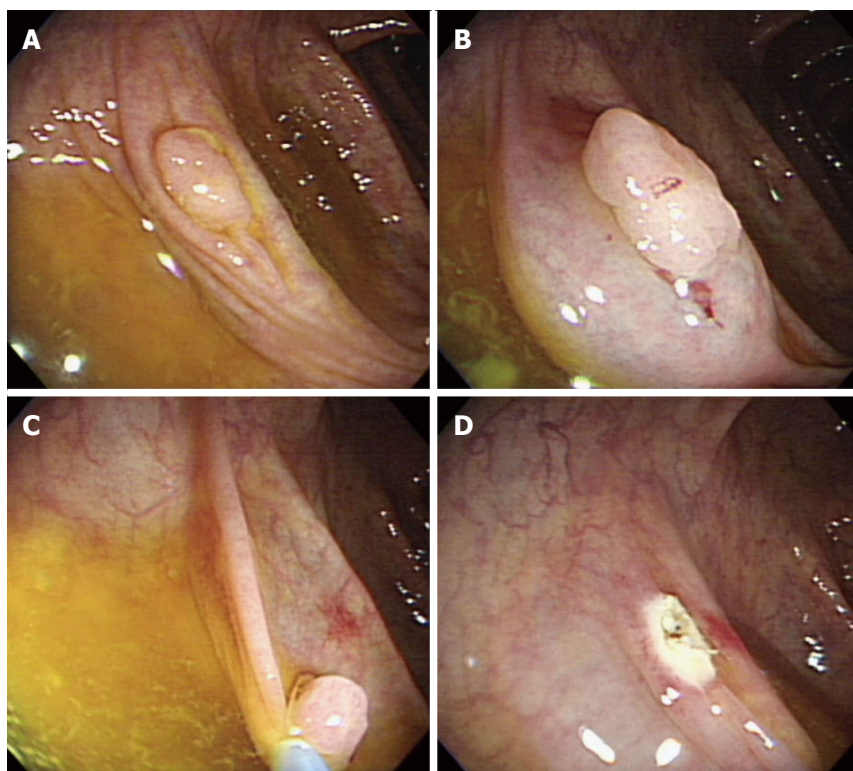


Figure 1 Colonoscopy showing a sessile polyp located in the ascending colon (A), after saline was injected (B), endoscopic mucosal resection was performed (C and D).

diarrhea, hematochezia, or melena. Her physical examination and medical history were unremarkable. All laboratory examinations, including complete peripheral blood cell counts, blood biochemistry, and carcinoembryonic antigen levels were within normal ranges. Colonoscopy revealed a sessile polyp about 9 mm in diameter in the ascending colon (Figure 1). We resected the polyp using an endoscopic mucosal resection (EMR) after a saline solution injection. No procedural-related complications were observed. A histopathological examination revealed a tumor composed of adipose tissue covered by hyperplastic and serrated epithelium consisting of columnar and goblet cells (Figure 2). The patient has been followed closely and has shown no recurrence. A follow-up colonoscopy revealed no remarkable findings 6 mo after the EMR.

DISCUSSION

Colonic lipomas are benign, slow growing tumors of mesenchymal origin that rarely cause symptoms and are usually detected incidentally^[1,11]. The most common sites of colonic lipomas are the cecum, ascending colon, and sigmoid colon, in decreasing frequency. These benign tumors arise from the submucosal layer in approximately 90% of cases and from the subserosal or intermucosal layer in the remaining cases^[2]. Pathologically, lipomas are composed of well-circumscribed, mature adipose tissue with varying amounts of fibrous stroma covered with intact colonic mucosa^[1,2,11].

Diagnostic tools for colonic lipomas include colonos-

copy, computed tomography, barium enema, and endoscopic ultrasonography. Among these, colonoscopy allows direct visualization of a colonic lipoma. Lipomas are seen as smooth, slightly yellow, rounded polyps with a thick stalk or broad-based attachment^[2]. Characteristic features include the “tenting sign” (grasping the overlying mucosa), the “pillow sign” (pressing forceps against the lesion results in depression or pillowing of the mass), and the “naked fat sign” (extrusion of yellowish fat after biopsy)^[1,2,11]. The current case did not show these three characteristic features of a lipoma but the morphology of an epithelial lesion such as hyperplastic polyp or sessile serrated adenoma. The resected specimen was a submucosal lipoma and the covering epithelium was hyperplastic, resembling a hyperplastic polyp. The epithelium was serrated and comprised of both columnar and goblet cells, but lacking atypia or mitotic activity. To the best of our knowledge the association of lipoma and hyperplastic polyp has been reported only once. Radhi *et al*^[3] showed a large lipoma in the sigmoid colon with overlying hyperplastic epithelium that was detected during an operation in a patient with diverticulitis. It was unclear whether the co-occurrence of these entities was coincidental or correlated. Hyperplastic polyps have been considered non-neoplastic lesions without malignant potential for many years. However, recent studies have shown that some hyperplastic polyps possess molecular features similar to those of colorectal carcinomas^[12,13]. Several subtypes of serrated polyps, such as sessile serrated adenomas, traditional serrated adenomas, and mixed polyps, have been proposed to be colorectal

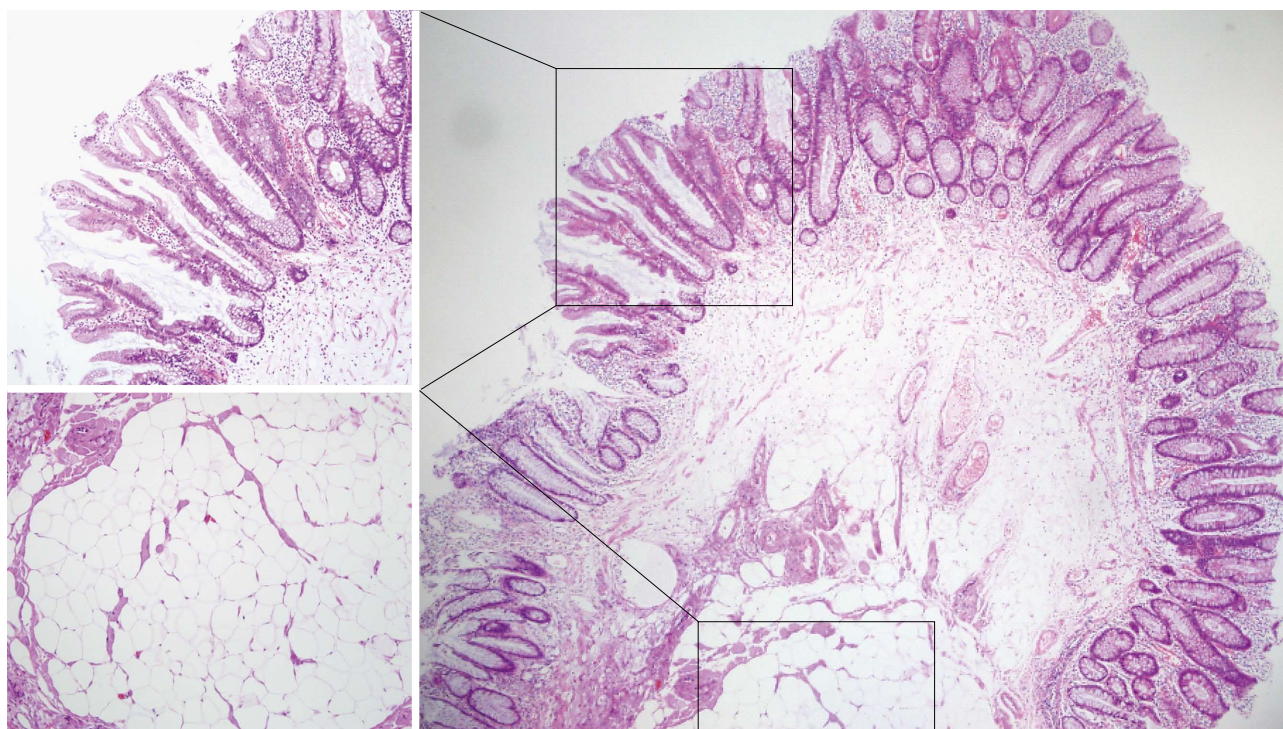


Figure 2 Microscopic image of the resected specimen showing a colonic lipoma with overlying hyperplastic epithelium in the low-magnified image (hematoxylin-eosin, $\times 40$). The lining epithelium resembles a hyperplastic polyp and a tumor composed of adipose tissue in the high-magnified image (hematoxylin-eosin, $\times 100$).

carcinoma precursors. In addition to hyperplastic changes of the epithelium lining in a lipoma, rare cases of adenomatous transformation have been reported^[6,7]. It is speculated that chronic trauma due to the passage of stools may lead to hyperplasia and adenomatous transformation of overlying mucosa^[7]. In rare cases, the colonoscopy may reveal ulcerations, a finding that may lead to a mistaken diagnosis of adenocarcinoma^[8-10].

Although most lipomas require no treatment, a small subgroup requires surgical intervention, including those with suspected malignancy, symptomatic lipomas, surgical emergencies such as intussusception, and obstruction with ulceration and bleeding^[1,2,11]. Colonic lipomas < 2 cm can be safely removed endoscopically, whereas larger lesions should be removed by segmental resection^[1,2,14]. In the present case, the polyp was initially suspected as a small epithelial lesion based on the colonoscopic findings and was resected endoscopically.

In conclusion, we report a rare case of a colonic lipoma with overlying hyperplastic epithelium. Removing an asymptomatic colonic lipoma is not necessary, as it may have no clinical significance. However, treatment plans for colonic lipomas might be reconsidered as transformation of the mucosa lining of a lipoma could occur in small and asymptomatic lesions.

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Peripheral cemento-ossifying fibroma: A case report with review of literature

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Abstract

Peripheral cemento-ossifying fibroma (PCOF) is a rare osteogenic neoplasm that ordinarily presents as an epulis-like growth. This is of a reactive rather than neoplastic nature and its pathogenesis is uncertain. PCOF predominantly affects adolescent and young adults with greatest prevalence around 28 years. We report here a rare clinical case of PCOF of the mandible, 1 cm mesio-distally and 1.5 cm occluso-gingivally in diameter, which caused difficulty in eating and speech, in a 42-year-old female patient. She was asymptomatic for 1 year and on follow-up for 6 mo post surgically showed gingival health and normal radiopacity of bone without any recurrence. Clinical, radiographic and histological characteristics are discussed and recommendations regarding differential diagnosis, treatment and follow up are provided. The controversial varied nomenclature and

possible etiopathogenesis of PCOF are emphasized.

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Key words: Peripheral cemento-ossifying fibroma; Gingivectomy; Granuloma

Core tip: The cemento-ossifying fibroma is a central neoplasm of bone as well as periodontium. The pathogenesis of this tumor is uncertain. Due to their clinical and histopathological similarities, some peripheral cemento ossifying fibromas (PCOFs) are believed to show fibrous maturation and subsequent calcification. The diagnosis of PCOF based only on clinical observation is difficult, hence radiographs and histopathological examination are essential for accurate diagnosis. In addition, a complete excision of the lesion is required to prevent recurrence.

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INTRODUCTION

Many types of localized reactive lesions may occur on the gingiva, including focal fibrous hyperplasia, pyogenic granuloma, peripheral giant cell granuloma and peripheral-cemento-ossifying fibroma^[1]. These lesions may arise as a result of irritants such as trauma, microorganisms, plaque, calculus, dental restorations and dental appliances^[2,3]

The 1992 World Health Organization classification groups under a single designation (cemento-ossifying fibroma) two histologic types (cementifying fibroma and ossifying fibroma) that may be clinically and radiographically indistinguishable^[4].

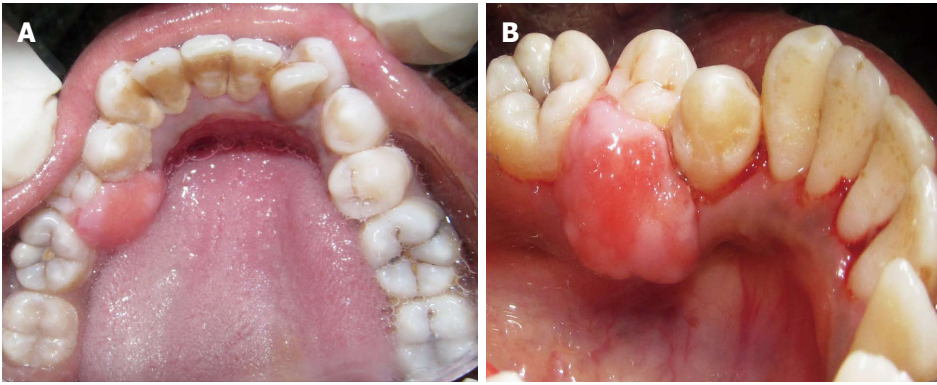


Figure 1 Lingual view of the lesion with smooth non-ulcerated surface and broad attachment base. A: The lesion with smooth non-ulcerated surface; B: Broad attachment base.

Peripheral cemento-ossifying fibroma (PCOF) is a relatively rare lesion with variable forms. It is defined as a well demarcated and occasionally encapsulated lesion consisting of fibrous tissue which contains variable amounts of mineralized material resembling bone (ossifying fibroma), cementum (cementifying fibroma) or both^[5,6].

PCOF usually follows a salient clinical course, except in the case of lesions affecting gingiva which present as an enlarging mass that grows progressively, finally producing a facial deformity. The pathogenesis of this lesion is uncertain and it is thought to arise from the periosteal and periodontal membrane^[7]. Because of the close proximity and similarity to the periodontal tissue, the term periodontoma sometimes is applied^[8]. There is however no proof to support this connection and their occurrence in areas distant from periodontal ligament remains unexplained^[9].

PCOF accounts for 3.1% of all oral tumors and 9.6% of gingival lesions^[10]. It may occur at any age but exhibits a peak incidence between the second and third decades. The average age is around 28 years with females being affected more than males^[11]. Female predilection has been reported to be as high as 5:112^[12,13]. Clinically PCOFs are sessile or pedunculated, usually ulcerated and erythematous or exhibit a color similar to that of surrounding gingiva^[14,15]. These lesions are generally < 2 cm in size although lesions larger than 10 cm are occasionally observed. About 60% of the tumors occur in the maxilla and more than 50% of all cases affect the region of the incisors and canines. A potential for tooth migration due to the presence of PCOF has been reported^[15-17]. In the vast majority of cases, there is no apparent underlying bone involvement visible on roentgenograms. However on rare occasions, there appears to be superficial erosion of bone^[16,17].

PCOF should be surgically excised and submitted to microscopic examination for confirmation of diagnosis. The extraction of adjacent teeth is seldom necessary or justified. Recurrences are uncommon but have been described^[2]. There have, however, been few reports on this rare lesion. A case of PCOF in the mandibular gingiva of a 42-year-old female patient is described here. In this age

group and in the mandibular anterior quadrant, PCOF is rare and has not previously been reported in the literature.

CASE REPORT

A 42-year-old female patient presented at the outpatient Department of Periodontics, Sri Aurobindo Institute of Dentistry and Post Graduate Institute Indore, Madhya Pradesh, India with the chief complaint of gum swelling in the lower right back tooth region (Figure 1). The swelling had been present for 1 year and had been slowly increasing in volume over that time. Occasionally bleeding occurred when the patient brushed her teeth and was associated with slight pain. She denied tobacco and alcohol use. The patient's past dental and medical histories were unremarkable.

Clinical examination

Extraoral examination showed facial symmetry and the overlying skin showed no signs of inflammation. The regional lymph nodes were palpable but were not enlarged or tender.

Intraoral examination revealed a solitary, diffuse, non-tender pinkish-red growth of approximately 1 cm × 1.5 cm, confined to the lingual gingiva in the mandibular II premolar region. The lesion was neither fluctuant nor did it blanch with digital pressure, and had firm consistency. The labial gingiva was not involved. The local irritants, plaque and calculus were abundant in the 44, 45 region.

Radiographic examination

Intraoral periapical, occlusal and ortho pantomo roentgenograms were obtained. The radiographic examination showed no signs of involvement of the alveolar ridge (Figure 2).

Blood investigations

The patient underwent complete blood investigation prior to the surgery and all readings, including hemoglobin, bleeding time, clotting time, total and differential leukocyte counts were within normal limits. The patient was negative for human immunodeficiency virus and

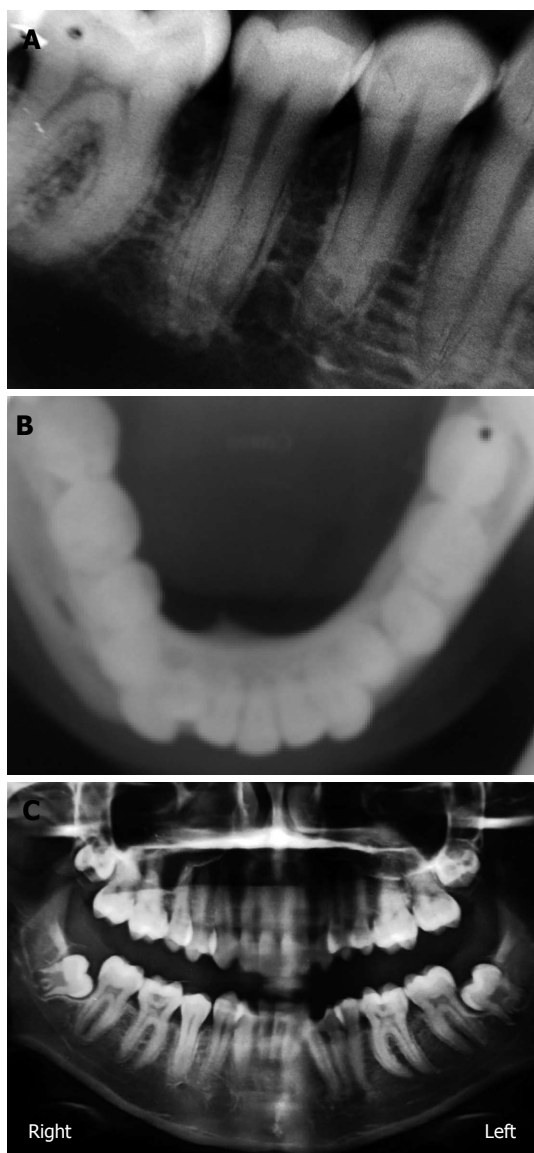


Figure 2 Non involvement of bone. A: Intra oral periapical radiograph; B: Maxillary occlusal radiograph; C: Ortho pantomo radiograph.

Australian antigen (hepatitis B surface antigen).

Diagnosis

Provisional diagnosis of PCOF was made. Clinically, the differential diagnosis included pyogenic granuloma, fibrous hyperplasia, peripheral ossifying fibroma and peripheral giant cell granuloma.

Treatment

Since the gingival growth was diffuse, surgical removal by internal bevel gingivectomy was chosen. Under local anaesthesia containing xylocaine with adrenaline 1:80000 concentration, the initial scalloped internal bevel incision was made with a 15 No. BP blade at a point far apical to the growth. While making this incision, care was taken to preserve as much attached gingiva as possible apical to the lesion. A second crevicular incision was made with a 12 No. BP blade at the base of the pseudopocket, until

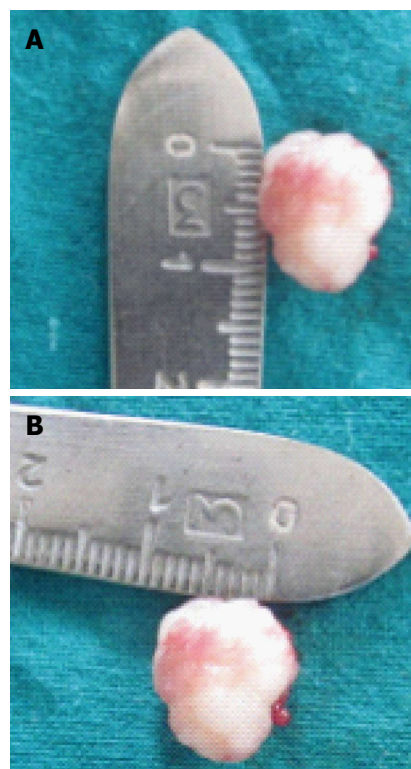


Figure 3 Excised tissue measuring 1.5 cm × 1 cm. A: Length 1.5 cm; B: Width 1 cm.

it met the first internal bevel incision. To split the labial and palatal, a third interdental incision was made with a 11 No. BP blade in the adjacent interproximal areas tissue. Only the lingual mucoperiosteal flap was reflected with periosteal elevators until the apical end of internal bevel incision was visible. The three incisions completely removed the gingival growth which measured 1 cm × 1.5 cm (Figure 3). The tissue removed was submitted for histopathological examination. Adjacent teeth were scaled to remove local irritants. Underlying bone was curetted to remove periodontal ligaments and periosteum. The flap was inspected for any tissue tags and sutured with interdental interrupted non-resorbable 3-0 silk sutures (Figure 4). Non-eugenol coe-pack was applied both lingually and labially. The patient was discharged with post-operative instructions and told to come-back after 7 d for suture removal. The patient was given cap. amoxicillin 500 mg every 8 h, beginning 1 d before the operation and continued for a 5-d postoperative period, and 500 mg of acetaminophen three times daily for 5 d along with 0.2% chlorhexidine gluconate for rinsing twice daily until proper plaque control technique could be resumed.

Microscopic examination

The microscopic examination of the excised tissue revealed a parakeratinized stratified squamous epithelium with long and slender rete ridges. Underlying connective tissue was fibrocellular, comprising collagen fibers. The connective tissue contained a few round to ovoid cementum-like calcified blood vessels, fibroblasts and dense in-



Figure 4 Interrupted sutures placed with 3-0 black braided silk.



Figure 6 Post operative photograph of surgical site showing satisfactory healing 30 d after surgery.

flammatory cell infiltrate. Deeper areas showed highly cellular connective tissue comprising plump cells with oval nuclei surrounding small globular areas of calcification, resembling cementoids. In some areas bone trabeculae with osteocytes and osteoblastic rimming was also seen. The features were suggestive of “PCOF” (Figure 5).

Follow-up

The patient presented for follow-up examination 7 d post operatively. The coe-pack and the sutures were removed and the operated area was irrigated with normal saline. The surgical site appeared to be healing well and there was no need to repack the site. At one month postoperatively the surgical site had healed completely, the flap was well adapted to the underlying bone with physiologically scalloped contours and thin knife-edge margins (Figure 6). There was no evidence of recurrence of the lesion at 6 mo and the patient was asymptomatic.

DISCUSSION

PCOFs have been described in the literature since the 1940s. Many names have been given to similar lesions such as epulis^[1], peripheral fibroma with calcifications^[2], peripheral ossifying fibroma^[2,3], calcifying fibroblastic granuloma^[18], peripheral cementifying fibroma^[3], peripheral fibroma with cementogenesis^[19], and peripheral cemento

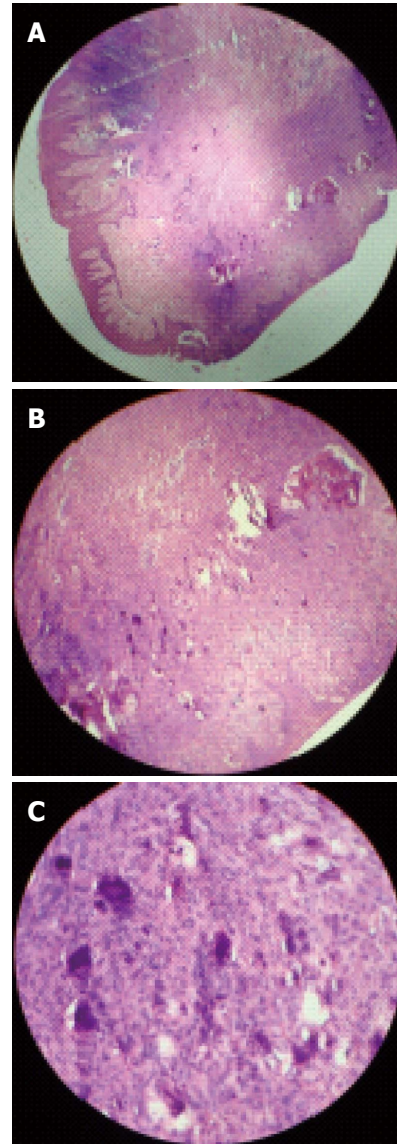


Figure 5 The features were suggestive of “peripheral cemento-ossifying fibroma”. A: Histological picture showing long slender rete ridges and parakeratinized stratified squamous epithelium; B: Round to ovoid basophilic cementum-like calcifications [hematoxylin-eosin (HE) staining, $\times 10$]; C: Basophilic globules of calcified mass along with osteoid tissue, round to ovoid basophilic cementum-like calcifications (HE staining, $\times 40$).

ossifying fibroma^[20]. The sheer number of names used for fibroblastic calcifying gingival lesions indicates that there is much controversy surrounding their classification^[19].

The basis of benign fibro-osseous lesions was established by Wladron^[5]. They are divided into three main categories: fibrous dysplasia, reactive lesions (periapical cemento-osseous dysplasia, focal cemento-osseous dysplasia and florid cemento-osseous dysplasia) and fibro-osseous neoplasms. PCOF is actually considered as a fibro-osseous dysplasia and has been included in the group of non odontogenic tumours since the 1992 WHO classification^[5,6].

Although the etiopathogenesis of PCOF is uncertain, an origin from cells of the periodontal ligament has been suggested^[20]. The reasons for considering a periodontal origin for PCOF include the exclusive occurrence of

PCOF in the gingiva, the proximity of gingiva to the periodontal ligament and the presence of oxytalan fibers within the mineralized matrix of same lesions^[19]. Excessive proliferation of mature fibrous connective tissue is a response to gingival injury, gingival irritation, subgingival calculus or a foreign body in the gingival sulcus. Chronic irritation of the periosteal and periodontal membrane causes metaplasia of the connective tissue and resultant irritation of bone formation or dystrophic calcification. It has been suggested that the lesion may be caused by fibrosis of the granulation tissue^[7]. The clinical evolution of tumors is usually as follows. Initially asymptomatic, the tumor progressively grows to the point where its size causes pain as well as functional alteration and cosmetic deformities^[11,6]. This was observed in our patient who presented with an enlarged mass accompanied by slight pain and cosmetic deformity. Cases of tooth migration and bone destruction have been reported, but these are not common^[15,21]. In the present case the lesion was pink, firm, slightly tender on palpation with a smooth non-ulcerated surface and a broad attachment base. The dimensions were 1 cm × 1.5 cm, well within the expected range. Although the majority of lesions occur in the second decade of life^[12], this female patient was 42-year-old with the lesion occurring in mandibular right premolar region^[11,14,22].

Hormonal influences may play a role, given the higher incidence of PCOF among females, the increasing occurrence in the second decade and declining incidence after the third decade^[16]. In an isolated case of multicentric PCOF, Kumar *et al*^[19] noted the presence of a lesion at an edentulous site in a 49-year-old women which gives rise to further questions regarding the pathogenesis of this types of lesion. The same type of lesion at a dentulous site in a 50-year-old female was documented by Mishra *et al*^[23].

Radiographically, PCOF may follow different patterns depending on the amount of mineralized tissue^[4-6]. Radio-opaque foci of calcification have been reported to be scattered throughout the central area of the lesion but not all lesions demonstrate radiographic calcifications^[7].

Underlying bone involvement is usually not visible on radiographs. In rare instances superficial erosion of bone is noted^[7]. In the present case no radiographic changes were found, indicating that this could be an early stage lesion. Frequently, PCOF shows similar clinical features to other extraosseous lesions. It may be misdiagnosed as pyogenic granuloma, fibrous dysplasia, peripheral giant cell granuloma, osteoid osteoma, osteoblastoma, low grade osteosarcoma, cementoblastoma, chronic osteomyelitis and sclerosing osteomyelitis of Garre^[4-6]. In general the pyogenic granuloma presents as a red soft friable nodule that bleeds with minimal manipulation but tooth displacement and resorption of alveolar bone are not observed. Although peripheral giant cell granuloma has features similar to those of PCOF, the latter lacks the blue discoloration commonly associated with peripheral giant cell granuloma and shows flakes of calcification, radiographically as well histologically. Thus, the diagnosis of PCOF based only on clinical observations can be dif-

ficult and histopathological examination of the surgical specimen obtained by excisional biopsy is essential for an accurate diagnosis. All the classic histopathological features of PCOF were present in this case. The preferred treatment is surgical, consisting of resection of the lesion as well as curettage of its osseous floor (Periodontal ligament and Periosteum) and scaling of adjacent teeth, as was performed in this case. Recovery was uneventful and the patient has remained tumor free for 24 wk. Because this lesion is poorly vascularized and well circumscribed, it is easily removed from the surrounding bone. This is one of the main differences with fibrous dysplasia^[5,6].

Prognosis is excellent and recurrence is rare if correctly managed^[4,5]. The recurrence rate of PCOF is high for reactive lesions^[11,16] and recurrence is probably due to incomplete removal of the lesion, repeated injury or persistence of local irritants^[16]. The rate of recurrence has been reported at 8.9%^[1], 9%^[21], 14%^[16], 16%^[11] and 20%^[2]. Therefore the patient is still on a regular schedule of follow up.

In conclusion, PCOF is a slowly progressive lesion generally with limited growth. Many cases will progress for long periods before the patient seeks treatment because of the lack of symptoms associated with the lesion. A slowly growing pink soft tissue nodule in the anterior maxilla of an adolescent should raise suspicion of PCOF. Since the diagnosis of PCOF based only on clinical features is very difficult, radiographs and histopathological examination are essential for accurate diagnosis.

Treatment consists of surgical excision including periodontal ligament periosteum and scaling of adjacent teeth. Close postoperative follow-up is required because of the growth potential for incompletely removed lesions and the 8%-20% recurrence rate.

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Elastic resistance of the spine: Why does motion preservation surgery almost fail?

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INTRODUCTION

In April 2009 and March 2011, two earthquakes in Abruzzo and Japan destroyed 65% of the buildings in reinforced concrete. In April 2011, the results of the Chi-Quadrato DIMS research project which evaluated the effects of high magnitude earthquakes on buildings built in wood was published. Wooden buildings proved to be those with the highest resistance to the mechanical movements of an earthquake owing to the physical properties of wood, elastic resistance to load-bearing and twisting. For this reason, in May 2011, 500 houses built in wood were delivered to the homeless Abruzzo population. The overall characteristics of the vertebral column are the same as those of wood, namely elastic resistance to movement, twisting potential and elastic resistance to load bearing. These aspects reflect the three main functional characteristics of the spine: motility in all 3 spatial planes, passive and active resistance to the axial load and elastic resistance to excessive degrees of movement. In the light of this, we can assert that motility at the level of a single metamere should not be interpreted merely as movement on the 3 planes but also, and above all, as elastic resistance to dynamic stress on these 3 planes. In fact, metameric movement depends on an active motility, involving the intervertebral disc, the articular masses and the muscular structures, and a passive motility, involving the disc, ligamentous system and articular capsules^[1-15]. In the light of this, the aim of motion preservation is to neutralize excessive movements while preserving the physiological biomechanical properties of the metamere involved in interrupting the progression of the degenerative process and to prevent adjacent segment disease (ASD). This procedure was firstly named "dynamic sta-

Abstract

Single metamere motility should not be interpreted merely as a movement on the 3 planes but also, and above all, as elastic resistance to dynamic stress on these 3 planes. In the light of this consideration, the aim of motion preservation is to neutralize excessive movements while preserving the physiological biomechanical properties of the metamere involved to interrupt the progression of degenerative processes and to prevent adjacent segment disease. Despite the fact that a myriad of devices have been developed with the purpose of achieving dynamic neutralization of the spine, there are now some doubts regarding the true efficacy of these devices.

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Key words: Elastic resistance; Disc prosthesis; Dynamic implant; Interspinous device; Biomechanics

Core tip: Elastic resistance of the spinal motor unit is a biomechanical property often underestimated but crucial for the stability of the spine. The biomechanics of dynamic implants take into account only the motility of the devices and not the elastic resistance. Is it possible that this is the reason why dynamic implants almost fail?

bilization” but nowadays the term “dynamic neutralization” (intended as neutralization of excessive degrees of movement) seems to be more appropriate^[16]. The numerous devices developed to achieve a dynamic neutralization of the spine have been divided into anterior (aimed at restoring or maintaining disc height and motion by total disc replacement) and posterior (aimed at restoring or maintaining articular movement or posterior tension band). These devices comprise total disc prosthesis, posterior interspinous or interlaminar systems, systems with pedicular screws and prosthesis of the facets or posterior ligaments. Despite the good intentions of dynamic neutralization, there are now some doubts regarding the efficacy of these devices.

DISC PROSTHESIS

The aim is to restore active movement in flexion-extension, rotation and lateral bending of the damaged disc. They provide excellent restoration of movement in all 3 planes but poor elastic resistance to movement, also due to removal of the anterior longitudinal ligament (ALL)^[17]. Disc prosthesis allows good movement of the metamere but with a greater range of motion (ROM) in comparison to a normal disc, especially in rotation. This causes overloading of the facet joints. This is the result of an underestimation of the properties of the disc whose principal characteristic is elastic resistance. Nowadays, the materials and design of disc prostheses are not able to completely guarantee the biomechanical characteristics of a healthy disc and the physiological role of the nucleus pulposus during segmental motion^[4,5,18-22]. Moreover, the surgical technique used for disc prosthesis insertion markedly reduces the elastic resistance of the metamere involved due to the elastic properties of the disc and the tension of the ALL. Hence, the results are very good in terms of movement but poor in terms of elastic resistance; this feature causes an acceleration of the degeneration of the spinal motor unit which often ends in heterotopic ossification of the prosthesis^[23-37]. Moreover, recent studies have shown that the incidence of the ASD, ASD is not influenced by the use of disc prosthesis or by the interbody cage. This feature explains the controversy regarding prevention of ASD^[38-43].

INTERSPINOUS-INTERLAMINAR SYSTEMS

The aim is to neutralize excessive movement in flexion and extension associated with distraction of the metamere to opening of the foramina. It provides fair control of flexion-extension but no control of active movements or passive resistance in rotation and lateral bending. Moreover, the insertion of the device in distraction causes an anterior overloading of the already damaged disc with a change in the 80-20 rule of the spine loading. This biomechanical aspect accelerates and does not prevent degenerative processes of the metamere, with

the possibility of developing spondylolisthesis^[44-53]. In a recent work, Ayturk *et al*^[2], reviewing the spinal literature concerning the postoperative status of interspinous devices (ID) followed over an average of 23.0-42.9 postoperative months, revealed that ID were burdened by an 11.6%-38.0% complication rate, 4.6%-85.0% reoperation rate and a 66.7%-77.0% incidence of poor outcomes. Last but not least, the devices implanted have a very high cost. In the light of the above, with high maximal complication rates (38%), reoperation rates (85%), poor outcomes (77%) and high costs, the utilization and implantation of ID remains extremely controversial^[54]. In my opinion, this sums up the real situation about ID: high costs and poor outcome.

PEDICULAR DYNAMIC SYSTEMS

The aim is to dynamically neutralize excessive movement and prevent ASD. They provide excellent control of movement in flexion-extension and lateral bending but minimal control in axial rotation. We can say that the intended functions of a motion preservation system are maintenance of the intervertebral ROM to reduce intradiscal pressure and reduce facet joint forces^[55]. In this regard, metameric movement in axial rotation plays an essential role as the biomechanical vector of force that solicits the facet joints and the disc^[56]. To be able to control this movement, the implant should have physical and mechanical characteristics. Biomechanically, the maintenance of the natural intervertebral motion, which especially includes the elastic resistance to torsion, can only be achieved if the elastic modulus of the longitudinal rod is high, but to considerably reduce the intradiscal pressure, high implant stiffness is required and in order to reduce facet joint forces, a rigid connection between longitudinal rod and pedicle screw is necessary. For these reasons the intended functions of a motion preservation system must have a contradictory implant stiffness^[57,58]. In fact, a dynamic system based on screws and elastic rods have to have some particular properties in order to maintain the biomechanical characteristics of the spinal motor unit, namely rigidity and flexibility that are not compatible with one other. Actually, since rigid systems guarantee rigidity and dynamic systems guarantee flexibility, the result is: (1) in the case of rigid systems, a complete loss of the ROM; (2) in the case of dynamic systems, an overload of the disc and the articular facets. Preservation of these structures relies exclusively on the control of the elastic twisting movements. Since the only way to control these forces is the rigid connection of the rods and since this connection does not preserve the physiological movement of the spinal motor unit, no dynamic pedicle system able to control such rotation movements currently exists^[57-63]. The screw insertion technique via the transverse process, such as the DYNamic NEutralization SYStem (DyNeSys) system, permits a rotational axis of the metamere posterior with respect to the physiological one, generating a movement with a fulcrum of metameric rotation different to that

of the other metameres. Screw insertion *via* the articular process, such as the Flex system, modifies the rotational axis that becomes more posterior than the DyNeSys and the physiological one. Both of these systems increase overloading of the facet joints with biomechanical variations^[64]; (3) normally, after distraction of the metamere, intradiscal pressure values are markedly reduced for rigid implants. The effect on intradiscal pressure is the same as in a dynamic implant; meaning that the mechanical effects of a dynamic implant on discs are similar to those of a rigid fixation device, except after distraction. In the light of this, as dynamic pedicle systems are incompatible with a distraction implanting, a dynamic implant does not necessarily reduce axial spinal loads compared to an un-instrumented spine^[57,58]; (4) pedicle-screw-based dynamic implants strongly reduce posterior disc bulging during extension since the presence of a dynamic rod controls the movements in compression on the posterior elements. However, in contrast to the intact spine, based on a posterior shift of the core, insertion of such an implant increases posterior disc bulging during flexion. The reason for this is that the dynamic rods, secured by the screw in the pedicle, prevent normal displacement of the nucleus pulposus within the disc during normal movements in flexion. This implies an increased tension on the fibers of the annulus which can lead to a higher risk of a recurrence of a bulging disc^[65-67]; and (5) the use of a dynamic system as a hybrid implant due to prevention of ASD has shown that there are no clinical benefits in the disc with initial degeneration^[41,68,69]. This is probably attributable to the fact that the biomechanics of the hybrid system do not control the hypermobility that is at the base of the initial degeneration of the adjacent disc. So if the disc is already degenerated, the hybrid system does not seem to protect against the progression of degeneration^[70].

TOTAL FACET REPLACEMENT

The aim is to dynamically neutralize hyper-movement of the facet joints and to restore the articular ROM. It provides excellent control of movement in flexion-extension and lateral bending and good control of movement in rotation and is indicated in cases of moderate disc degeneration, facet pain and arthrosis of the articular masses^[71,72].

TOTAL POSTERIOR ELEMENT REPLACEMENT TOPS

This procedure allows at least 85% of the ROM in the sagittal plane and mimics the flexibility of the metamere in lateral bending. In axial rotation, it mimics the biomechanical behavior of the posterior complex^[30,71,73].

These last two devices, in my opinion, mimic the physiological motility of the posterior elements of the spinal motor unit in an attempt to restore the biomechanical characteristics of the facet joints and posterior ligamentous system.

CONCLUSION

On the basis of this analysis, we can assert that dynamic neutralization systems seem to be very promising although long-term results are lacking for many of them. However, the certainty is that the future of vertebral stabilization will be dynamic systems instead of rigid ones. Unfortunately, to date, none of the dynamic systems used alone is capable of controlling movements on all 3 planes of motion of the functional motor unit. Moreover, motion preservation technology should take into account not only movement but also, and above all, the elastic resistance properties of the metamere involved. In the light of the above considerations, the future of dynamic neutralization will be the control of all the components of the motor unit. Only in this way will it be possible to preserve both motion and the biomechanical properties of the metamere, guaranteeing a degree of vertebral motion and elasticity as physiological as possible.

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Zinc: Role in the management of diarrhea and cholera

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Abstract

Diarrhea and cholera are major health problems. *Vibrio cholera*, the causative agent of cholera, infects the small intestine, resulting in vomiting, massive watery diarrhea and dehydration. Reduced water and electrolyte absorption is also due to zinc deficiency. Zinc has an important role in recovery from the disease. The combination of zinc with cholera vaccine and oral rehydration solutions has a positive impact on cholera and diarrhea. It has led to a decrease in the mortality and morbidity associated with diarrhea.

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Key words: Diarrhea; Cholera; *Vibrio cholera*; Zinc; Oral rehydration solutions

Core tip: In diarrhea and cholera, reduced water and electrolyte absorption is due to zinc deficiency. Therefore, zinc has an important role in recovery from the symptoms. The use of zinc with cholera vaccine and oral rehydration solutions has been shown to affect positive impacts in cholera and diarrhea.

INTRODUCTION

Diarrhea and cholera are major global health problems. Cholera toxin produced by the causative agent increases cyclic adenosine monophosphate (cAMP) production. This results in massive electrolyte and water secretion into the intestinal lumen, resulting in severe dehydration^[1]. *Vibrio cholera*, the causative agent of cholera, infects the small intestine. Vomiting, massive watery diarrhea and dehydration (Figure 1) are associated with cholera and may lead to death if not managed properly^[2]. Reduced water and electrolyte absorption is also due to zinc deficiency^[3]. Zinc has an important role in recovery from the disease^[4] and can reduce the morbidity and mortality, associated with diarrhea, in the population^[5].

ZINC WITH CHOLERA VACCINE

Clinically, zinc has a positive effect in children with complications of diarrhea^[6]. Young children are immunized with oral inactivated whole cell cholera vaccine containing recombinant cholera toxin B subunit. This vaccine induces T-cell responses that are further enhanced by zinc supplementation^[7]. Zinc combined with oral cholera vaccine shows increased vibriocidal antibody effects and suppresses cholera toxin antibody response^[8]. Zinc supplementation enhances oral cholera vaccine efficacy and also improves seroconversion to vibriocidal antibody^[9]. Oral administration improves immune response to antigens applied to mucosal surfaces and also improves antibacterial response in serum and reduces antitoxin levels^[10].

Administration of two doses of oral inactivated cholera vaccine, containing cholera B subunit and killed cholera vibriosis, combined with zinc supplementation, to 6-8 mo old children was found to be safe and immunogenic^[11].

Qadir MI, Arshad A, Ahmad B. Zinc: Role in the management of diarrhea and cholera. *World J Clin Cases* 2013; 1(4): 140-142

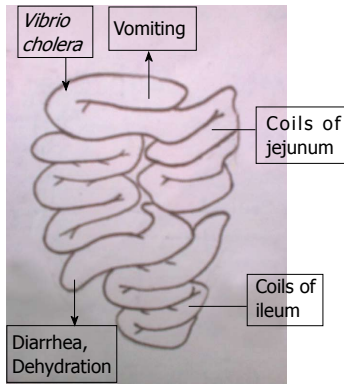


Figure 1 Effect of *Vibrio cholera* on small intestine.

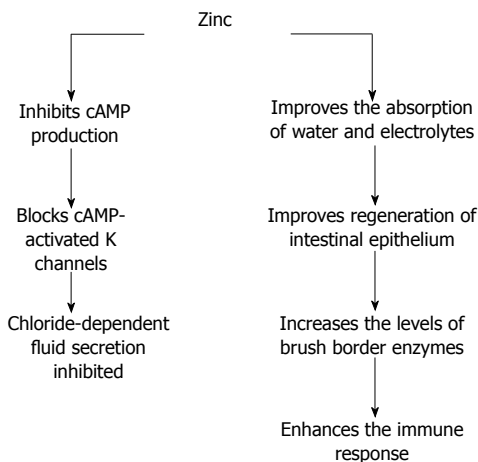


Figure 2 Physiological effects of zinc. cAMP: Cyclic adenosine monophosphate.

ZINC WITH ORAL REHYDRATING SOLUTIONS

Diarrhea and cholera are major global health problem and have caused seven pandemics. Cholera toxin produced by *Vibrio cholera* increases cAMP production. This results in massive electrolyte and water secretion into intestinal lumen, leading to severe dehydration. The World Health Organization emphasises the use of oral rehydration solutions (ORS) in the treatment of diarrhea. Various modifications have been made to standard ORS, to treat non cholera diarrhea^[12] and cholera diarrhea. These include addition of zinc, amino acids and amylase-resistant starch^[1], to decrease the morbidity and mortality associated with acute diarrhea^[12]. Zinc with ORS is an attempt to improve ORS for cholera diarrhea management^[1]. The presence of zinc in ORS improves physiological condition, reduces the risk of recurrent diarrhea attacks^[4] and also has positive effects in dehydrating acute diarrhea in malnourished children^[13]. Studies in various countries showed that the duration and severity of diarrhea can be reduced by zinc addition and this also allows limitation of the use of antibacterials and antimicrobials^[14] (Figure 2).

WATER SOLUBLE ACTIVE ZnTe NANOCOMPOSITES

Water soluble active ZnTe nanocomposites (average size range of 2.9-6.0 nm) show potential against enteropathogenic bacteria including enterotoxigenic *Escherichia coli* (*E. coli*) and *Vibrio cholera* serogroup 01, having positive effects in diarrhea and cholera without toxic effects on humans^[15].

EFFECT OF ZINC

A study on an animal model showed that zinc deficiency in the intestine resulted in reduced water and electrolyte absorption^[3]. Cholera toxin increases cAMP production, thereby causing electrolyte and water secretion^[1]. Zn reduces cAMP concentration and cholera toxin-induced ion secretion, as well as increasing ion absorption, but does not inhibit *E. coli* heat stable enterotoxin-induced ion secretion^[16].

In children suffering from acute diarrhea and persistent diarrhea, the effect of zinc on intestinal integrity is unknown. However, in patients with acrodermatitis enteropathica infection, zinc induced more mucosal repair. Zinc also effects excretion of urinary probe sugars, increasing lactulose excretion and decreasing mannitol excretion^[17].

EFFECT OF SCHEDULED DOSES OF ZINC

Children and older patients both show zinc deficiency in cholera^[18]. Zinc supplementation showed beneficial impact on diarrhea in infants but its impact was masked by the protective action of breastfeeding^[19].

Zinc supplementation administered on a daily or weekly schedule is effective in decreasing diarrhoeal morbidity without adverse reactions^[20].

Children with cholera supplemented with zinc show reduction in stool output and in the duration of diarrhea. Children with diarrhea may benefit from zinc supplementation but its cost effectiveness and optimal mode of delivery are not yet clear^[21].

CONCLUSION

In diarrhea and cholera, reduced water and electrolyte absorption is due to zinc deficiency. Therefore, zinc has an important role in recovery from the symptoms. Zinc combined with cholera vaccine and ORS has been shown to have positive impacts in cholera and diarrhea.

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Giant hibernoma of the thoracic pleura and chest wall

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Abstract

Hibernoma is a rare tumor containing prominent brown adipocytes that resemble normal brown fat. Brown fat (versus white fat) is predominantly found in hibernating mammals and infants. Brown fat adipocytes contain a higher number of small lipid droplets and a much denser concentration of mitochondria. The tumor can occur in a variety of locations however the extremities, followed by the head and neck, have been the most common sights. All variants of hibernoma described have followed a benign course with the majority presenting as a small, lobulated, nontender lesions. We present a case of a giant hibernoma arising from the pleura which invaded the intra and extra-thoracic chest.

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Key words: Hibernoma; Lipoma; Thoracic wall; Pleural neoplasm; Thoracic neoplasms

Core tip: Hibernomas are rare tumors containing brown fat. They are uncommonly located on the chest or pleura. Differentiation for other malignant tumors requires histologic evaluation. Surgical excision is the treatment

of choice. Treatment of large and symptomatic hibernomas is surgical excision. This is curative in the majority of patients with the exception of a rare case reported having recurrence after unclear resection margins.

Jaroszewski DE, De Petris G. Giant hibernoma of the thoracic pleura and chest wall. *World J Clin Cases* 2013; 1(4): 143-145
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INTRODUCTION

Hibernomas are a type of lipid tumor containing prominent brown adipocytes similar to the brown fat of hibernating animals^[1-3]. The tumor can occur in a variety of locations however the extremities, followed by the head and neck, have been the most common sights^[1-4]. Hibernomas are reported to follow a benign course with the majority presenting as a small, lobulated, nontender lesions^[5,6]. We present a case of a giant hibernoma arising from the pleura which invaded the intra and extra-thoracic chest.

CASE REPORT

A 50-year-old woman presented for evaluation of a long-standing right anterior chest wall mass. She had vague sensation of "pressure" at the sight and believed that the mass had been there at least 5-6 years with gradual enlargement over time. A computerized tomography scan with intravenous contrast was obtained of the chest (Figure 1). A circumscribed lobulated mass was seen arising from the upper anterior right pleura at the second intercostal space. The mass extended both intra thoracic and extra thoracic. The intrathoracic portion measured 9.3 cm × 5.0 cm and the extra thoracic component measured 6.6 cm × 2.9 cm. The extrathoracic component anteriorly displaced the upper portion of the pectoralis minor muscle. Subsequent needle biopsy showed features consistent with hibernoma.

The patient underwent surgical excision of the mass.

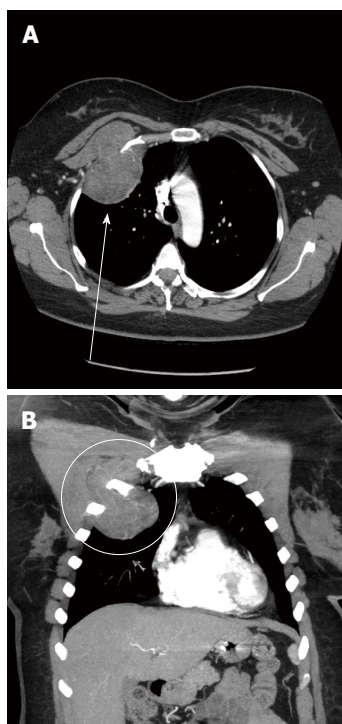


Figure 1 A computerized tomography scan with intravenous contrast was obtained of the chest. A: A circumscribed lobulated mass was seen arising from the upper anterior right pleura at the second intercostal space. The mass extended both intra thoracic and extra thoracic; B: The extrathoracic component anteriorly displaced the upper portion of the pectoralis minor muscle (circle).

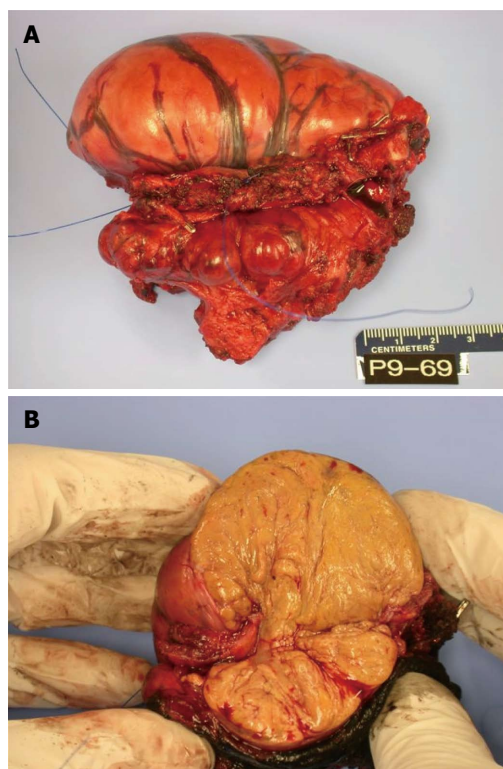


Figure 2 Pathology showed a specimen with dimensions 10.5 cm medial to lateral, 7.5 cm superior to inferior and 6 cm anterior to posterior containing lobular, brown fat. A: The specimen with dimensions 10.5 cm medial to lateral, 7.5 cm superior to inferior and 6 cm anterior to posterior; B: Grossly the tumor contained lobular, brown fat.

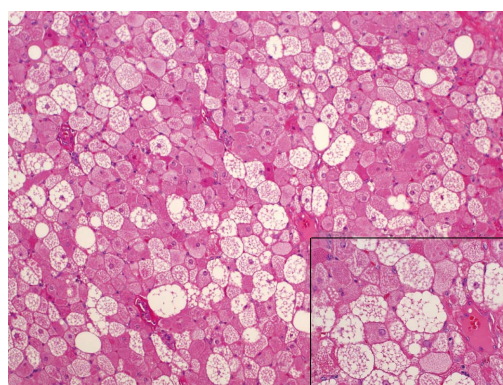


Figure 3 Microscopic evaluation of the hibernoma is characterized by vacuolated granular eosinophilic cells (hematoxylin-eosin, × 100). The inset (hematoxylin-eosin, × 400) shows a high power view of granular and multivacuolated cells in hibernoma.

She was positioned with a roll under the shoulders and arms tucked at the side. The skin overlying the mass was incised and dissection taken down to the subcutaneous fat surrounding the mass. The pectus major was elevated off the chest wall on the right with careful preservation of its major blood supply. En-block resection including the pectus minor was then performed of the chest wall providing a 1 cm circumferential margin. A piece of Gore® Dualmesh® Biomaterial (WL Gore and Assoc Inc., Flagstaff, AZ, United States) was then cut to fill the defect in the chest wall which was approximately 8 cm × 11 cm. Interrupted suture was then used to attach the mesh to the edges of the chest wall defect. A chest tube was placed and the overlying pectoralis muscle flap secured to the sternum medially. A flat drain was placed between the mesh reconstruction and the muscle to prevent seroma. The wound was closed in layers and dressings placed. Compression wrapping was performed to help reduce the cavity and prevent fluid collection. The patient's hospitalization was uncomplicated. She was discharged home on day 3 and has not evidence of recurrence.

Pathology showed a specimen with dimensions 10.5 cm medial to lateral, 7.5 cm superior to inferior and 6 cm anterior to posterior (Figure 2A) containing lobular, brown fat (Figure 2B). The mass extended within the intercostal space creating bulging exophytic mass of the pleural aspect of the specimen. Immunohistochemical staining for S-100 was positive and CD34 negative. The pathologic exam of the tumor showed a well defined, solid, soft mass microscopically composed of lobules of cells with granular eosinophilic cytoplasm and multivacuolated cells (Figure 3). Intermixed were also adipocyte with large single clear vacuole.

DISCUSSION

Lipomas are common benign soft tissue tumors of white fat^[3]. Hibernomas are a type of lipid tumor that contain prominent brown adipocytes similar to the brown fat of hibernating animals^[1,3,5-9]. The term “brown fat” was originally used by Gery^[10]. They are traditionally regarded as benign tumors without the potential for malignant degeneration, however may cause symptoms as they increase in size and encroach upon other structures^[6]. Clinically,

hibernoma is indistinguishable from malignant tumors. As with other benign lipomatous tumors, they manifest typical cytogenetic aberrations. The most commonly reported is 11q13-21 without a common translocation partner^[1,4]. Radiographically, these tumors can be difficult to distinguish from malignant tumors such as liposarcomas. Imaging can vary based upon the mixture of white versus brown fat contained in the mass^[7,8]. Although magnetic resonance imaging can yield a differential diagnosis of lipomatous tumors, it cannot definitively rule out well-differentiated liposarcomas and other malignant variants^[7].

The definitive diagnosis of the tumor is made by histologic confirmation. Microscopically the hibernoma is distinctive and readily differentiated from other tumors. The differential microscopic diagnosis includes adult rhabdomyoma (larger cells, glycogen rich cells with striations and crystals) and granular cell tumor (no lipid vacuoles). Hibernomas have large multi-vacuolated cells with abundant mature adipose cells, several small capillaries and no significant decomposition or adipocytic atypia^[7]. Immunohistochemical staining should show S-100 positivity for lipidic cells. Oil red O-positive droplets of cytoplasmic lipid can be seen in most cases. CD34 which is seen in spindle cell and other lipoid component tumors is usually negative. Several histologic variations have been described based on the quality of hibernoma cells, nature of the stroma, and the presence of spindle cell components^[3].

The majority of publications relating to hibernoma have been small series and case reports. A single clinicopathologic review from the Armed Forces Soft Tissue Registry assessed 170 cases of hibernoma confirming benign behavior and a spectrum of morphologic features^[3]. The majority of tumors presented as slow growing, progressively enlarging, pain-free masses. The most common sites of occurrence were the thigh, shoulder, back and neck^[3].

Treatment of large and symptomatic hibernomas is

surgical excision^[1,2,5,6]. This is curative in the majority of patients with the exception of a rare case reported having recurrence after unclear resection margins^[4,6].

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Noncoronary sinus of Valsalva rupture into the right atrium with a coexisting perimembranous ventricular septal defect

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Abstract

Ruptured sinus of Valsalva is very uncommon, and is < 1% of all congenital defects. The incidence ranges from 0.1%-3.5%. There is a male to female predominance of 4:1, with the highest incidence in the Asian population. Higher incidence is also seen in patients with Marfan's syndrome and Ehlers Danlos syndrome. There is a higher association of ruptured sinus of Valsalva with ventricular septal defect (VSD), aortic stenosis, and bicuspid valve defect. While most patients with VSD often have rupture of their right coronary sinus of Valsalva into the right ventricle due to poor structural integrity, we present a rare case of a patient with VSD who had rupture of his noncoronary sinus of Valsalva into the right atrium.

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Key words: Sinus of Valsalva; Rupture; Ventricular septal defect; Wind sock deformity

Core tip: It is important to understand that aneurysms and or rupture of the coronary sinus of Valsalva can

occur from any sinus and into any chamber, which will affect management and treatment.

Cao LB, Hannon D, Movahed A. Noncoronary sinus of Valsalva rupture into the right atrium with a coexisting perimembranous ventricular septal defect. *World J Clin Cases* 2013; 1(4): 146-148 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i4/146.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i4.146>

INTRODUCTION

Ruptured sinus of Valsalva is very uncommon, and is < 1% of all congenital defects. The incidence ranges from 0.1%-3.5%. There is a male to female predominance of 4:1, with the highest incidence in the Asian population. Higher incidence is also seen in patients with Marfan's syndrome and Ehlers Danlos syndrome. There is a higher association of ruptured sinus of Valsalva with ventricular septal defect (VSD), aortic stenosis, and bicuspid valve defect. Sinus of Valsalva aneurysm is commonly seen in patient ages 13 to 65-year-old with a mean age of 35 years. Rupture often occurs before the age of 40 and after puberty^[1]. The frequency at which the right coronary sinus of Valsalva ruptures is approximately 75% in comparison to the noncoronary cusp, which is approximately 20% and rarely does the left coronary cusp rupture^[2]. Typically, sinus of Valsalva aneurysms involve the right ventricle 60% of the time, the right atrium approximately 30% of the time and less than 10% of the time with the left atrium, left ventricle or pericardium combined^[3].

Structural defects often lead to lack of continuity between the aortic media and the aortic annulus leading to subsequent weakening, avulsion and aneurismal formation. Congenitally, there may be incomplete fusion of the right and left distal bulbous septum, the base of which forms the right and the non coronary sinuses of Valsalva. Acquired causes often involve severe infections with syphilis and or endocarditis, trauma, severe athero-

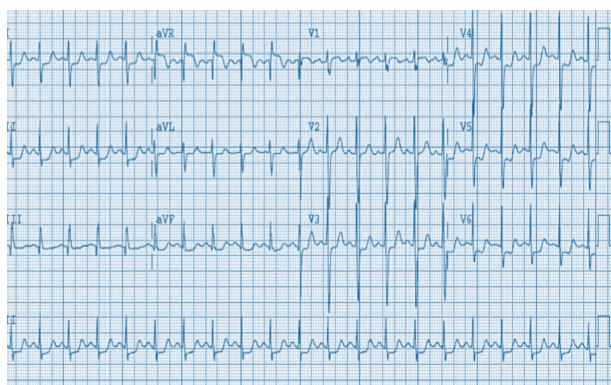


Figure 1 Electrocardiogram shows sinus tachycardia with a rate of 130, 1 mm to 3 mm ST depressions in leads I, II, and V3 to V6 and 1 mm to 2 mm ST elevations in aVR and V1.

sclerosis and aortic dissection that alter the anatomy and structural integrity of the sinuses leading to aneurismal formations^[4].

CASE REPORT

A 20-year-old man with documented history of VSD presents to the Emergency Department with symptoms of nausea and vomiting. Patient had denied chest pain, but admits to shortness of breath and fatigue. He was sweaty, and diaphoretic. His heart rate was 124; blood pressure was 117/33 mmHg, he was tachypnic and saturating on room air at 88%. He had a continuous murmur on exam, with jugular venous distention. His lab results show an elevated white count of 13, creatinine of 1.65, troponin of 1.70 and lactic acid of 3.80, with normal liver enzymes. Chest X-rays shows bilateral lung congestion without cardiomegaly. Electrocardiogram shows sinus tachycardia with a rate of 130, 1 mm to 3 mm ST depressions in leads I, II, and V3 to V6 and 1 mm to 2 mm ST elevations in aVR and V1 (Figure 1).

Transthoracic echocardiogram initially done showed a poorly visualized echogenic flap in the right atrium. Subsequent transesophageal echocardiogram done, showed a ruptured aneurysm of the noncoronary sinus of Valsalva, that is Windsock in morphology, into the right atrium (Figure 2). Coincidentally, IV medications given during the echocardiogram had micro air bubbles that transiently traveled through the small membranous VSD communicating with the right coronary sinus of Valsalva (Figure 2). Continuous flow through a relatively low pressure right atrium prevented the micro air bubbles from entering the aortic root through the rupture lumen, yet higher pressures in the right ventricle allowed for the micro air bubbles to travel through the VSD. Patient underwent immediately surgery to repair both the ruptured aneurysm of the noncoronary sinus of Valsalva and the VSD (Figure 3).

DISCUSSION

What makes our case unique is that the non coronary

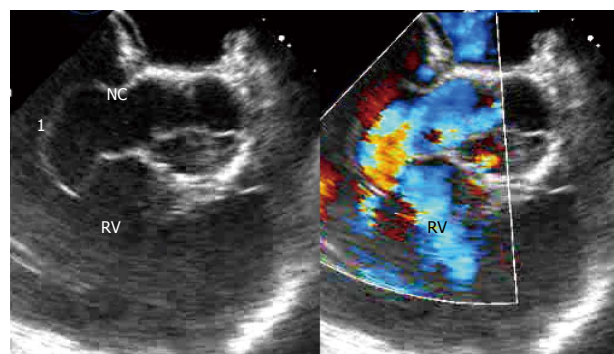


Figure 2 Subsequent transesophageal echocardiogram done, showed a ruptured aneurysm of the noncoronary sinus of Valsalva, that is Windsock in morphology, into the right atrium. A: Sinus of Valsalva defect with; B: Color-Doppler. 1: Windsock aneurysm; RV: Right ventricle; NC: Noncoronary cusp.

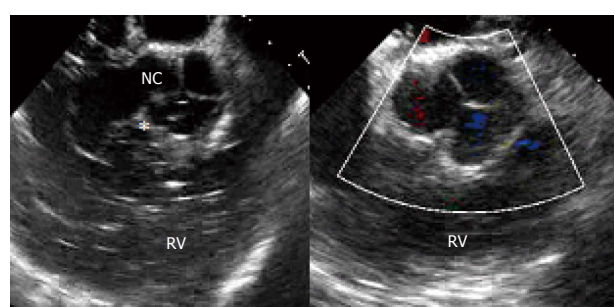


Figure 3 Patient underwent immediately surgery to repair both the ruptured aneurysm of the noncoronary sinus of Valsalva and the ventricular septal defect. A: Bubbles going through membranous ventricular septal defect; B: The repaired defect. Asterisk indicates micro air bubble traversing the membranous VSD. RV: Right ventricle; NC: Noncoronary cusp.

sinus of Valsalva rarely ruptures into the right atrium in the presence of a perimembranous septal defect. In the largest retrospective analysis of a rupture of sinus of Valsalva ($n = 67$) done by Dong *et al*^[5], only 18/32 (56%) of the patients had perimembranous VSD with rupture, and among this group, only 1 of the 32 patients presented with a “non coronary sinus of Valsalva rupture” in the presence of perimembranous VSD. Our patient also had a unique wind-sock aneurysmal morphology to his non coronary sinus of Valsalva rupture.

The gold standard for diagnosis is echocardiogram. The treatment of choice is surgery, which has a 90% ten year survival rate with closure of aneurysm and perimembranous VSD^[6]. Percutaneous intervention with an Amplatzer Duct Occluder has been found to be successful in selective cases and has been utilized in Europe^[7].

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L- Editor A **E- Editor** Yan JL



Vulvar granular cell tumor

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Key words: Granular cell tumor; Vulvar tumor; Vulvar neoplasm

Core tip: Granular cell tumors are rare, usually benign, soft tissue tumors of neural origin. They can occur anywhere in the body with up to 15% situated in the vulva. Malignancy has been reported in about 2% of cases. We report a woman with a granular cell tumor of the vulva who underwent tumor excision but with focal extension to the resection margin on microscopy. Recurrence rates are 2%-8% with clear margins and 20% with positive margins. We conclude that intraoperative assessment by frozen section is advisable such that further excision can be performed for positive margins.

Abstract

Granular cell tumors are rare, usually benign, soft tissue neoplasms of neural origin. They occur more often in females than males, the peak age incidence is in the fourth through fifth decades. They can occur anywhere in the body with up to 15% situated in the vulva. The commonest presentation is as an asymptomatic mass. Microscopic findings are usually sufficient, but immunohistochemistry can also be helpful in confirming the diagnosis. The vulvar tumors are benign in 98% of cases with 2% reported as malignant. In this case report we describe a woman with a granular cell tumor confirmed by biopsy who underwent excision of the mass but with focal extension to the resection margin on microscopy. Our recommendation of re-excision was declined. Since it is not uncommon with these tumors to find groups of tumor cells extending beyond the macroscopic limits of growth, we conclude that it is advisable to have margins assessed intraoperatively by frozen section such that further excision can be performed for positive margins. Our patient has been followed for 18 mo without recurrence, should the tumor recur, re-excision, with frozen section control, is indicated. Recurrence rates are reported as 2%-8% with clear margins and 20% with positive margins.

Rivlin ME, Meeks GR, Ghafar MA, Lewin JR. Vulvar granular cell tumor. *World J Clin Cases* 2013; 1(4): 149-151 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i4/149.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i4.149>

INTRODUCTION

Granular cell tumors (GCT), first described by Abrikossoff in 1926, are rare, usually benign soft tissue tumors of neural origin which can occur throughout the body and in any age or race^[1]. They occur more often in females than males and in blacks than whites, the peak age incidence is in the fourth through fifth decades. While common sites are the tongue and breast, vulvar involvement has been reported in 7%-16% of cases^[2]. The vulvar tumors are benign in 98% of cases with 2% reported as malignant and in a review by Kardhashi *et al*^[3], of 130 cases in the literature, 7 were malignant, while 5%-25% exhibited multiple lesions. We report a further case of vulvar GCT complicated by incomplete surgical excision.

CASE REPORT

A 52-year-old woman with a 12 year history of a "growth" on her vulva had undergone a biopsy of the lesion which

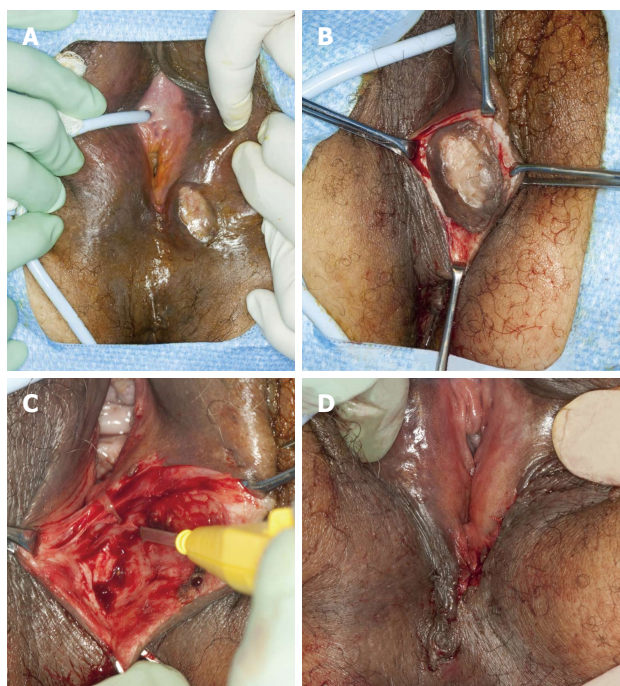


Figure 1 Operative photograph. A: Tumor in the left labium majus; B: Commencement of excision; C: Completion of excision; D: Closure of the surgical incision.



Figure 2 Gross appearance of bisected specimen, note fleshy consistency and gray/white coloration.

was read as a GCT. Initially resistant to surgical excision because she was asymptomatic, she had changed her mind because she felt it was getting bigger and now agreed to the procedure. Examination of the vulva revealed a 3 cm × 3 cm hard, non-tender, mobile mass extending to the superficial dermis with depigmentation of the overlying skin (Figure 1A). The lesion was situated on the left labium majus, midway between the anal verge and the anus. There was no regional adenopathy.

She underwent wide local excision of the mass (Figure 1B-D). The gross specimen was firm, white and fleshy in appearance (Figure 2). The microscopic appearance was, as in the biopsy, typical of a GCT (Figure 3). However excision was incomplete with tumor extending focally to the resection margin. She was fully counseled and re-excision was recommended, however she declined further surgery unless there was a recurrence of the growth. She

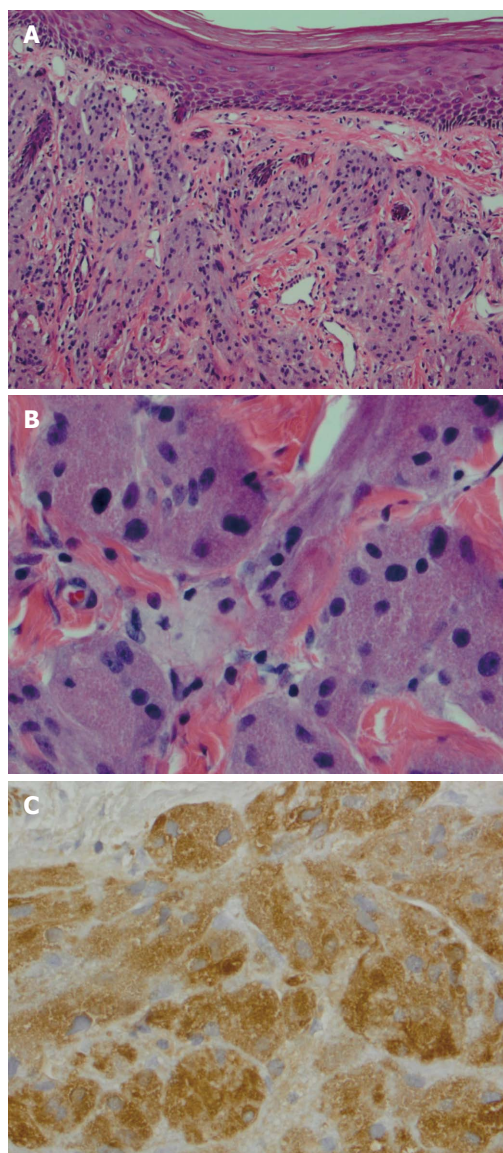


Figure 3 Photomicrograph. A: clusters of nests of cells in lamina propria with squamous epithelium on the surface (HE, × 100); B: cells with granular eosinophilic cytoplasm. (HE, × 400); C: S-100 uptake, the brown color indicates the positive stain (S-100, × 400).

has been followed for 18 mo since the surgery without evidence of recurrence. She has been warned that the tumor is slow growing and may take years to reappear. Therefore she needs to return on a regular basis for physical examination. She should alert her clinician if any growth recurs at the surgical site or if any nodular growth appears elsewhere on her body.

DISCUSSION

GCT are thought to be derived from neural tissue as supported by immunophenotypic and ultrastructural evidence, possibly from Schwann cell derivatives^[1]. The vulvar lesion develops in the dermis or subcutaneous tissue as a slow growing, non-tender, lump over months or years, rarely larger than 4 cm in diameter. The mass is mobile and the overlying skin may be depigmented, oc-

casionally ulcerated or may be thickened with a “cobblestone” appearance. The tumor is poorly circumscribed with irregular margins and is yellow-gray and fleshy on cross section. On microscopy the cells are round to polyhedral with indistinct margins and granular cytoplasm. They occur in ribbons or clumps separated by hyalinised stroma and collagen fibers. Nuclei are uniform, small and dark staining. The granular appearance is due to the accumulation of lysosomes^[4]. In about half the cases the squamous epithelium overlying the tumor shows pseudoepitheliomatous hyperplasia which may be mistaken for squamous carcinoma. The cells are immunoreactive for S-100 protein, are periodic acid Schiff positive, diastase resistant^[5]. The rare malignant cases may show necrosis, nuclear polymorphism and increased mitoses, however they may present morphologically benign^[1].

The differential diagnosis includes fibroma, lipoma, papilloma, hidradenoma, epidermal cyst, Bartholin cyst and melanoma. There is no association with neurofibromatosis unlike another benign slow-growing tumor originating from Schwann cells of the nerve sheath, the Schwannoma which may be associated with neurofibromatosis. Schwannomas are also S-100 protein positive but are histologically completely different composed of spindle non granular cells with compact (Antoni A) and loose (Antoni B) areas. There may be enlarged atypical nuclei which represent degenerative type change (so called ancient Schwannoma). GCT usually do not have spindle cells though the very rare malignant variety may have such cells^[6]. Immunohistochemistry is a helpful diagnostic tool and diagnosis is confirmed by punch or excisional biopsy^[7].

Treatment is by surgical excision. Because the tumors often have irregular margins and because groups of tumor cells often extend beyond the macroscopic limits of growth wide excision is necessary. While usually found on the labia majora, they may be clitoral, perineal, perianal or on the mons. Depending on their position and size, wide excision may be complex with risks of blood loss and scarring complicating the procedure^[5]. Therefore incomplete excision is not uncommon. Papalas *et al*^[8] reported 17 cases, 7 of whom had positive margins, 2 progressed and required re-excision 8 and 14 years later respectively. Recurrence rates are 2%-8% with clear margins and 20% with positive margins^[1]. Therefore some authors advocate

Mohs-repeat sectioning with fresh horizontal frozen tissue mapping until clear margins are achieved^[9]. In the event of positive margins, re-excision is recommended, but our patient declined further surgery unless the lesion recurred. Although malignant GCT is very rare, malignant change may occur even if the primary tumor showed no malignant features. Older age, lesion larger than 4-5 cm and local recurrence may be prognostic markers. Unfortunately the malignant variety are very aggressive with regional and metastatic spread, these tumors do not respond to radiation or chemotherapy and treatment is surgical^[3].

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Rare case of a solitary huge hepatic cystic lymphangioma

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Abstract

A hepatic lymphangioma is a rare benign neoplasm and is usually associated with lymphangiomas of other viscera. A hepatic lymphangioma can be solitary, cystic or associated with multiple liver lesions and is characterized by cystic dilatation of lymphatic vessels in the hepatic parenchyma. A solitary lymphangioma is unusual. Here we report a rare case of a solitary huge primary hepatic cystic lymphangioma in a 42-year-old woman. It was discovered on routine physical examination and the patient had no obvious symptoms. Ultrasonography and computed tomography (CT) showed a giant "hepatic neoplasm" that occupied the right liver lobe. The lesion was approximately 20.0 cm × 15.0 cm × 10.0 cm in size and contained cystic and solid components. There were multiple septa inside the tumor, with some calcifications in the septa. Surgical resection was performed. Histological examination revealed multiple cystic structures lined with epithelial cells on the inner walls, accompanied by interstitial

swelling and necrosis. The patient has now been followed up for nearly two years after surgery, with no recurrence to date.

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Key words: Liver; Lymphangioma; Cyst

Core tip: Lymphangiomas are congenital malformations of the lymphatic system. A hepatic lymphangioma is a rare benign neoplasm that is usually associated with lymphangiomas of other viscera. A solitary lymphangioma is unusual. Here, we report a rare case of a solitary huge primary hepatic cystic lymphangioma. It was discovered on routine physical examination and the patient had no obvious symptoms. The diagnosis was confirmed by histological examination. The patient has now been followed up for nearly two years after surgery and has had no recurrence.

Zhang YZ, Ye YS, Tian L, Li W. Rare case of a solitary huge hepatic cystic lymphangioma. *World J Clin Cases* 2013; 1(4): 152-154 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i4/152.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i4.152>

INTRODUCTION

A hepatic lymphangioma is a rare benign tumor and is usually associated with lymphangiomas of other viscera. It can be solitary, cystic or associated with multiple liver lesions and is characterized by cystic dilatation of lymphatic vessels in the hepatic parenchyma^[1]. It can occur at any age and the majority of lesions are found incidentally^[2]. Surgical resection is normally performed due to the symptoms or because of concern about malignancy. In this report, we describe a rare case of a solitary huge primary hepatic lymphangioma which was incidentally found in a 42-year-old woman. We additionally provide a current literature review on this topic.

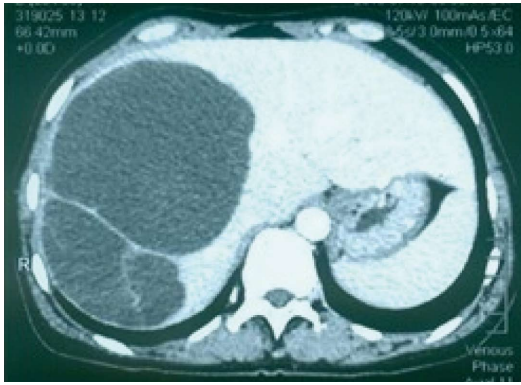


Figure 1 Computed tomography scan: A huge cystic mass with multiple septations is seen in the right lobe of the liver. There was no enhancement in the cystic regions but the septa were enhanced and seemingly had calcification.



Figure 2 Gross sample: cystic mass in the right liver lobe, measuring 23 cm × 15 cm × 7 cm.

CASE REPORT

A 42-year-old woman was admitted because of a mass in the right lobe of her liver which was discovered on routine physical examination. There were no obvious symptoms, such as pain, fever, jaundice or weight loss. Ultrasonography showed a giant “hepatic neoplasm” occupying the right liver lobe. The mass measured approximately 20.0 cm × 15.0 cm × 10.0 cm and contained cystic and solid components. There were multiple septa inside the tumor. There was no internal or external hepatic bile duct expansion. Contrast-enhanced computed tomography (CT) showed a huge, non-homogeneous, relatively well-defined, low density cystic mass with multiple septa occupying the right lobe of the liver. The inner margin was near the middle hepatic vein. There were some calcifications in the septa. There was no enhancement in either the arterial or venous phases in the cystic areas, but the septa were seemingly enhanced (Figure 1). Laboratory tests also did not produce any positive findings. Exploratory laparotomy revealed that the tumor was a 15.0 cm × 15.0 cm brown soft mass in the right lobe of the liver. Hemihepatectomy and cholecystectomy were performed (Figure 2). Histological examination showed that there were multiple cystic structures; two larger ones measured 6.0 cm × 3.0 cm × 1.0 cm and 13.0 cm × 10.0 cm × 3.0 cm, respectively, and contained coffee-like fluid. There were

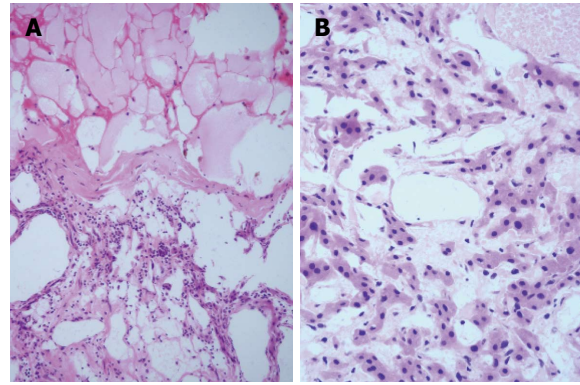


Figure 3 Histopathological findings. A: Dilated lymphatic cavities accompanied with partial infarction. Lymph cells were seen lining the wall of the cyst, hematoxylin and eosin (HE), × 100; B: Simple squamous epithelia and eosinophilic hepatic cells (HE, × 200).

cystic structures lined with epithelial cells on the inner walls, accompanied by interstitial swelling and necrosis (Figure 3). Immunohistochemistry showed endothelium markers CD34(+), AFP(-), D2-40(-), Hepatocyte(-), CK117(-), CK8(focal+) and Ki67(< 1%+). The pathological diagnosis was liver lymphangioma. The patient has now been followed up for nearly two years post surgery, with no sign of any recurrence to date.

DISCUSSION

Lymphangiomas are the results of congenital malformations of the lymphatic system. The condition is due to obstruction of lymphatic fluid drainage between the cystic lymphatics and the central veins, or abnormal development of the lymphatic branches, or formation of separated lymphatics and cysts which result in lymphangiomas^[1,2]. Lymphangiomas are typically featured in both malformations and neoplasms. Lymphangiomas have been classified into three types: simple lymphangioma, cavernous lymphangioma and cystic lymphangioma^[3]. Other authors have divided lymphangiomas into five types: simple lymphangioma, cavernous lymphangioma, cystic lymphangioma, lymphangiohemangioma and lymphangiosarcoma^[4]. Among these five types, cystic lymphangiomas are the most common. The fluid component of a lymphangioma can be serous or chylaceous, depending on the location of the lymphangioma. In the presence of hemorrhage or infection, a lymphangioma can be bloody or purulent. In the present case, the fluid was coffee-like, indicating that hemorrhage might have occurred (Figure 2).

More than 95% of lymphangiomas occur in the neck and axilla. Abdominal lymphangiomas are rare (less than 1%) and usually occur in the mesentery and retroperitoneum. Although hepatic lymphangiomas are considered as a subset of multiple abdominal lymphangiomas, they rarely occur in the liver alone. Hepatic lymphangiomas are single or multiple occurrences of lymphangiectasia, containing blood in the lumen and lined with endothelial cells which have inconspicuous nuclei on the inner

walls^[4-6]. Hepatic lymphangiomas usually cause liver tissue destruction due to extrusion of the normal liver tissue (Figure 3).

Normally, most hepatic lymphangiomas are found by routine physical examination or from other complaints and have no specific clinical presentation. Occasionally, abdominal pain is caused due to the compression of surrounding tissues or organs^[1]. In the present case, the patient's liver mass was discovered during her wellness physical examination; no other abnormalities were found. Ultrasonography or CT imaging may lead to a misdiagnosis of hepatic hemangioma or hepatic cystadenocarcinoma. Thickness of the cyst wall, number of cystic septations and internal echoes may be helpful to differentiate lymphangioma from other mesenteric cysts^[7]. CT imaging can reveal the cystic characteristics. When containing chylous fluid, the cysts may manifest as a negative CT value. Other reports have also revealed that the characteristic CT imaging features of a lymphangioma are a cystic or multicystic lesion with no enhancement in the central region and enhancement in the septa. If a lymphangioma and hemangioma co-exist, the lesion will be enhanced. This feature correlates with the present case, in which there were no enhancement regions in the cystic areas but the septa were seemingly enhanced (Figure 1)^[1,2,5]. Magnetic resonance imaging (MRI) of a lymphangioma usually shows a multiloculated heterogeneous mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images because of the content of the lymphangioma^[6]. MRI is very helpful for determining such characteristic features of a lesion because T2-weighted and heavily T2-weighted imaging are sensitive to the presence of water. However, when hemorrhage or infection occur, the CT value of the cystic region will rise and may lead to misdiagnosis^[8]. The image as seen on MRI corresponds to dilated lymphatic spaces and is useful in differentiating a lymphangioma from a true solid neoplasm.

Lymphangiomas are benign hamartomas but have a risk of cancerization. Continuing enlargement can cause rupture. Surgical resection of lymphangiomas has been considered standard treatment. Histopathological examination from frozen section is helpful for intraoperative diagnosis if it is difficult to make a clear diagnosis during

the operation. For huge or multiple lymphangiomas, liver transplantation is also considered^[9].

The prognosis of hepatic lymphangiomas is good and patients have no need for further treatment after resection. It has been found that a lymphangioma rarely recurs or progresses^[10]. In the present case, the patient has now been followed up for nearly two years and has had no sign of any recurrence to date.

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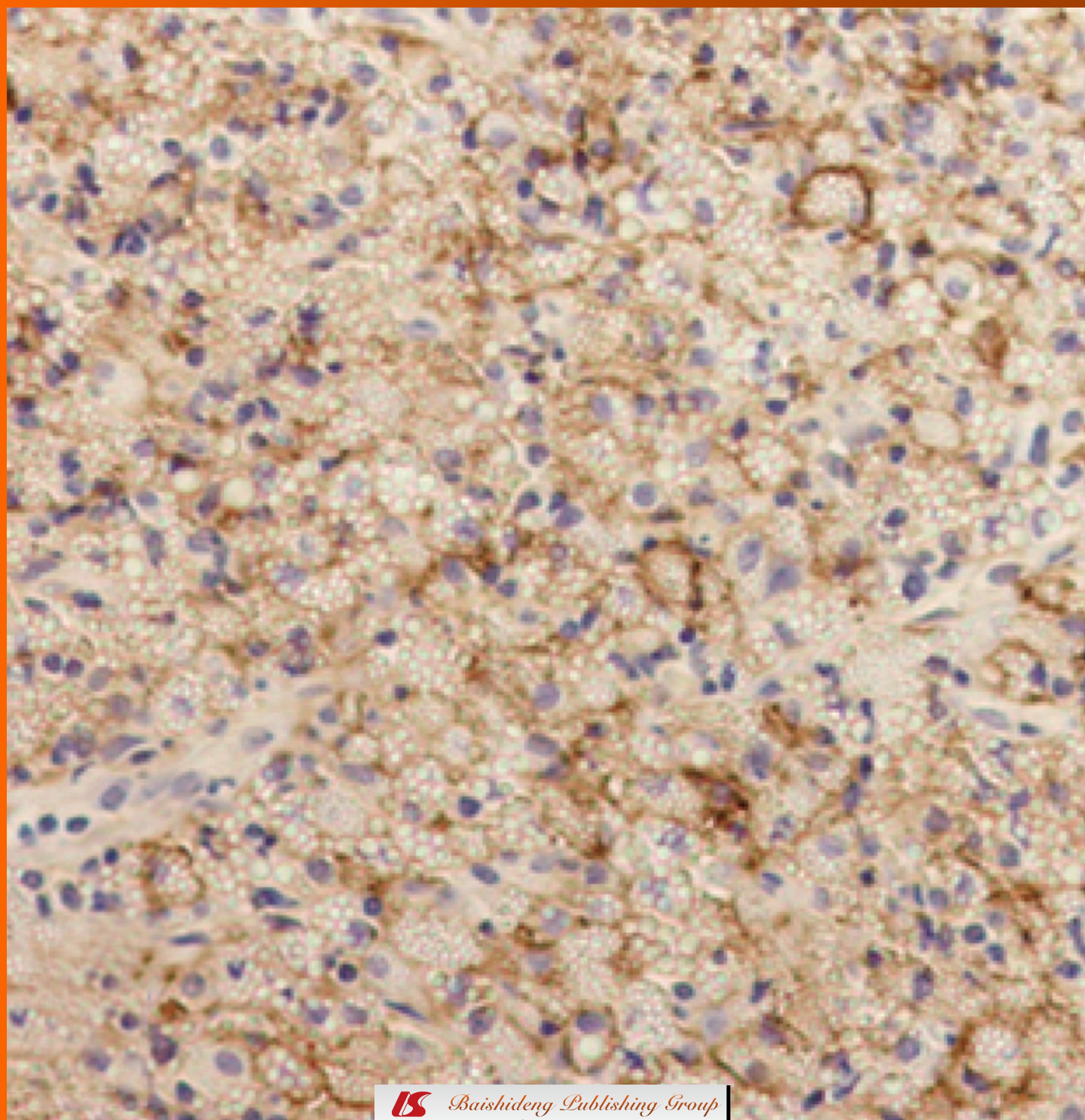
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Desmopression is an effective adjunct treatment for reversing excessive hyponatremia overcorrection

Kamel A Gharaibeh, Matthew J Craig, Christian A Koch, Anna A Lerant, Tibor Fülöp, Éva Csongrádi

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Abstract

We report a case of a 50-year-old malnourished African American male with hiccups, nausea and vomiting who was brought to the Emergency Department after repeated seizures at home. Laboratory evaluations revealed sodium (Na^+) 107 mmol/L, unmeasurably low potassium, chloride < 60 mmol/L, bicarbonate of 38 mmol/L and serum osmolality 217 mOsm/kg. Seizures were controlled with 3% saline IV. Once nausea was controlled with *iv* antiemetics, he developed large volume free water diuresis with 6 L of dilute urine in 8 h (urine osmolality 40-60 mOsm/kg) and serum sodium rapidly rose to 126 mmol/L in 12 h. Both intravenous desmopressin and 5% dextrose in water was given to achieve a concentrated urine and to temporarily reverse the

acute rise of sodium, respectively. Serum Na^+ was gradually re-corrected in 2-3 mmol/L daily increments from 118 mmol/L until 130 mmol/L. Hypokalemia was slowly corrected with resultant auto-correction of metabolic alkalosis. The patient discharged home with no neurologic sequelae on the 11th hospital day. In euvoletic hyponatremic patients controlling nausea may contribute to unpredictable free water diuresis. The addition of an antidiuretic hormone analog, such as desmopressin can limit urine output and prevent an unpredictable rise of the serum sodium.

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Key words: Hyponatremia; Hypokalemia; Overcorrection; Polyuria; Antidiuretic hormone; Vasopressin; Desmopressin; Osmotic demyelination syndrome; Central pontine myelinolysis

Core tip: In euvoletic hyponatremic patients, controlling the underlying reason of excessive vasopressin secretion may lead to sudden, large-volume free water diuresis and rise of serum sodium exceeding 12 mmol/L per day. Polyuria after presentation with symptomatic hyponatremia is a serious warning sign and should not be ignored. These patients need frequent electrolyte monitoring and, in case of excessive rise of serum sodium, pure water replacement with 5% dextrose in water to achieve a targeted reduction in serum sodium levels. Early addition of an antidiuretic hormone analog, such as desmopressin, can limit urine output and improve patient outcome.

Gharaibeh KA, Craig MJ, Koch CA, Lerant AA, Fülöp T, Csongrádi É. Desmopression is an effective adjunct treatment for reversing excessive hyponatremia overcorrection. *World J Clin Cases* 2013; 1(5): 155-158 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i5/155.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i5.155>

INTRODUCTION

Acute hyponatremia can cause death if cerebral edema and seizures are not treated promptly^[1]. Conversely, osmotic demyelination syndrome (ODS) will occur with rapid correction of severe chronic hyponatremia (serum sodium concentration 120 mmol/L or less) that has been present for more than 2 or 3 d, the time required for the cerebral adaptation to occur^[2]. Excessive correction of chronic hyponatremia triggers a cascade of injury in the brain beginning with breakdown of the blood-brain barrier and culminating in the programmed death of oligodendrocytes, the cells that form myelin sheaths in the central nervous system^[3]. Known risk factors for ODS are hyponatremia (both in duration and severity), rapid correction of hyponatremia with more than 12 mmol/L in less than 24 h, hypokalemia on presentation^[4-6], low BUN with malnourished state, alcoholism, liver disease and seizures on presentation^[7,8].

CASE REPORT

A 50-year-old African American male with history of hypertension and chronic intractable hiccups was brought to the emergency department (ED) by family members after three episodes of seizures at home, with the last episode few hours prior to admission and lasting for 10 min. The patient has been having hiccups for several years, which worsened acutely over 3 wk prior to admission. In order to control his hiccups, he has been drinking large amount of water and a proprietary carbonated beverage (Sprite®), as well. He reported nausea and daily vomiting and avoided solid food for the last two weeks prior to admission. He observed that his hiccups have improved temporarily with vomiting and the persisting and crescendo hiccups frustrated him enough to induce voluntary vomiting repeatedly.

On admission, his vital signs included a temperature of 36.4 °C, blood pressure of 168/73 mmHg with a heart rate of 81 beats/min, respiratory rate 18/min and body weight of 72.7 kg. General physical examination revealed an alert malnourished African-American male, oriented to person, place, and time with no focal neurological findings. Physical exam was unremarkable with no detectable peripheral edema. In the ED, the patient's serum electrolyte concentrations were: sodium of 107 mmol/L, potassium less than 1.5 mmol/L, chloride less than 60 mmol/L, bicarbonate of 38 mmol/L with a pH of 7.60. Blood urea nitrogen (BUN) measured 4 mg/dL, creatinine 0.7 mg/dL and serum osmolality 217 mOsm/kg. Liver function tests were within normal limits. EKG noted prolonged QT intervals (616 ms) and non-specific ST-T abnormalities. No arrhythmia was observed. Emergent treatment included 150 mL 3% saline IV bolus to control seizures, intravenous chlorpromazine (Thorazine®) and baclofen to control hiccups, nausea and vomiting and 1 L of normal saline with 40 mmol/L of potassium-chloride over 5 h. Six hours after the ED presentation, he was admitted to

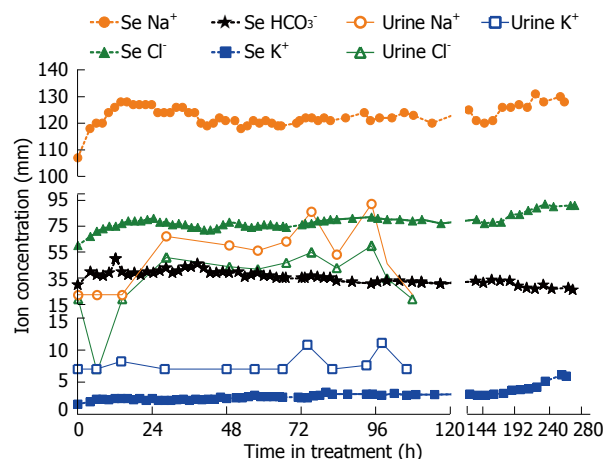


Figure 1 Serum and urine electrolyte concentrations over time. The patient spent 0-120 h in the intensive care unit.

the medical intensive care unit (ICU) for close monitoring.

Shortly after admission to the ICU, the patient developed large volume free water diuresis with 6 L of dilute urine over 8 h (initial U_{osm} 60 mOsm/kg; repeat 4 h later 40 mOsm/kg). The patient's serum sodium rapidly rose to 126 mmol/L within 12 h and he became drowsy. At that point of time, the decision was made to start desmopressin at 1 mcg *iv* twice a day to minimize dilute urine output, increased to 2 mcg *iv* twice daily the next day. We also administered 5% dextrose in water (D₅W) to replace free water over 10 h, calculated to decrease serum sodium to 120 mmol/L. The patient's serum sodium concentration dropped to 118 mmol/L in 12 h after starting desmopressin and his urine output decreased to ≤ 2 L/d for the next several days. Thereafter, serum sodium was corrected gradually in 2-3 mmol/L daily increments until 130 mmol/L was reached with continued water restriction (Figure 1). After that point, serum potassium was slowly corrected with *per os* potassium supplements, with the resultant and expected auto-correction of metabolic alkalosis, once serum potassium normalized. The patient was released from the medical ICU on day 5 to the medical ward and discharged home on day 11th day with a weight of 71.4 kg. The patient fully recovered without any neurological sequelae and was discharged home with appropriate instructions, including limiting his fluid intake and avoiding self-induced nausea and vomiting.

DISCUSSION

Based on the co-morbid features during admission (hypokalemia, seizures, low BUN, rapid rise of sodium), our patient was at a very high risk of developing ODS^[9,10]. In our patient, nausea and vomiting contributed to the development of both hyponatremia^[11] and metabolic alkalosis^[12]. The presenting clinical picture for our patient on arrival was similar to the syndrome of inappropriate anti-diuretic hormone secretion (SIAD)^[13,14]. In his case, however, the causes for excessive release of vasopressin (or anti-diuretic hormone) were reversible ones: nausea

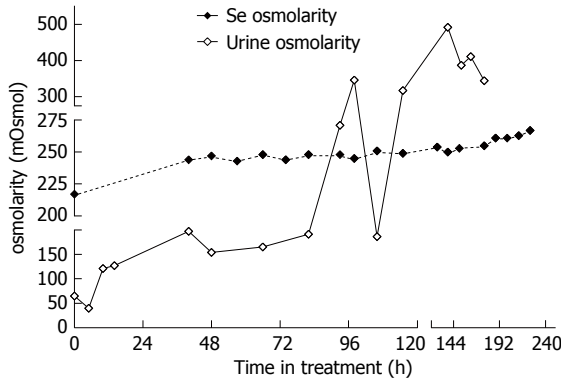


Figure 2 Serum and urine osmolality over time. The patient spent 0-120 h in the intensive care unit.

and hiccups. Nonetheless, once his nausea was resolved, alternative stimuli to maintain the vasopressin level (*e.g.*, hypovolemia) were absent. The patient excreted the free water accumulated prior to admission in the form of dilute urine, leading to the observed large rise of serum sodium. We could not correct metabolic alkalosis with *iv* acid infusions, as neither ammonium chloride nor hydrochloric acid^[15] were available either in our institution or from any of the surrounding healthcare facilities. We specifically monitored serum osmolality to reflect on all osmotically active substances (sodium, potassium and BUN; Figure 2) and avoided sudden correction of hypokalemia, which could have resulted in increased global osmolality^[3,10]. Immediate correction of hypokalemia is associated with ODS^[6,16,17], perhaps due to rise in intracellular potassium.

This case illustrates that administration of desmopressin can be a successful strategy both to ameliorate sodium overcorrection and to avoid inadvertent overcorrection of hyponatremia, if significant free water diuresis emerges during recovery from hyponatremia. Inadvertent overcorrection of hyponatremia is, in fact, common^[18] and should be viewed as a medical emergency^[19]. The administration of hypertonic saline sometimes increases serum sodium more than expected because of unanticipated water diuresis that may develop during the course of therapy. This was the case in our patient, who had additional risk factors for concentration impairment in the kidneys. This prompted us, along with free water administration, to use desmopressin to minimize urine output and alleviate overcorrection of hyponatremia (Figure 3). Avoiding overcorrection with oral intake is difficult since hyposmolality suppresses thirst and patients may reject water that is offered to them. Oral intake is not an option in patients with altered mental status. Finally, attempting to match urinary water losses with intravenous or orally administered electrolyte-free water requires intensive monitoring of fluid balance that is often impractical. Such a strategy has been reported in the medical literature^[20], including in a series of 20 patients, where pre-emptive administration of desmopressin prevented excessive water diuresis and fewer patients required 5% dextrose in water (D₅W) administration for therapeutic re-lowering of the sodium^[21].

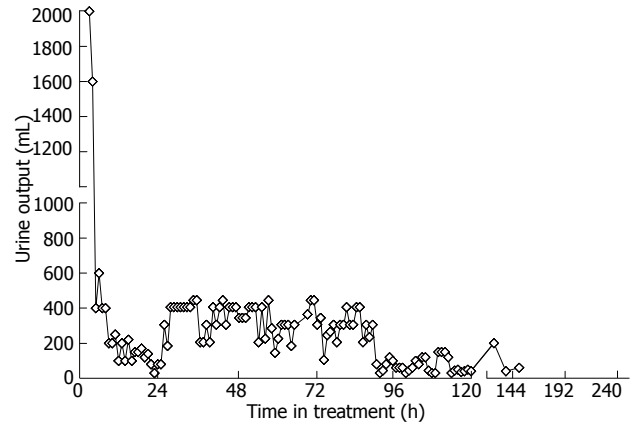


Figure 3 Urine output over time. The patient spent 0-120 h in the intensive care unit.

For these reasons, administration of vasopressin or synthetic vasopressin analog, such as desmopressin may be a more attractive strategy. Our paper strengthens and confirms the limited published experience to date with the use of desmopressin to prevent or reverse overcorrection of hyponatremia, in face of co-existing complex electrolyte disturbances^[22].

In conclusion, controlling nausea or any other reversible causes of excessive vasopressin release may lead to unpredictable free water diuresis in euvoletic hyponatremic patients. Polyuria after symptomatic hyponatremia on presentation is a serious warning sign. Early addition of an antidiuretic hormone analog, such as desmopressin, can limit urine output and prevent unpredictable free water losses with sudden rise in serum sodium, simplifying the managements of these complex and high-risk scenarios.

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Side matters: An intriguing case of persistent left superior vena-cava

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Abstract

Persistent left superior vena cava, usually an incidental finding, is the most common thoracic vein anatomical variation draining into the coronary sinus. Central venous catheter procedures may be complicated secondary to the presence of a persistent left superior vena cava, leading to life-threatening complications such as arrhythmias, cardiogenic shock, and cardiac arrest. We present a case of persistent superior vena cava diagnosed on transthoracic echocardiogram (TTE) in a patient with congestive heart failure. A dilated coronary sinus was identified on TTE, followed by injection of agitated saline into the left antecubital vein resulting in filling of the coronary sinus prior to the right atrium—an indication of persistent left superior vena-cava. This also was confirmed on cardiac computed tomography. Such a diagnosis is critical in patients who may undergo central venous catheter procedures such as our patient's potential requirement for an implantable cardioverter defibrillator due to severe global left ventricular systolic dysfunction. The presence of a persistent left superior vena cava should always be suspected when the guidewire takes a left-sided downward course towards the right

atrium at the level of the coronary sinus. Therefore, special attention should be paid to the imaging work-up prior to central venous catheter procedures.

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Key words: Persistent superior vena-cava; Thoracic vein anomaly; Central venous catheter; Coronary sinus; Left cardinal vein

Core tip: Although the diagnosis of persistent left superior vena cava (LSVC) does not make a pacemaker or implantable cardioverter-defibrillator placement impossible, it does pose significant challenges and complications during the procedure. Accordingly, when patients are being considered for such central venous catheter devices, special attention should be paid to the imaging work-up prior to implantation to identify persistent LSVC if present.

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INTRODUCTION

Persistent left superior vena cava (LSVC) was first described by Edwards *et al*^[1]. This is the most common thoracic vein anatomical variation with a prevalence of 0.3% in the general population^[2]. The persistent LSVC drains into right atrium (RA) *via* the coronary sinus (CS). This is caused by failure in the degeneration of the left cardinal vein^[1]. Central venous catheter based procedures, such as a right heart catheterization, implantable cardioverter-defibrillator (ICD) implantation, and electrophysiological procedures, may become complicated by technical

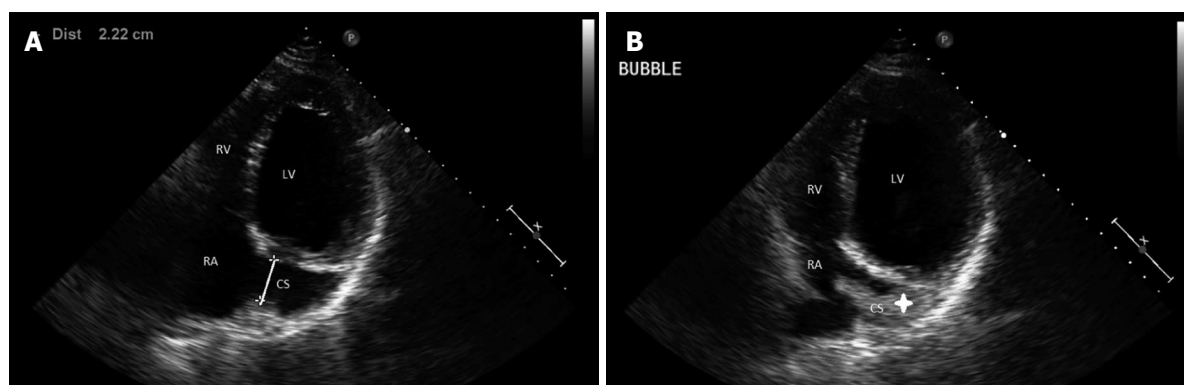


Figure 1 Ultrasonography. A: Modified apical 4 chamber two-dimensional echocardiographic view showing dilated coronary sinus; B: Injection of agitated saline into the left antecubital vein results in filling of the coronary sinus first (star), followed by the filling of the right atrium. CS: Coronary sinus; LV: Left ventricle; RA: Right atrium; RV: Right ventricle.



Figure 2 The axial image of cardiac computed tomography angiography shows the persistent left superior vena cava (arrow).

difficulties to access the right ventricle secondary to the presence of such an anomaly. Persistent LSVC is usually an incidental finding or recognized when a left cephalic or subclavian approach is used for the procedures mentioned above.

CASE REPORT

A 68 year-old Hispanic male with a past medical history of hypertension was referred to the cardiology clinic with shortness of breath, paroxysmal nocturnal dyspnea, lower extremity edema, but no associated chest pain or syncope episodes. His cardiac risk factors include hypertension and class I obesity with a body mass index of 31 kg/m². He was only taking hydrochlorothiazide 25 mg po daily. Twelve-lead electrocardiogram revealed frequent premature ventricular contractions, otherwise unremarkable. Pertinent labs include a brain natriuretic peptide level of 46.8. No cardiac biomarkers were drawn. Transthoracic echocardiogram (TTE) revealed dilated left ventricle with a diminished left ventricular ejection fraction (LVEF) of 30% visually. By Modified Simpson's method, an LVEF of 23% was calculated. In the parasternal long axis view, the interventricular septal diameter was 0.967 cm, the left ventricular posterior wall diameter (LVPwd) was 0.919

cm, the left ventricular end diastolic diameter was 6.29 cm, and the left ventricular mass index was greater than 138 g/m². There was eccentric hypertrophy by relative wall thickness calculation. Grade 1 diastolic dysfunction was observed with E:A reversal, lateral e' of 6.3 and medial e' of 4.8. The left atrial size and volume was in the upper limits of normal. There was normal pulmonary vein flow. Tricuspid annular plane systolic excursion was 2.1 cm/s. No reliable right ventricular dimensions were obtained. Additionally, the CS was dilated at 22 mm (Figure 1A). During injection of agitated saline into the left antecubital vein, it was found that opacification in the CS occurred prior to that in the RA (Figure 1B), contrary to what would normally be expected in such a study. This finding led to the diagnosis of a persistent LSVC. He was additionally noted to have a dilated ascending aorta of 4.3 cm. The aortic root measured 4.1 cm at the sinotubular junction. For further evaluation, the patient underwent a cardiac computed tomography angiography (CCTA) revealing no significant coronary artery disease. The patient's coronary CCTA further demonstrated a persistent LSVC (Figure 2). The patient was started on appropriate medical therapy of bisoprolol fumarate 2.5 mg and lisinopril for non-ischemic dilated cardiomyopathy upon discharge. He has responded well to these therapies (currently New York Heart Association class I) and is due for a follow-up to evaluate his left ventricular function and potential for ICD placement.

DISCUSSION

Multiple imaging modalities can be used to diagnose persistent LSVC including TTE, transesophageal echocardiography, computed tomography, and magnetic resonance imaging^[3]. Our case illustrates how a persistent LSVC was diagnosed on a routine TTE. Although this patient had systolic dysfunction, he did not have chest pain or a history of unstable angina, with normal B-type natriuretic peptide on presentation, and thus, we elected for CCTA *vs* a cardiac catheterization to further evaluate his aortic aneurysm, but to also rule out significant coro-

nary artery disease as CCTA's negative predictive value of assessing coronary artery disease is high. In 2001, 1.73 million coronary angiograms were performed for diagnostic purposes only. Because coronary angiography is associated with a small but not negligible risk of complications (inherent in invasive procedures), inconvenience to patients, and significant costs, coronary CTA may be an attractive alternative to invasive selective coronary angiography, with the potential to reduce the number of purely diagnostic angiograms. Patients with an intermediate likelihood of CAD (between 30% and 70% probability of having significant CAD, as determined by age, sex, and quality of chest pain) may benefit from coronary CTA. According to "2013 ACCF/ACR/ASE/ASNC/SCCT/SCMR Appropriate Utilization of Cardiovascular Imaging in Heart Failure" by Patel *et al*^[4], cardiac catheterization utilization is rarely appropriate in intermediate to low risk patients. Nonetheless, the importance of diagnosing a persistent LSVC can be realized when considering the complications of misplacing a central venous catheter or catheters for electrophysiological procedures that can result in complications such as angina, arrhythmia, cardiogenic shock, and cardiac arrest^[5]. It is imperative to consider the presence of persistent LSVC during a central venous catheter implantation when the guide wire takes a left-sided downward course towards the right atrium at the level of the coronary sinus^[6]. Although the diagnosis of persistent LSVC does not make a pacemaker or ICD placement impossible, it does pose significant challenges and complications during the procedure. Accordingly, when patients are being considered for such central venous catheter devices, special attention should be paid to the imaging work-up prior to implantation to

identify persistent LSVC if present.

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Biventricular pulsus alternans: An echocardiographic finding in patient with pulmonary embolism

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embolism has not been previously reported in the medical literature. We present and discuss the mechanisms of pulsus alternans and its clinical implications.

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Key words: Pulsus alternans; Biventricular alternans; Pulmonary embolism

Core tip: Biventricular pulsus alternans is a rare phenomenon and has only been described in few cases of severe left ventricle systolic dysfunctions and left anterior descending coronary artery disease. Pulsus alternans is an ominous sign that suggests severe heart failure; early recognition can aid in appropriate management and intervention, which may change patient outcome.

Abstract

Pulsus alternans is characterized by regular rhythm with beat-to-beat alternation of systolic pressures. Left ventricular alternans is usually found in severe left ventricular dysfunction due to cardiomyopathy, coronary artery disease, systemic hypertension, and aortic stenosis. Right ventricular alternans is usually associated with left ventricular alternans, right ventricular dysfunction, pulmonary embolism, and pulmonary hypertension. Biventricular alternans is rare and associated with severe left ventricular dysfunction and left anterior descending coronary artery disease. The exact mechanism of pulsus alternans has not been clearly delineated, and it has been remained a subject of investigation and conjecture since the nineteenth century. Two fundamental mechanisms have been proposed to explain ventricular alteration. The first, based on the Frank-Starling mechanism, proposes beat-to-beat alteration in end-diastolic volume accounted for the alternating contractile force. The second proposed mechanism which explains the physiology of pulsus alternans involves the abnormal calcium handling by cardiac myocytes. To the best of our knowledge, biventricular alternans in pulmonary

Nguyen T, Cao LB, Tran M, Movahed A. Biventricular pulsus alternans: An echocardiographic finding in patient with pulmonary embolism. *World J Clin Cases* 2013; 1(5): 162-165 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i5/162.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i5.162>

INTRODUCTION

Pulsus alternans was first described by Traube in 1872, characterized by regular rhythm with beat-to-beat alternation of systolic pressure^[1,2]. Left ventricular alternans occurs commonly in setting of severe left ventricular dysfunctions. Right ventricular alternans are rare, and biventricular alternans are even less common, with only a few case reported in the literature^[3]. To the best of our knowledge, biventricular pulsus alternans in pulmonary embolism has not been previously reported in the medical literature. We describe a case report of biventricular pulsus alternans in pulmonary embolism and discuss its mechanisms and clinical implications.

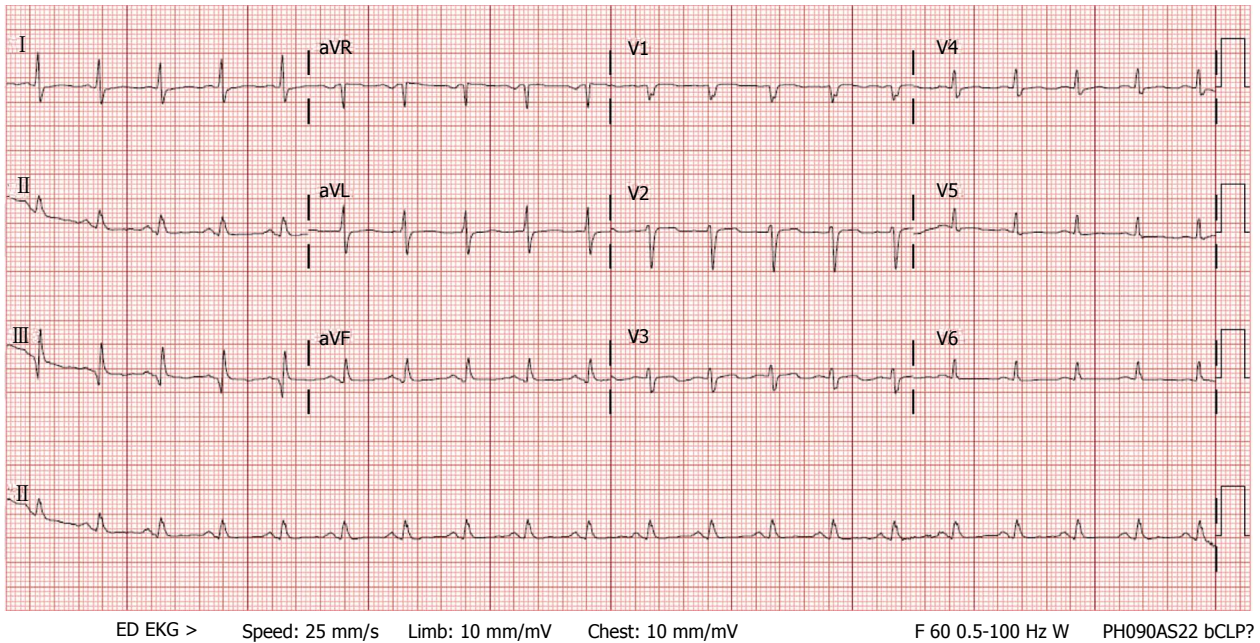


Figure 1 Electrocardiogram shows sinus tachycardia with S1Q3T3, a sign of acute cor pulmonale.

CASE REPORT

A 47-year-old African American male with obstructive sleep apnea, noncompliant with continuous positive airway pressure and stage II chronic kidney disease developed what he thought was the “flu” associated with shortness of breath and chest pressure for the past 6 d. On the morning prior to his hospital admission, the symptoms persisted and were accompanied by rapid palpitations and syncope. Physical examination revealed a morbidly obese man in respiratory distress with a heart rate of 122 beats/min, blood pressure of 120/87 mmHg, respiratory rate of 33 breaths/min, and room air oxygen saturation of 88%. Patient had no jugular venous distention or lower extremity edema, lungs clear to auscultation, no gallops, murmurs or rubs. The electrocardiogram showed sinus tachycardia with S1Q3T3 consistent with acute cor pulmonale (Figure 1). Ventilation perfusion scan showed multiple perfusion defects highly suspicious for multiple pulmonary emboli. Echocardiogram revealed marked biventricular alternans with elevated pulmonary systolic pressure of 50 mmHg. The right ventricle was visually larger than the left ventricle in the four chamber view. In diastole, the right ventricle basal diameter measured approximately 4.8 cm. TAPSE was 1.2 cm. Left ventricular ejection fraction (LVEF) was 60% visually. By Modified Simpson’s method, an LVEF of 70% was calculated. In the parasternal long axis view, the interventricular septal diameter was 1.4 cm, the left ventricular posterior wall diameter was 1.5 cm, the left ventricular end diastolic diameter was 4.6 cm, and the left ventricular mass index was increased at 103 g/m² (Figure 2). There was concentric remodeling by relative wall thickness calculation. Pulmonary embolism was diagnosed, and the patient was

treated with intravenous heparinization, followed by 6 mo of coumarin therapy.

DISCUSSION

Pulsus alternans is usually found in severe left ventricular systolic dysfunctions due to cardiomyopathy^[3], coronary artery disease^[2], systemic hypertension^[2], and aortic stenosis^[4]. It has also been reported in acute transient ischemia and in patient with normal heart during or after supraventricular tachycardia^[5] (Table 1). Right ventricular alternans is usually associated pulsus alternans on the left side^[3]. Isolated right ventricular alternans seems to be related to right ventricular dysfunctions and increased pulmonary resistance due to reactive air way disease^[2], pulmonary embolism^[6], and pulmonary hypertension^[7]. Biventricular alternans is rare, and only few cases have been described in patient with severe left ventricular dysfunction and left anterior descending coronary artery disease^[1,3]. Cournand *et al*^[8] reported biventricular alternans in 9 patients, most of whom had dilated cardiomyopathy, systemic hypertension, congestive heart failure and myocardial fibrosis. In comparison, the patient we described has marked biventricular alternans secondary to pulmonary embolism without left ventricular dysfunction. Massive pulmonary embolisms can cause acute cor pulmonale and can lead to right ventricular alternans; however, it has not known to cause biventricular alternans.

There has been continuing interest in understanding the mechanisms and clinical manifestations of pulsus alternans since its first description by Traube in 1872, although its cause and exact mechanism are poorly understood. Two main mechanisms have been proposed to account for pulsus alternans. The first, based on the Frank-

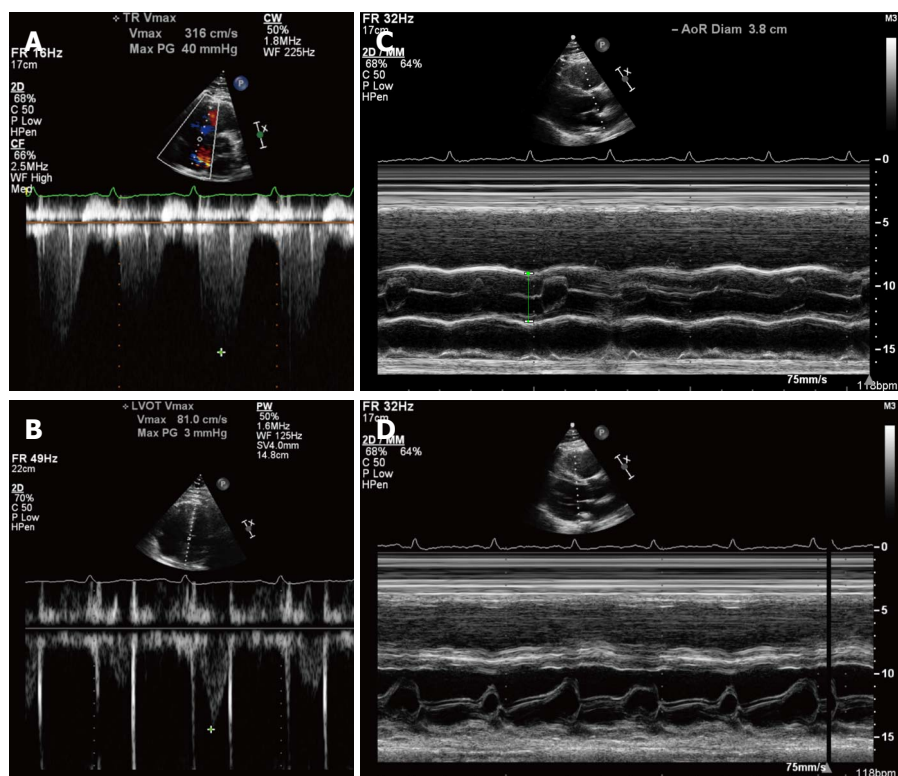


Figure 2 M-mode tracing. A: Beat to beat marked variation of continuous wave Doppler blood flow velocities of tricuspid regurgitation indicative of right ventricular pulsus alternans; B: Beat to beat marked variations of continuous wave Doppler blood flow velocities of left ventricular outflow tract indicative of left ventricular pulsus alternans; C: M-mode tracing showing beat to beat marked variation of aortic valve opening indicative of left ventricular pulsus alternans; D: M-mode tracing showing beat to beat marked variation of mitral valve opening indicative of left ventricular pulsus alternans.

Table 1 Causes of left ventricular alternans

Left ventricular dysfunctions
Systolic and diastolic dysfunctions ^[6,13]
Coronary artery disease ^[2]
Hypertrophic cardiomyopathy ^[3]
Outflow track resistance
Systemic hypertension ^[2]
Aortic stenosis ^[4]
Mitral stenosis ^[5]
Prosthetic valve dysfunction ^[14]
Normal heart
Transient ischemia ^[5]
Marked acceleration of rate ^[9] -dobutamine infusion ^[15]
Hypocalcemia, hypothermia, acidosis ^[11,12]

Starling mechanism, proposes beat-to-beat alteration in end-diastolic volume accounted for the change in force of contraction^[1,9]. Impaired systolic contraction of a failing ventricle reduces stroke volume, resulting in an elevated end diastolic volume for the next contraction. Elevated end diastolic volume results in increased myofibril length and therefore, increased contraction on the next beat^[1,9]. An increase heart rate accentuates this process as diastolic filling is further impaired. Although this mechanism may be contributory, the popularity of this mechanism has waned over the recent years as there is experimental evidence which suggests the absence of alternation in end diastolic volume with the stronger beats of pulsus alternans^[10]. Also in animal studies, pulsus alternans has been produced and maintained with constant preload and lack of alternation in mitral inflow^[5]. The alternation in the contractile state of the myocardium, the “myocardial

theory,” underlies some instances of pulsus alternans but in no way negates the possibility that Frank-Starling principle accounting for some instances of pulsus alternans^[10].

The second proposed mechanism which explains the cause of pulsus alternans is the alteration in cellular handling of calcium during the cardiac contractility^[11,12]. The physiological action-involves the abnormality of intracellular calcium cycling, involving the sarcoplasmic reticulum^[11]. Calsequestrin is a protein in the inner membrane surface of the sarcoplasmic reticulum that binds and stores calcium. Schmidt *et al*^[11] found that mice that overexpressed calsequestrin had pulsus alternans during high heart rates. The study concluded that the mice had a delay between the uptake and release of calcium from the sarcoplasmic reticulum and this alteration in calcium cycling and use led to development of pulsus alternans *in vivo*.

In conclusion, isolated left and right ventricular alternans usually occur in the failing hearts. Biventricular pulsus alternans is a rare phenomenon and has only been described in few cases of severe left ventricle systolic dysfunction and left anterior descending coronary artery disease. To our knowledge, this is the first reported case of pulmonary embolism with echocardiographic finding of biventricular pulsus alternans. In most cases, pulsus alternans is an ominous sign that suggests severe heart failure; early recognition can aid in appropriate management and intervention, which may change patient outcome.

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Long lasting response to second-line everolimus in kidney cancer

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therapy of metastatic renal cell carcinoma after a Tyrosine kinase inhibitor. In the case presented here, everolimus was administered after first line therapy with sunitinib. The prolonged progression-free survival (PFS) obtained with everolimus in this case is of peculiar interest, as it is a multiple of the median PFS obtained in with everolimus in the regulatory trial.

Virtuoso A, Policastro T, Izzo M, Federico P, Buonerba C, Rescigno P, Di Lorenzo G. Long lasting response to second-line everolimus in kidney cancer. *World J Clin Cases* 2013; 1(5): 166-168 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i5/166.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i5.166>

Abstract

In the case presented here, everolimus was administered after first line therapy with sunitinib in a patient with metastatic renal cell carcinoma. The safety profile was excellent. The prolonged progression-free survival (PFS) obtained with everolimus in this case is of peculiar interest, as it is a multiple of the median PFS obtained in with everolimus in the regulatory trial. Such finding suggests that a subset of patients with renal cell carcinoma may particularly benefit from everolimus.

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Key words: Metastatic renal cell carcinoma; Everolimus (RAD001); Sunitinib; Progression-free survival

Core tip: Everolimus (RAD001) is an orally administered inhibitor of the mammalian target of rapamycin pathway. Everolimus is recommended for the second line

INTRODUCTION

After years of disappointing results obtained with the use of cytokines in metastatic renal cell carcinoma (mRCC)^[1,2], the therapeutic armamentarium for the treatment of this disease has recently dramatically expanded to include a variety of multiple agents, such as everolimus, sunitinib, sorafenib, bevacizumab, temsirolimus, and pazopanib, each having a distinct mechanism of action^[3]. Contrary to chemotherapy agents, which simply interfere with cellular replication, these six novel drugs, at the present time approved both in Europe and in the United States, are classified as “targeted agents” because of their ability to interfere with the intra- or extra-cellular signaling of cancerous cells, *via* enzyme inhibition or blockage of growth factors. While bevacizumab is a monoclonal antibody directed against vascular-endothelial growth factor (VEGF), sunitinib, sorafenib, and pazopanib inhibit several tyrosine kinase receptors (TKRs), such as the VEGF receptor, c-KIT, BRAF and others^[3]. On the other hand, temsirolimus and everolimus exert their anti-tumour effect through inhibition of the universal pathway of

Table 1 Food and Drug Administration and European Medicines Agency drug labels

Drug	FDA approval in kidney cancer for	EMA approval in kidney cancer for
Everolimus	Treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib	Advanced renal cell carcinoma (kidney cancer that has started to spread). It is used when the cancer has progressed during or after previous treatment with a medicine that targets vascular endothelial growth factor
Sunitinib	The treatment of advanced renal cell carcinoma	Metastatic renal cell carcinoma, a type of kidney cancer that has spread to other organs
Bevacizumab	The treatment of metastatic renal cell carcinoma in combination with interferon- α	Advanced or metastatic kidney cancer, in combination with interferon- α -2a
Sorafenib	The treatment of patients with advanced renal cell carcinoma	Advanced renal cell carcinoma when anticancer treatment with interferon- α or interleukin-2 has failed or cannot be used
Temsirolimus	The treatment of advanced renal cell carcinoma	Advanced renal cell carcinoma. "Advanced" means that the cancer has started to spread
Pazopanib	The treatment of patients with advanced renal cell carcinoma	Advanced renal cell carcinoma. It is used in patients who have not received any previous treatment or in patients who have already been treated for their advanced disease with anticancer medicines called "cytokines". "Advanced" means that the cancer has started to spread.
Axitinib	Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy	Treatment of advanced renal cell carcinoma when treatment with Sutent (sunitinib) or "cytokines" has failed

EMA: European Medicines Agency; FDA: Food and Drug Administration; RCC: Renal cell carcinoma.

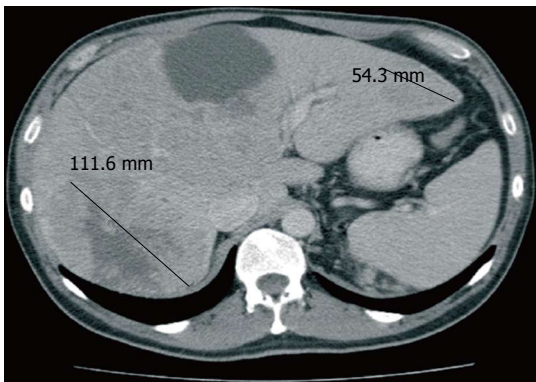


Figure 1 Liver metastasis from metastatic renal cell carcinoma.

mammalian target of rapamycin (mTOR)^[3]. The process of identifying the optimal sequence of administration of these agents is complex and requires execution of large phase III trials. Currently, sorafenib is the standard therapy after unsuccessful treatment with cytokines^[4] and sunitinib is the standard first-line treatment for mRCC^[5]. At present, the only approved targeted agent for second-line treatment of mRCC after failure of a tyrosine kinase inhibitor (TKI) is everolimus (Table 1). This approval was based on the strong results of the large, well-conducted RECORD-1 trial^[6]. The case reported here is highly explicative of the excellent efficacy and safety profile of everolimus employed as second-line treatment of mRCC after failure of a TKI.

CASE REPORT

The subject of this report is a male patient with a history of cigarette use and hypertension controlled with angiotensin-converting enzyme (ACE) inhibitors. In 2006, at the age of 65 years, the patient underwent left radical nephrectomy with lymphadenectomy. Histological analysis

showed the presence of a clear cell carcinoma, presenting intravascular emboli, but no lymph node metastasis and tumour necrosis. According to the radiographic and pathological staging procedures performed, the patient was affected by stage 3 disease (pT_{3a}N₀M₀G₃). The patient's World Health Organization (WHO) performance status was 1. On the basis of staging, grading, and clinical data, the patient could be considered at a high risk of relapse^[7] and underwent a close clinical and radiological follow up performed by his attending urologist. In March 2009, the patient presented a fever and a rash on the face and lamented intense fatigue and flank pain located on the right side. A computed tomography (CT) whole body scan with contrast showed the presence of multiple liver metastases, one of which presented a maximum diameter greater than 10 cm (Figure 1). Considering that haemoglobin levels were 10 g/dL and lactate dehydrogenase (LDH) levels were more than twice the upper limit of normal, with normal serum calcium levels, the WHO performance status of 1 and a disease-free time of approximately 3 years, the patient was classified as being at intermediate prognosis.

In accordance with current available evidence for metastatic kidney cancer^[3], the patient was treated with first-line sunitinib, which was administered according to the standard approved regimen (50 mg/d; 4 wk on, 2 wk off), with a close monitoring of arterial blood pressure, thyroid function, as well as blood count and chemistry. Treatment was well tolerated. The patient presented a single event of Grade 3 leukopenia, Grade 1 mucositis, mild skin discoloration and Grade 1 diarrhoea. In October 2009, after four cycles of sunitinib, the patient showed signs of progressive disease indicated by the whole body CT scan, with multiple lateral cervical adenopathies (maximum 26 mm), a thyroid nodule (30 mm), subpleural lesions in left upper lobe (maximum 6 mm), multiple pulmonary hilar adenopathies (maximum 20 mm) and retro-

crural adenopathies (maximum 24 mm). An echo-guided fine needle aspiration biopsy (FNAB) confirmed the presence of thyroid metastases. Following the patient's diagnosis, everolimus treatment was initiated which was obtained for compassionate use at the dose of 10 mg/d, every day (1 cycle = 30 d), with periodic clinical, radiological, and blood chemistry monitoring.

After 4 mo, the thyroid nodule and laterocervical lymphnodes showed a partial response according to the revised Response Evaluation Criteria In Solid Tumours and was documented by CT scan, which was further confirmed by ecography and physical examination. Liver disease appeared to be stable on CT scan and treatment was well tolerated. The patient only reported a mild itch since the completion of the fourth cycle, which completely regressed with the administration of antihistamines. The patient also experienced an episode of Grade 1 thrombocytopenia during the third, sixth, and eighth cycle, a Grade 1 hypercholesterolaemia, and an acne-like rash during the fifth cycle which was treated with emollient lotions and clindamycin.

The patient continued everolimus until February 2011, receiving a total of 16 cycles of treatment until the patient presented a marked clinical deterioration with progressive disease in the liver and lymph nodes detected by CT scan. The patient received best supportive care recommended for patients with deteriorating performance status and died four months after the interruption of everolimus.

DISCUSSION

The RECORD-1 trial, which compared everolimus to placebo in a population of pretreated mRCC, indicated that median progression-free survival was 4.9 mo in the everolimus group (95%CI: 4.0-5.5), more than double the duration obtained in the placebo group^[6]. The progression-free survival time of this case appears exceptionally prolonged. This notable effect was obtained in addition to an excellent toxicity profile. This case indicates that there is a subset of patients for whom everolimus may work better than other targeted therapies such as sunitinib. Identification of this peculiar subset *via* histological, serum, or radiographic markers, may have substantial clinical implications. Given the current lack of validated markers, we are unable to provide a plausible explanation

for the prolonged disease control obtained in our patient. It is also difficult for us to explain the reasons why a disease which had been stable for several months presented such a rapid progression, although it is clear that selection of resistant neoplastic clones can manifest itself as an aggressive disease.

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Hypoglycemia associated with fluoxetine treatment in a patient with type 1 diabetes

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Abstract

We report on a patient with type 1 diabetes mellitus who presented with recurrent episodes of hypoglycemia and a marked reduction in her daily insulin requirements after introduction of fluoxetine. This 25-year-old Caucasian woman had been followed up at the outpatient clinic for type 1 diabetes mellitus and pre-pregnancy care. She used a continuous subcutaneous insulin infusion with lispro and her daily insulin dose was 0.5 IU/kg per day. She had no chronic diabetic complications or hypoglycemia unawareness. Fluoxetine at a daily dose of 20 mg had been started because of depressive symptoms and within one week, she presented recurrent hypoglycemic episodes that prompted a progressive reduction in the insulin dose down to 0.3 IU/kg per day. The reduced insulin requirements continued during the period of fluoxetine treatment while glycated hemoglobin remained stable. She had no concurrent additional cause to explain the reduced insulin requirements. After fluoxetine was stopped, insulin re-

quirements progressively increased and returned to the patient's usual dose.

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Key words: Fluoxetine; Selective serotonin-reuptake inhibitor; Hypoglycemia; Diabetes mellitus

Core tip: A patient with type 1 diabetes mellitus presented with hypoglycemia and a marked reduction in insulin requirements associated with fluoxetine treatment. Hypoglycemia accompanying treatment with fluoxetine has been reported in patients with type 1 or type 2 diabetes mellitus. Healthcare professionals should be aware of this association for the sake of patient safety.

Biagetti B, Corcoy R. Hypoglycemia associated with fluoxetine treatment in a patient with type 1 diabetes. *World J Clin Cases* 2013; 1(5): 169-171 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i5/169.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i5.169>

INTRODUCTION

Diabetic patients have an increased risk of developing depression (8.5% to 20.0% higher than the general population)^[1-3]. Reports on the impact of antidepressant drugs on glucose homeostasis are diverse: hypoglycemic, hyperglycemic and neutral effects have been described depending on the specific drug^[4]. As to mechanisms, insulin sensitivity seems to be the main effector^[4], with some reports referring to an interaction with hypoglycemic agents^[5,6]. Specifically, fluoxetine has been associated with hypoglycemia^[7,8], hypoglycemia unawareness^[9] and increased insulin sensitivity^[9-11]. In addition, some case reports describe symptoms that suggest hypoglycemia although this was not confirmed on further analysis^[12,13].

Table 1 Summary of studies addressing fluoxetine and glucose metabolism

Reference	Study design	Results
Deeg <i>et al</i> ^[7]	Case report, patient with type 2 DM	Repeated episodes of hypoglycemia in a patient treated with glyburide. Fasting hypoglycemia (with hyperinsulinemia) continued 2 wk after glyburide was suspended and while receiving fluoxetine
Khoza <i>et al</i> ^[8]	Case reports, review of published reports	17 patients with glucose dysregulation (9 hyperglycemia; 8 hypoglycemia, one of them with fluoxetine) after initiation of treatment with antidepressant agents The authors concluded it was not clear whether changes in glucose regulation were due to antidepressants or to changes in mood and lifestyle
Sawka <i>et al</i> ^[9]	Case report, patient with type 1 DM	Reduced insulin requirements and hypoglycemia unawareness during treatment with fluoxetine
Maheux <i>et al</i> ^[10]	Experimental design, obese subjects with type 2 DM	Fluoxetine improved insulin sensitivity in a clamp study, independent of weight loss
Potter van Loon <i>et al</i> ^[11]	Experimental design, obese subjects with and without type 2 DM	Fluoxetine improved hepatic and peripheral insulin sensitivity in a clamp study
Lear <i>et al</i> ^[12]	Case report, patient with type 1 DM	Fluoxetine side effects mimicked hypoglycaemia
Fernández López <i>et al</i> ^[13]	Case report, non-diabetic woman	Clinical presentation with symptoms of hypoglycemia but without analytical confirmation
Briscoe <i>et al</i> ^[14]	Experimental design, patients with type 1 DM	6-wk administration of fluoxetine amplified autonomic nervous system and metabolic counter-regulatory mechanisms during moderate hypoglycemia.
Erenmemisoglu <i>et al</i> ^[15]	Experimental design, healthy and alloxan-induced diabetic mice	Fluoxetine and sertraline did not modify insulin concentrations but reduced plasma glucose
Gomez <i>et al</i> ^[16]	Experimental design, diabetic and non-diabetic rats	Sertraline prevented the increase in glycemia induced by an oral glucose load while fluoxetine had the opposite effect
Kesim <i>et al</i> ^[17]	Experimental design, healthy and diabetic mice	Paroxetine and fluoxetine had no significant or controversial effects on glycemia

DM: Diabetes mellitus.

In one experimental study, it was shown that the autonomic nervous system and metabolic counter regulatory responses to moderate hypoglycemia were amplified by fluoxetine^[14], with symptoms mimicking hypoglycemia. A few studies have reported the influence of fluoxetine on glucose homeostasis to be neutral or hyperglycemic^[15-17].

As severe hypoglycemia is associated with both morbidity and mortality^[18], and non-severe episodes can be the harbinger of severe episodes. For the sake of patient safety, healthcare professionals need to be aware of potential drug interactions that could lead to hypoglycemia^[19].

CASE REPORT

The patient was a 25-year-old Caucasian woman who was diagnosed with type 1 diabetes mellitus when she was 15. At 23 years, she had an infant with a severe cardiac anomaly and at age 24 an insulin pump using lispro insulin was initiated to improve glycemic control as part of pre-pregnancy care. She had no chronic diabetic complications. The patient was receiving a total daily dose of 0.5 IU/kg per day. Her mean self-monitored blood glucose level was stable at 100-130 mg/dL, and she had around two non-severe hypoglycemic episodes per month but no episodes of severe hypoglycemia. Her most recent glycated hemoglobin measurement was 6.8% and her body mass index was 24.0 kg/m². The only previous relevant

event in her medical history was a minor depressive episode two years earlier, resolved without drug treatment.

Following a new depressive episode, the patient was started on fluoxetine, 20 mg *p.o.* a day. Approximately one week later, the frequency of hypoglycemic episodes increased to around 2 per week, prompting a decrease in her insulin requirements to 0.3 IU/kg per day. Over in this period, she reported no relevant modifications in her diet, exercise, and drug treatment or associated conditions. She did not have hypothyroidism or adrenal failure. Glycated hemoglobin decreased to 6.5% and 6.3% one and two months, respectively, after starting fluoxetine and stabilized again at 6.8% at 3 mo. Fluoxetine was stopped several months later and insulin requirements returned to previous values.

DISCUSSION

The mechanisms by which fluoxetine could induce hypoglycemia are listed in Table 1 and include pseudo-hypoglycemia^[12-14], increased insulin sensitivity^[9-11] and interference in the metabolism of sulphonylureas^[5,6]. Some studies, however, have reported that fluoxetine has no influence on glucose metabolism^[15-17]. Experimental studies have shown that fluoxetine improves insulin-mediated glucose disposal independently of weight loss^[10,11]. Nevertheless, the mechanism(s) underlying the association between fluoxetine treatment and increased insulin

sensitivity remain largely hypothetical. Some scientific evidence suggests that fluoxetine can act through a central mechanism^[4], decreasing triglycerides and free fatty acids^[11], or have an effect on glucose oxidation^[10] or on insulin binding to the insulin receptor^[10]. In the present case insulin requirements showed a substantial temporary modification, associated with fluoxetine treatment. This modification points to an effect of fluoxetine on insulin sensitivity, since an increase in insulin secretion would be highly unlikely in a patient with type 1 diabetes mellitus. The time interval did not allow the effect to be mediated through a decrease in body weight. A weakness of this report is that the drug was not reintroduced, and reintroduction is one of the criteria for establishing causality^[20].

Antidepressant drugs can have a variety of effects on glucose homeostasis. Selective serotonin-reuptake inhibitors have been associated with hypoglycemic episodes, as outlined in the technical data sheet of fluoxetine^[21]. The present case expands on these data. For the sake of patient safety, treatment of depression in diabetic patients must take into account the influence of antidepressant agents on glucose homeostasis.

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Burr hole evacuation for infratentorial subdural empyema

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Key words: Infratentorial; Subdural empyema; Burr hole; Evacuation

Core tip: It is general belief that subdural infratentorial empyema needs to be approached through an ample decompressive craniectomy. We present a case of infratentorial empyema managed successfully with burr hole evacuation of infratentorial empyema. We analyzed the characteristics of the case and reviewed the surgical techniques.

Alimehmeti R, Seferi A, Stroni G, Sallavaci S, Rroji A, Pilika K, Petrela M. Burr hole evacuation for infratentorial subdural empyema. *World J Clin Cases* 2013; 1(5): 172-175 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i5/172.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i5.172>

Abstract

Infratentorial empyema is a life threatening condition and constitutes a neurosurgical emergency. Purulent mastoiditis and medial otitis is the most common origin and a thorough eradication of the purulent foci is mandatory. Decompression craniectomy has been primarily advised in the literature as the gold standard of the surgical treatment but burr hole evacuation when there the lack of cerebellar edema is less invasive and deemed equally efficient in the few reported cases. This is the report of a seventeen year old female who presented in a comatose state due to infratentorial empyema with acute hydrocephalus and who improved immediately after burr hole evacuation. Details of the surgical procedures are given. Mastoidectomy was completed, with the patient under combined antibiotherapy. She leads a normal life now, more than six years after surgery.

INTRODUCTION

Infratentorial empyema has been reported most frequently as a complication of middle ear or mastoid purulent infection. The neurological diagnosis may present with difficulties due to insidious development. However, it represents a serious condition necessitating prompt surgical evacuation. Suboccipital craniectomy is claimed to be the gold standard for the treatment of subdural empyema in the posterior fossa, aiming at brainstem and cerebellar decompression together with pus evacuation^[1].

CASE REPORT

A 17-year-old female was admitted to the department of infectious diseases with high fever, moderate headache, right ear pain, general fatigue and malaise. Right hypoacusia and neck rigidity was revealed at physical examination. One week's dosage of oral amoxiclav before hospitalization was ineffective. A fundoscopy did not reveal any evident papillary edema.

Table 1 Summary of cerebrospinal fluid and blood tests

Date	Cerebrospinal fluid				Blood		
	CSF appearance	CSF cells/dL	Composition of CSF cells	Proteinorrachia	Leukocytes	Erythrocyte sedimentation rate	HGB mg/dL
March 11, 2006	Turbulent	8900	Lymph 80% Mening 8% Neutro 12%	1.65	25200	45	12.8
March 21, 2006	Light turbulent	212	Lymph 90% Mening 5% Neutro 5%	0.33	18700	43	12

Neutro: Neutrophils; HGB: Hemoglobin; Lymph: Lymphocytes; Mening: Meningeal cells; CSF: Cerebrospinal fluid.

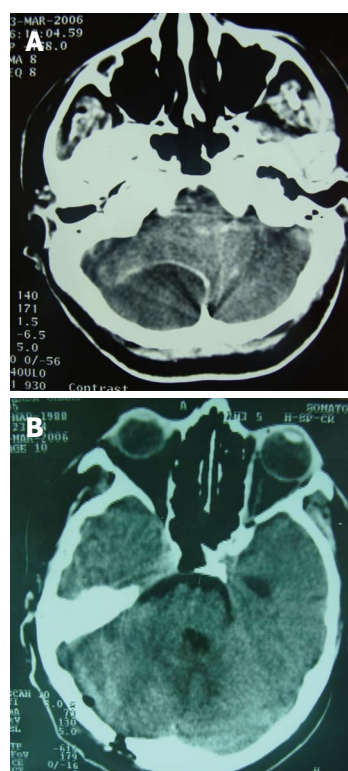


Figure 1 Computed tomography. A: Head computed tomography showing subdural empyema of right cerebellar convexity; fourth ventricle compression and occlusion; B: Burr hole on the right occipital infratentorial convexity; reappearance of fourth ventricle; complete evacuation of subdural cerebellar empyema.

In the absence of an intracranial hypertension, a lumbar puncture (LP) was done (November 3, 2006) and turbulent cerebrospinal fluid (CSF) was extracted. Laboratory examination revealed 8900 cells/dL, proteinorrachia 1.65 g/L. Blood test showed leukocytosis 25200, erythrocyte sedimentation rate 45 s within the first hour, hemoglobin 12.8 mg/dL. A computed tomography (CT) of the head excluded any mass occupying lesion. Despite the negative cultures of the CSF, the diagnosis of purulent meningitis was made and combined therapy was started with ampicillin 3.0 g four times a day (*qid*), amikacin 0.5 g twice daily (*bid*) and kemicetine 1.0 g thrice daily (*tid*).

Another LP (March 21, 2006) revealed 212 cells/dL, proteinorrachia 0.33 g/L, lymph cells 90%, meningeal

cells 5%, neutrophils 5% (Table 1).

With combined antibiotic therapy, the headache, ear pain and neck rigidity improved until the night of March 22, 2006 when the patient presented with confusion, somnolence, neck rigidity, positive Brudzinski and Kernig signs and horizontal nystagmus. The next morning, the patient had a Glasgow Coma Score (GCS) of 8 (E = 2; V = 3; M = 3). CT of the head with intravenous contrast injection documented right posterior cranial fossa empyema 6 cm × 5 cm compressing the right cerebellar lobe that appeared slightly edematous. There was compression of the fourth ventricle and herniation of cerebellar tonsils beyond the occipital foramen associated with three ventricular hydrocephalus. Right mastoid cells were opaque as in case of mastoiditis (Figure 1A). The patient was immediately transferred to neurosurgery for emergency evacuation of empyema. On admission, the patient was in coma GCS 5 (E = 1; V = 2; M = 2), with spontaneous extension of the head in the lateral recumbent position. Under local anesthesia with the patient in left lateral position with the head posed on the head support of the surgical bed, a 6 cm hockey stick incision over the right suboccipital area was made. A burr hole was drilled 2 cm on the right side and 2 cm under the right transverse sinus that corresponded to just in the center of the empyema. Dura mater was discovered attached to the inner layer of the bone without any extradural collection. The tip of a 20 F needle in a syringe was introduced through the dura and 22 mL of pus was withdrawn. At the end of aspiration, a small incision of the dura exposed at the burr hole was done. Cerebellar flocculi were visible without any space left for a catheter to be introduced in the subdural space for eventual drainage. The soft tissue around the burr hole was rinsed with gentamycin and iodopovidone solution and closure of the wound was done. Intravenous vancomycin 1.0 g *tid*, ciprofloxacin 200 mg *tid* was administered. Within one hour, the patient became conscious GCS 12 (E = 3; V = 4; M = 5) and the day after surgery was GCS 15. The culture exam showed no growth of microorganisms. Four days after surgery, the neurological status was normal except for the right hypoacusia. A control CT of the head in the third postoperative day showed complete evacuation of empyema, return of right cerebellar lobe to the normal position and reappearance in the midline of the fourth

ventricle with resolution of the supratentorial hydrocephalus (Figure 1B). Right mastoid cells were still hyperdense. The patient was transferred to the department of otorhinolaryngology for the surgical treatment of mastoiditis. On March 27, 2006, the patient underwent radical right mastoidectomy under general anesthesia. Treatment with vancomycin 1 g *tid*, ciprinol 200 mg *tid*, flagyl 500 mg *tid* was administered until April 4, 2006. After that, ceporin 1 g daily was continued until April 10, 2006. The patient was discharged on April 22, 2006.

More than six years after surgery, the patient remains disease free and leads a normal life. She does not complain of hypoacusia on the right ear and refuses a control magnetic resonance imaging (MRI) of the head.

DISCUSSION

Infratentorial empyema is a rare complication of bacterial infection of the middle ear or mastoid and constitutes only a small percentage of intracranial empyema. It is a life threatening condition due to its mass effect of direct compression to the brain stem and associated supratentorial hydrocephalus. Clinical diagnosis of infratentorial empyema is easily delayed due to its insidious onset and progression^[2].

Clinical signs of infratentorial empyema were mostly absent, with lack of cerebellar findings and cranial nerve deficits in approximately 75% of the patients^[2]. In our case, herniation of cerebellar tonsils manifested with head extension after the patient had already entered a stuporous state.

Most of the reviews on the subject advise an ample decompressive occipital craniectomy, especially in cases of extension of empyema to the cerebellopontine angle^[1]. Ample decompression may serve for managing of cerebellar edema, even after pus evacuation, but it carries other risks, such as brain swelling, infarction or hemorrhage that may result from an injudicious aggressive opening of the dura^[3].

In the presented case, there was no evident extension of the pus to the cerebellopontine angle. Furthermore, pus collection was limited to one side of the occipital squama without excessive cerebellar edema. Most of the mass effect seemed to be caused by empyema. We believe that the consequential three ventricular hydrocephalus was the cause of the comatose state. Spontaneous positioning of the head in extension came with the herniation of cerebellar tonsils in the foramen magnum. Our surgical choice was also influenced by the emergency for immediate evacuation of empyema. In such a situation, we adapted burr hole evacuation of empyema that reopened the fourth ventricle, resolving the hydrocephalus. Through a burr hole, we were able to drain the complete volume of empyema calculated in the CT, verified after the small dura opening that showed cerebellar flocculi, having reached the dura, leaving no space for a subdural drain. Intravenous perfusion with mannitol solution 20% and 15 degree upright position of the head were adapted to alle-

viate possible cerebellar edema and restore CSF dynamics.

In their review, Bok *et al*^[3] conclude that burr holes should not be disregarded as a method of treating subdural empyema.

The successful management of our patient demonstrates that a complete evacuation of subdural empyema can be obtained with equal efficiency through a single burr hole, as with other more invasive approaches such as craniotomy or craniectomy. The mass effect reduction after evacuation of pus was sufficient in our case to remove obstruction from the fourth ventricle and treat the hydrocephalus.

The combination of antibiotics was directed by clinical judgment since the culture study of pus and blood did not reveal any pathogens for a subsequent antibiogram^[4]. Blood culture is reported to be sensitive in only 15% of cases^[4]. *Streptococcus pneumoniae* has been known to be the most common cause of acute otitis media, sinusitis and pneumonia and one of the most important causes of bacterial meningitis^[5-7]. In critically ill patients, cefotaxime or ceftriaxone is most often the primary alternative^[8]. Other alternative drugs include the carbapenems, newer quinolones, clindamycin, telithromycin, linezolid and vancomycin. Treatment guidelines often recommend the use of β -lactam/macrolide combinations as empirical therapy for patients with severe illness^[8-10].

Mastoidectomy was done four days after empyema evacuation, with the patient neurologically recovered from coma. Combined surgical and medical treatment led to complete cure of our patient.

In conclusion, burr hole evacuation may be equally as efficient as other more invasive surgical approaches in the case of infratentorial empyema. This is true especially in the case of cerebellar convexity empyema without extension to the cerebellopontine angle. Once the mass effect of the pus is removed, resolution of hydrocephalus may be expected because of decompression of the fourth ventricle. Whenever complete pus evacuation is possible and there is a lack of extensive cerebellar edema in preoperative CT or MRI, such a technique may be the efficient approach for emergent treatment.

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A case of mucosa-associated lymphoid tissue lymphoma of the gastrointestinal tract showing extensive plasma cell differentiation with prominent Russell bodies

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Abstract

A 73-year-old Japanese woman was hospitalized for detailed examination of nausea, diarrhea and loss of appetite. Atypical erosion in the ileum was found on endoscopy. Biopsy of this erosion showed proliferation of cells containing numerous Russell bodies. Differential diagnoses considered were Russell body enteritis, crystal-storing histiocytosis, Mott cell tumor, immunoproliferative small intestinal disease (IPSID) and mucosa-associated lymphoid tissue (MALT) lymphoma. The cells containing prominent Russell bodies showed diffuse positivity for CD79a and CD138, but negative results for CD20, CD3, UCHL-1, CD38 and CD68. Russell bodies were diffusely positive for lambda light chain, but negative for kappa light chain, and immunoglobulin (Ig)

G, IgA and IgM. Based on these findings, Russell body enteritis, crystal-storing histiocytosis and IPSID were ruled out. As the tumor formed no mass lesions and was restricted to the gastrointestinal tract, MALT lymphoma with extensive plasma cell differentiation was finally diagnosed. The patient showed an unexpectedly aggressive clinical course. The number of atypical lymphocytes in peripheral blood gradually increased and T-prolymphocytic leukemia (T-PLL) emerged. The patient died of T-PLL 7 mo after admission. Autopsy was not permitted.

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Key words: Mucosa-associated lymphoid tissue lymphoma; Plasmacytoma; Russell body; Mott cell tumor; T-prolymphocytic leukemia

Core tip: This report describes an extremely rare case of B-cell neoplasm, comprising mucosa-associated lymphoid tissue (MALT) lymphoma of the gastrointestinal tract showing extensive plasma cell differentiation with prominent Russell bodies. The pathological diagnostic strategy is also discussed. The patient died of sequentially emerging T-prolymphocytic leukemia (T-PLL). Concomitant T-PLL and MALT lymphoma has not been reported previously.

Kai K, Miyahara M, Tokuda Y, Kido S, Masuda M, Takase Y, Tokunaga O. A case of mucosa-associated lymphoid tissue lymphoma of the gastrointestinal tract showing extensive plasma cell differentiation with prominent Russell bodies. *World J Clin Cases* 2013; 1(5): 176-180 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i5/176.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i5.176>

INTRODUCTION

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal lymphoma composed of morphologically heterogeneous small B-cells, including marginal zone cells, cells resembling monocytoid cells, small lymphocytes and scattered immunoblasts and centroblast-like cells. Plasmacytic differentiation is frequently found in cutaneous MALT lymphomas and is a constant and often striking feature in thyroid MALT lymphomas, but is relatively rare in MALT lymphoma of the gastrointestinal tract including gastric lesions^[1]. We encountered a rare case of MALT lymphoma of the gastrointestinal tract showing extensive plasma cell differentiation with prominent intracytoplasmic immunoglobulin (Ig) called Russell bodies. Furthermore, T-prolymphocytic leukemia (T-PLL) emerged sequentially. To the best of our knowledge, no such case has been reported previously in the English literature.

CASE REPORT

A 73-year-old Japanese female was admitted to hospital for detailed examination after she presented with nausea, diarrhea and loss of appetite. She had been taking medication for hypertension and a pacemaker had been implanted for sick sinus syndrome. Laboratory tests on admission revealed mild pancytopenia (red blood cell count, $2.73 \times 10^6/\mu\text{L}$; hemoglobin, 8.3 g/dL; hematocrit, 24.0%; white blood cells, $3.3 \times 10^3/\mu\text{L}$; platelets, $3.3 \times 10^4/\mu\text{L}$). Serology and coagulation tests showed no abnormality: total protein, 5.1 g/dL (normal range, 8.3-6.7 g/dL); albumin, 2.4 g/dL (normal range, 5.0-3.8 g/dL); and C-reactive protein, 1.4 mg/dL (normal range, < 0.30 mg/dL). Protein compartmentation was almost normal. Serological testing revealed positivity for serum anti-human T-lymphotropic virus (HTLV)-1 antibody.

Contrast-enhanced computed tomography of chest, abdomen and pelvic regions showed no specific finding. Endoscopy of the upper gastrointestinal tract showed findings of mild chronic gastritis. Biopsy from the stomach yielded no specific findings such as amyloid or neoplastic lesions. *Helicobacter pylori* (*H. pylori*) infection was histologically examined using hematoxylin and eosin, Giemsa and immunohistochemical staining, but no evidence of *H. pylori* infection was found. Endoscopic study of the colorectum and ileum revealed color-faded cobblestone like erosion in the ileum (Figure 1). Biopsy of this erosion showed proliferation of mononuclear cells with extensive cytoplasm containing numerous eosinophilic globules in the submucosal layer (Figure 2). Morphologically, the eosinophilic globules were considered to represent Russell bodies. Similar histology was observed in a biopsy specimen obtained from an erosion of the rectum found on colonoscopy 2 mo later. Immunohistochemistry for light chain gamma-globulin revealed monoclonality of the lambda chain (Figure 3A). Initial pathological diagnosis of this lesion was crystal-storing histiocytosis.

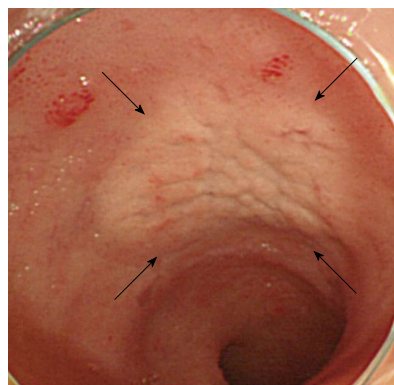


Figure 1 Color-faded cobble-stone like erosion in the ileum (arrows).

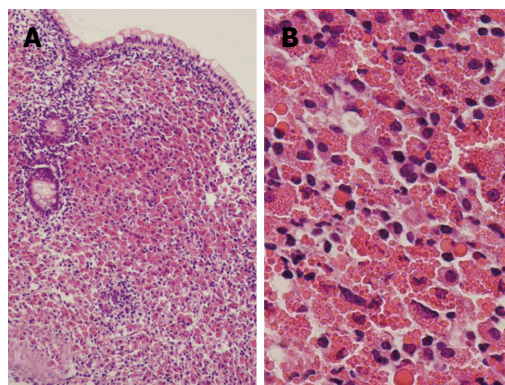


Figure 2 Biopsy specimen taken from the erosion in the ileum, showing proliferation of mononuclear cells containing numerous Russell bodies in the submucosal layer. A: HE, $\times 100$; B: $\times 400$.

The possibility of underlying lymphoproliferative or plasma cell disorders that produce monoclonal Ig, such as plasma cell myeloma, lymphoplasmacytic lymphoma, and monoclonal gammopathy of undetermined significance (MGUS) was clinically considered. Additional examination of peripheral blood revealed high levels of soluble interleukin-2 receptor (sIL-2R) (2280 U/mL; normal range, 122-496 U/mL) and Bence-Jones protein (BJP) was detected from first examination of urine. However, no abnormality was observed on examination of bone marrow and BJP was never detected second or subsequent urine examinations. A definite clinical diagnosis of lymphoproliferative or plasma cell disorder thus could not be made.

The patient was clinically observed using intravenous drip infusion for nutrition. However, the number of atypical lymphocytes in peripheral blood (Figure 3B) and the serum level of sIL-2R gradually increased (maximum: white blood cells, $9.8 \times 10^4/\mu\text{L}$; atypical lymphocytes, 78%; sIL-2R, 4810 U/mL). Analysis by flow cytometry revealed that atypical lymphocytes in peripheral blood expressed CD2, CD3, CD5 and CD7. As this patient was a HTLV-1 carrier, adult T-cell leukemia/lymphoma was initially considered. However, negative results for proviral DNA of HTLV-1 in tumor cells and the evidence of gene rearrangement of T-cell receptor (TCR)-beta/

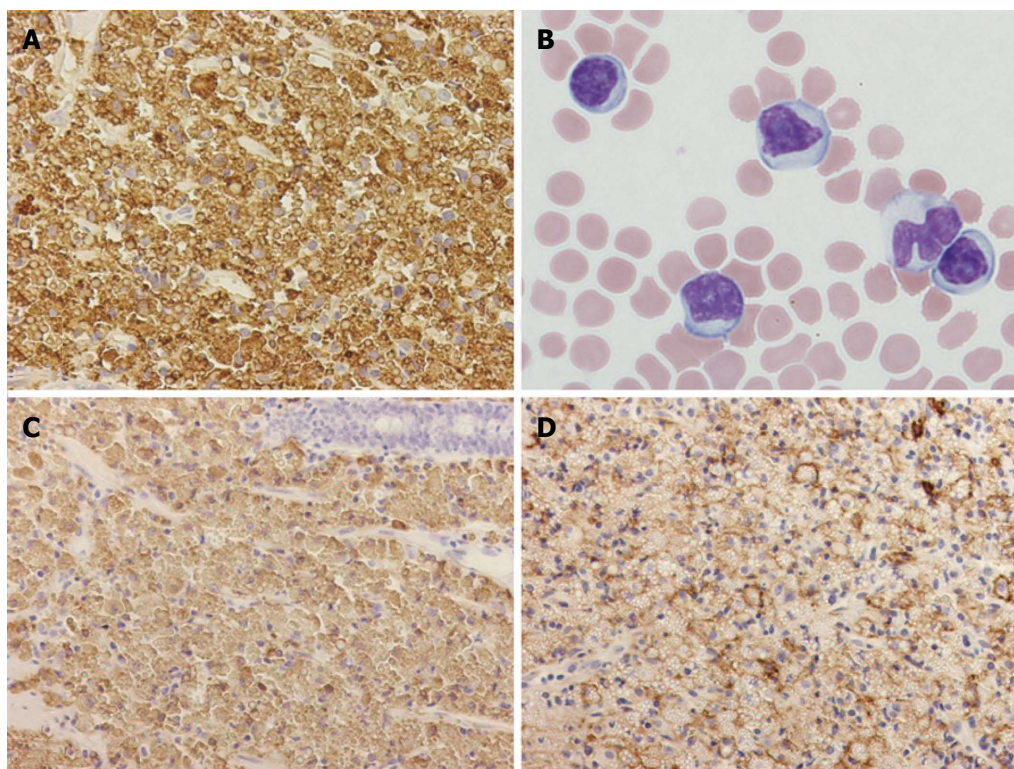


Figure 3 Immunohistochemistry. A: Immunohistochemistry for lambda light chains using biopsy specimen from the ileum ($\times 400$); B: Atypical lymphocytes in peripheral blood diagnosed as T-lymphocytic leukemia (Giemsa stain, $\times 1000$); C: Immunohistochemistry for CD79a using biopsy specimen from the ileum ($\times 200$); D: Immunohistochemistry for CD138 using biopsy specimen from the ileum ($\times 200$).

gamma indicated a diagnosis of T-PLL. The diagnosis of T-PLL was reached 4 mo after admission, but the patient showed complications with several infectious diseases. Although therapies to control infections were performed, chemotherapy for T-PLL could not be initiated because of poor general condition. The patient died of T-PLL 3 months after diagnosis. No autopsy was permitted.

Pathological diagnosis

Although the initial pathological diagnosis of the erosion in the ileum was crystal-storing histiocytosis, further pathological investigation and discussion of the ileal lesion was performed. The cells containing prominent Russell bodies were diffusely positive for CD79a and CD138 (Figure 3C and D), but negative for CD20, CD3, UCHL-1, CD38 and CD68. This indicated the neoplastic tumor cells with plasma cell differentiation rather than secondary deposition of Ig produced by plasma cell disorders of another site. The tumor cells were negative for IgG, IgA and IgM. Immunoproliferative small intestinal disease in the form of alpha heavy chain disease was thus ruled out. The remaining difficulty was whether the case should be categorized as MALT lymphoma or plasmacytoma. As the tumor formed no nodules and was restricted solely to the gastrointestinal tract (ileum and rectum), the final pathological diagnosis was MALT lymphoma showing extensive plasma cell differentiation with prominent Russell bodies.

DISCUSSION

The characteristic feature of ileal lesions in the present case was cells containing prominent Russell bodies. Similar pathology could be observed in Russell body gastritis, crystal-storing histiocytosis and Mott cell tumor. These entities are all rare and therefore not well-known and potentially easily confused.

Crystal-storing histiocytosis is a rare condition in which crystalline material accumulates in the cytoplasm of histiocytes, typically in association with lymphoproliferative or plasma cell disorders such as plasma cell myeloma, lymphoplasmacytic lymphoma, or MGUS^[2,3]. In the present case, although abundant cytoplasm containing numerous globules suggested that these cells were macrophages that had phagocytosed Ig, negative expression of the macrophage marker CD68 ruled out the pathological diagnosis of crystal-storing histiocytosis.

The other potentially confusing entity is Russell body enteritis. Tazawa *et al.*^[4] described a very peculiar, localized accumulation of plasma cells with Russell bodies in the gastric mucosa, which they named Russell body gastritis. Relationships of *H. pylori* have been documented in several series^[5-7], but *H. pylori*-negative cases have also been reported^[8,9]. Only two cases with duodenal lesions have been reported as Russell body duodenitis^[10,11], and lesions of the small intestine, colon and rectum have not previously been described. Russell body gastritis is considered a non-neoplastic, inflammatory lesion and therefore the

Ig produced is usually polyclonal. In the present case, Russell bodies were diffusely positive for lambda light chain. This indicates the produced Ig was monoclonal and additional findings of diffuse positivity for CD79a (B-cell marker) and CD138 (plasma cell marker) indicated that this lesion was a B-cell neoplasm showing extensive plasma cell differentiation with production of monoclonal Ig. The diagnosis of Russell body enteritis was thus ruled out.

The remaining problem is whether to categorize this lesion as MALT lymphoma with extensive plasma cell differentiation or plasma cell neoplasm. Extensive plasmacytic differentiation is frequently found in cutaneous MALT lymphomas^[12] and thyroid MALT lymphomas^[13], but is rare in the gastrointestinal tract. Plasma cell myeloma is a bone marrow-based, multifocal plasma cell neoplasm^[1], and thus is not compatible with the present findings. Although distinction between lymphomas that exhibit extreme plasma cell differentiation and extraosseous plasmacytoma is difficult^[14,15], the present case was finally diagnosed as MALT lymphoma because plasmacytoma usually forms mass lesions, while no mass lesions were identified in the present case.

A Mott cell (also known as a grape cell) is a specific form of plasma cell that contains multiple Russell bodies. Plasmacytoma involving such cells is called Mott cell tumor or grape cell plasmacytoma^[16,17]. Extramedullary Mott cell tumors are rare. Several cases of Mott cell tumor of the gastrointestinal tract including Mott cell tumor-like lesions have been reported^[18-22]. These reported cases were all gastric lesions. We consider the diagnosis of Mott cell tumor as more suitable for plasmacytoma consisting of Mott cells than MALT lymphoma with Russell bodies and/or Dutcher bodies. Given this consideration, the term "Mott cells" was avoided in the diagnosis of the present case.

From the site of involved organs, IPSID, as an alpha heavy chain disease, must be included in the differential diagnosis because the small intestine is typically involved in this pathology. IPSID typically occurs in the Middle East^[23], the Cape region of South Africa^[24] and a variety of other tropical and subtropical locations and plasma cells in IPSID produce IgA. The diagnosis of IPSID did not fit the present case, given the location and absence of IgA production.

The patient died of T-PLL, representing a key aspect of this case. T-PLL is rare, representing approximately 2% of cases of mature lymphocytic leukemia in adults^[25]. The diagnosis is made based on peripheral blood films showing a predominance of small to medium-sized lymphoid cells with non-granular basophilic cytoplasm, round oval or markedly irregular nuclei and a visible nucleolus. TCR genes, TCR beta (TRB@ at 7q34), and gamma (TRG@ at 7p14) are commonly rearranged in T-PLL^[1]. Although response to alemtuzumab (anti-CD52) has been reported^[26,27], the majority of cases show a clinical course of aggressive, chemotherapy-resistant malignancy with a median survival of less than one year. T-PLL has been

associated with the development of second lymphoma. Among the associations reported in the literature are T-PLL and classic Hodgkin disease^[28] in which patients diagnosed and treated for T-PLL developed diffuse large B-cell lymphoma (DLBCL)^[29-31]. Although DLBCL could occur *via* MALT lymphoma, no previous reports have described T-PLL accompanying MALT lymphoma.

Because no autopsy was performed, the spread of MALT lymphoma by the terminal stage was unknown. If nodal involvement, bone marrow involvement or mass lesions of B-cell tumor had been found at autopsy, this case might have been categorized as plasmacytoma and might have been reported as Mott cell tumor. It is also unclear whether the patient's chief complaints involving the digestive tract depended on MALT lymphoma or indolent T-PLL.

In summary, this report describes an extremely rare case of B- and T-cell neoplasms along with the pathological diagnostic strategy. Although unsolved questions remained, we reported this case because of the rarity of the pathology and the educational value of the discussion.

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Fine needle aspiration diagnosis of isolated pancreatic tuberculosis: A case report

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Abstract

Tuberculosis (TB) involving the pancreas are uncommon, especially when present in immunocompetent hosts. Pancreatic TB is more frequently associated with miliary TB or widely disseminated disease. Pancreatic TB may present as cystic or solid pancreatic masses, pancreatic abscess or acute or chronic pancreatitis. Majority of the cases are diagnosed after surgical exploration for presumed pancreatic malignancy and pre-operative diagnosis is quite difficult. However, improvement in imaging techniques and the resulting image-guided interventions gradually can obviate the need for more invasive diagnostic surgical procedures and expedite the planning of therapy. Herein, we report a rare case of isolated pancreatic TB which presented with pancreatic mass lesion in an immunocompetent host. Diagnosis was made by contrast enhanced computed tomography and guided fine needle aspiration of the pancreatic mass which revealed acid-fast bacilli

on Ziehl-Neelsen stain. The case was treated successfully with antituberculous drugs. Pancreatic tuberculosis should be considered in the differential diagnosis of a pancreatic mass when the patient is young, residing in the endemic zone of tuberculosis. Every attempt should be made to diagnose the cases to prevent unnecessary operation.

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Key words: Pancreatic tuberculosis; Pancreatic mass; Pre-operative diagnosis; Computed tomography; Fine needle aspiration; Antituberculous drugs

Core tip: Isolated pancreatic tuberculosis is rare, even in countries with a high incidence of tuberculosis. Pancreatic tuberculosis (TB) is more frequently associated with miliary TB or widely disseminated disease. Pancreatic tuberculosis most commonly presents as a solitary lesion with multiple cystic components. The most important differential diagnosis includes pancreatic malignancy. Majority of the cases are diagnosed after surgical exploration for presumed pancreatic malignancy and pre-operative diagnosis is quite difficult. In the present study, we describe a rare case of isolated pancreatic TB in a 24-year-old man, presented with pancreatic mass lesion in an immunocompetent host. Diagnosis was made by contrast enhanced computed tomography (CT) and fine needle aspiration of the pancreatic mass revealed acid-fast bacilli. The case was treated successfully with antituberculous drugs. Pancreatic tuberculosis should be considered in the differential diagnosis of a pancreatic mass when the patient is young, residing in the endemic zone of tuberculosis.

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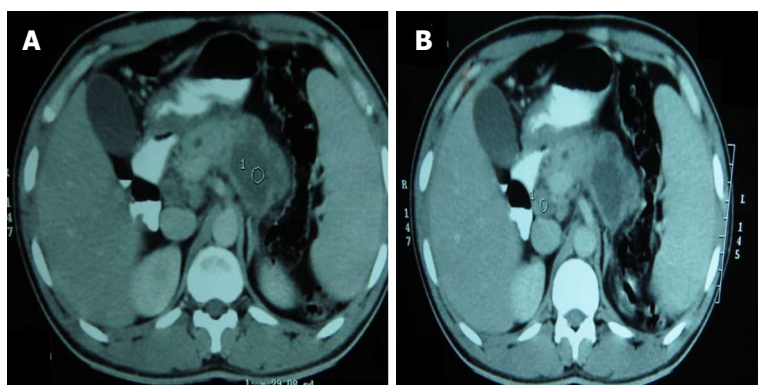


Figure 1 Contrast-enhanced computerized tomography of abdomen showing bulky pancreas (A), retro pancreatic lymphadenopathy (B) and hypodense lesion in the body and tail of the pancreas (3.5 cm × 2.4 cm) with peripheral enhancement.

INTRODUCTION

The abdomen is a common site in setting of extrapulmonary tuberculosis (TB). The prevalence of abdominal TB in developing countries has been estimated to be as high as 12%^[1]. It commonly affects the intestinal tract, lymph nodes, peritoneum and solid organs in varying combinations. Pancreatic and peripancreatic involvements are rare. Majority of the cases occur as a part of disseminated tuberculosis^[2-4]. Isolated involvement of the pancreas is even rarer, probably due to biological resistance imparted by the pancreatic enzymes^[5]. The incidence of pancreatic TB is reported to be less than 4.7% worldwide^[3]. Pancreatic tuberculosis was first reported by Auerbach^[3] in 1944. This review was done as available literature related to pancreatic tuberculosis is mostly in the form of case reports or series and we still lack a complete clinical picture of the disease. Literature search revealed that only nine cases of pancreatic tuberculosis have been reported from India in last 5 years. Clinico-radiologically pancreatic TB closely resembles a pancreatic malignancy. Therefore, most cases of pancreatic TB have been diagnosed after exploratory laparotomy surgery for suspected malignancy. However, with the use of improved imaging techniques computed tomography (CT) or more recently endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and image-guided interventions preoperative diagnosis of pancreatic masses is now possible without going for surgery^[6]. We present a case of isolated pancreatic TB presenting as discrete pancreatic mass in the body and tail with mesenteric lymphadenopathy in an immunocompetent host diagnosed without laparotomy and treated successfully with antituberculosis drugs (ATD).

CASE REPORT

A 24-year-old man presented with, abdominal pain, intermittent episodes of bilious vomiting and low-grade fever of three months duration. The pain was located in the upper abdomen without any radiation to the back. He also admitted having a 5 kg weight loss over this period, anorexia and generalised weakness. He denied any hematemesis, melena, jaundice or altered bowel habits. There was no history of alcohol ingestion. He had no history of exposure to tuberculosis had never partici-

pated in any sexual activity. Physical examination was unremarkable except mild pallor and epigastric tenderness without guarding.

His laboratory studies showed hemoglobin of 10.6 g/dL, total leukocyte count of 9800/ μ L with a normal differential count, an elevated erythrocyte sedimentation rate (86 mm in first hour). Serum amylase was 200 IU/L (reference range: 40-140 U/L) and lipase was 82 IU/L. Liver function tests were normal. A chest radiograph did not reveal any abnormality. The Mantoux test was negative and results of human immunodeficiency virus serology were negative. Ultrasound of the abdomen revealed bulky, inhomogeneous pancreas with a 3.19 cm × 2.2 cm hypoechoic space occupying lesion (SOL) with inner necrosis in body and tail of pancreas with few peripancreatic and a mesenteric lymph node with inner necrosis. Contrast-enhanced CT (CECT) of the abdomen demonstrated bulky pancreas, retropancreatic lymphadenopathy and a low-density lesion in body and tail of pancreas (3.5 cm × 2.4 cm) with peripheral enhancement (Figure 1) without any ascites, bile or pancreatic duct compression or dilatation and ileo-caecal or omental thickening. As the patient had ongoing chronic pain with loss of weight and appetite and a bulky head and body of the pancreas, CT-guided fine needle aspiration was carried out to exclude a pancreatic malignancy. The cytological examination of the fine needle aspiration revealed serosanguinous aspirate, microscopical examination of which suggested granulomatous inflammation with epithelioid cells, pancreatic acinar and ductal cells with patchy necrotic material (Figure 2A). Zeil-Neelsen stain revealed abundant acid-fast bacilli (AFB) on the background of proteinaceous material and inflammatory cells (Figure 2B).

The diagnosis of isolated pancreatic tuberculosis was made based on the above findings and subsequently the patient was treated with antituberculous therapy (ATT) for twelve months. Initial two months he was treated with Isoniazide 300 mg/d, Rifampicin 450 mg/d, Ethambutol 800 mg/d and Pyrazinamide 1500 mg/d. Subsequently for next ten months he was treated with rifampicin 450 mg/d and isoniazide 300 mg/d. The patient improved with the therapy and was asymptomatic after completing two months of therapy. Repeat ultrasound revealed significant resolution of pancreatic hypoechoic collection

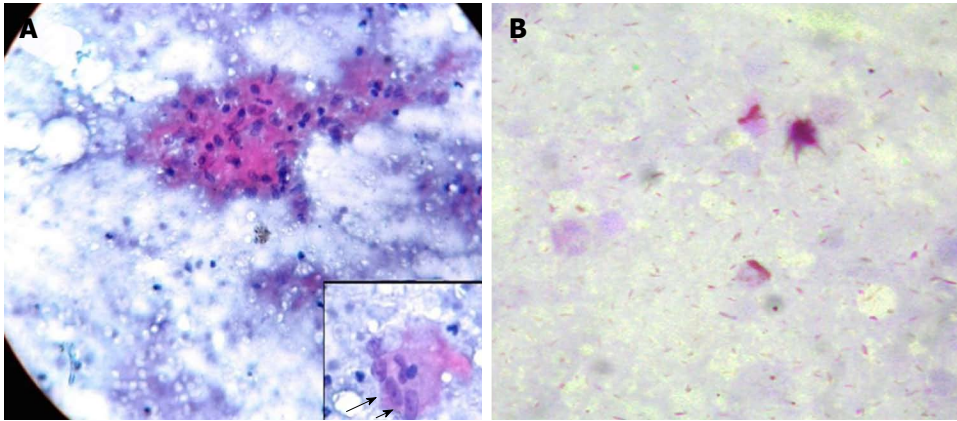


Figure 2 CT guided fine-needle aspiration cytology from the pancreatic lesion shows collection of epithelioid cells (inset) forming granuloma along with pancreatic ductal and acinar cells with patchy necrotic material (Giemsa staining) (A), Ziehl-Neelsen stain showing acid fast bacilli in the background of proteinaceous material (B).



Figure 3 Review Contrast-enhanced computerized tomography of the abdomen performed at 9 mo of ATT showing near complete regression of pancreas size and resolution of hypodense lesion at body and tail.

and regression of lymph node. A repeat CECT of the abdomen performed after 9 mo of the therapy revealed a normal pancreas with near complete resolution of hypoechoic lesion (Figure 3). No varices were noted on upper gastrointestinal endoscopy. After three months of follow-up, the patient is asymptomatic.

DISCUSSION

Tuberculosis is a major health problem in developing countries, with an annual incidence of 9.7 million cases of TB; highest incidence being in Asia, South America, Eastern Europe, and most sub-Saharan African countries. Although pulmonary TB is the most common presentation of disease; extrapulmonary TB (EPTB) accounts for nearly 20% of all cases of TB in immunocompetent hosts^[7]. Abdominal TB includes infection of varying combinations of the intestinal tract, peritoneum, and solid organs such as the spleen, liver, and pancreas. Isolated pancreatic TB is extremely uncommon, with pancreatic involvement usually occurring in the setting of miliary or widely disseminated TB; often in immunocompromised

hosts^[8,9]. Pancreatic tuberculosis was first reported by Auerbach in 1944. In his series of 1656 autopsies of tuberculous patients, only 14 cases had pancreatic involvement that may have mimicked neoplasia but did not find any cases of isolated pancreatic tuberculosis. The incidence of pancreatic TB is reported to be less than 4.7% worldwide^[3,10]. It has been speculated that tubercular involvement of the pancreas might occur as a result of direct extension, lymphohematogenous dissemination, and reactivation of a previous abdominal focus or immune reaction to generalized tuberculosis^[8,11].

Pancreatic tuberculosis usually affects young adults but convincing epidemiological data with regards to age and sex distribution is not available. Nine cases of pancreatic tuberculosis have been reported from India in last 5 years^[12-18]. Clinical data are summarized as Table 1. Among this group are 3 men and 6 women with an overall mean age of 33.2 years. The mean age among men was 36 years and mean age among women was 31.83 years. In all of these cases a presumptive diagnosis other than tuberculosis were made reflecting the diagnostic challenge faced when encountered with such cases. The challenge is partly because of rarity of the disease itself and partly due to its nonspecific presentation mimicking pancreatic malignancy.

In a study by Saluja *et al*^[19], the three most common presenting complaints in patients found to have pancreatic TB were abdominal pain, jaundice, and weight loss. Individuals infected with pancreatic TB may also present with fever, gastrointestinal hemorrhage secondary to splenic vein thrombosis, and anorexia. In our case, there was involvement of the body and tail of the pancreas. Xia *et al*^[20] have summarized characteristic features of pancreatic tuberculosis as follows: (1) mostly occurs in young people, especially female; (2) have past history of tuberculosis or come from endemic zone of tuberculosis; (3) often present with epigastric pain, fever, and weight loss; and (4) ultrasound or CT scan show pancreatic mass and peripancreatic nodules, some with focal calcification.

Table 1 Summary of reported cases of pancreatic tuberculosis from India in the last 5 years

Ref.	Age (yr)/sex	Presenting symptoms	Pulmonary tuberculosis	Location	Nature of mass	Lymph nodes	Invasion	Pancreatic duct and bile ducts	Presumptive diagnosis	Confirmation of diagnosis	ATT with duration	Outcome
Ray <i>et al</i> ^[12]	50/Female	Pain abdomen	-	Head	Cystic	Present	None	Normal	Pancreatic malignancy	CT guided FNAC	HRZE 6 mo	Good
	15/Female	Pain abdomen, weight loss	-	Head	Cystic	Present	None	Normal	Pancreatic malignancy	EUS guided FNAC	HRZE 6 mo	Good
	13/Female	Pain abdomen, weight loss	-	Head	Cystic	Present	None	Normal	Pancreatic malignancy	EUS guided FNAC	HRZE 6 mo	Good
Arora <i>et al</i> ^[13]	48/Male	Pain abdomen, weight loss	-	Head	Cystic	Absent	None	Bile Duct dilatation	Pancreatic malignancy	EUS guided FNAC	HRZE 6 mo	Good
Gupta <i>et al</i> ^[14]	24/Male	Pain abdomen, jaundice	-	Head	Cystic	Absent	Portal vein, splenic artery, hepatic artery	Biliary radicles and bile duct dilatation	Pancreatic malignancy	EUS guided FNAC	HRZE 8 mo	Good
Rana <i>et al</i> ^[15]	40/Female	Pain abdomen, jaundice	-	Head	Cystic	Absent	Portal vein	Pancreatic and common bile duct dilatation	Pancreatic malignancy	EUS guided FNAC	HRZEx2, HRx10	Good
Singh <i>et al</i> ^[16]	45/Female	Pain abdomen, bilious vomiting	-	Head and uncinate process	Cystic	Present	Duodenum, portal vein	Pancreatic and common bile duct dilatation	Pancreatic malignancy	Laparotomy and Whipple's Pancreaticoduodenectomy	HRZE x 3 until first follow up	Good
Pandita <i>et al</i> ^[17]	28/Female	Pain abdomen, dyspepsia	-	Head and body	Cystic	Absent	None	Normal	Pancreatic malignancy	CT guided FNAC	HRES 1 yr	Good
Bhatia <i>et al</i> ^[18]	36/Male	Epigastric pain abdomen	Past history: 4 yr back	Head and body	Cystic	Absent	Right lobe of liver	Not dilated	Intraductal pancreatic mucinous tumour	EUS guided FNAC	HRZE 8 mo	Good

CT: Computed tomography; EUS: Endoscopic ultrasound; FNAC: Fine needle aspiration cytology.

Other reported presentations are obstructive jaundice, acute or chronic pancreatitis, pancreatic abscess, portal vein thrombosis causing portal hypertension, *etc.* Tuberculin skin testing and an interferon- γ release assay for TB may be negative in patients with abdominal tuberculosis because of poor nutritional status leading to a weak immune response as happened in our case^[8,15].

Several imaging methods like transcutaneous ultrasound, CT scan and endoscopic ultrasound are used for assessment of pancreatic pathology. The imaging findings may suggest the possibility of tuberculosis, but none of the findings are pathognomonic for pancreatic tuberculosis. Ultrasound is often the first investigation used for diagnosis of pancreatic tuberculosis which may reveal focal hypoechoic mass or cystic lesion of the pancreas mostly situated in the head and uncinate process of the pancreas. CT scan is still regarded as the investigation of choice for pancreatic pathology. CT scan may show hypodense lesion with irregular border in the head of the pancreas, diffuse enlargement of the pancreas or enlarged peripancreatic lymph nodes^[21,22]. The presence

of hypodense peripancreatic lymph nodes with rim enhancement, ascites and/or mural thickening affecting the ileo-caecal region suggests the pancreatic tuberculosis^[22]. Magnetic resonance imaging (MRI) findings of focal pancreatic tuberculosis include a sharply delineated mass in the pancreatic head showing heterogeneous enhancement which is hypointense on fat-suppressed T1-weighted images and show a mixture of hypo- and hyperintensity on T2-weighted images^[23]. An important image finding in pancreatic tuberculosis is the normal appearing common bile duct and the pancreatic duct, even if the mass is positioned centrally in the head of the pancreas. This in contrast to pancreatic adenocarcinoma where the pancreatic duct is dilated in centrally located tumors in the head region. The diffuse form of pancreatic tuberculosis is characterized by pancreatic enlargement with narrowing of the main pancreatic duct and heterogeneous enhancement^[23]. Bile cytology on endoscopic retrograde cholangiopancreatography (ERCP) may occasionally help in establishing the diagnosis^[19,24]. D'Cruz *et al*^[25] further suggested that there is no radiographical difference between

cystic neoplasm of the pancreas and pancreatic TB abscess formation, as both can present as septated masses with surrounding hypodense lymphadenopathy.

Since there are no clinical, laboratory or radiological features which are specific for pancreatic tuberculosis, histopathological or cytological as well as bacteriological confirmation is necessary for establishing the diagnosis of isolated pancreatic tuberculosis. Percutaneous imaging or endoscopic ultrasound-guided fine needle aspiration of the pancreatic lesion have been reported for establishing a diagnosis of pancreatic tuberculosis^[6,26-28]. EUS is preferred for obtaining tissue biopsy because of less chances of needle tract dissemination particularly if the mass seems to be malignant. In a recent series by Song *et al.*^[29], EUS-FNA was able to diagnose pancreatic/peripancreatic tuberculosis in 76.2% of patients. The microscopic features of tuberculosis are caseation necrosis and presence of acid fast bacilli. Caseating granuloma is seen in 75%-100% of cases, and acid-fast bacilli are identified in 20%-40% of cases^[29]. In our case the diagnosis was done by CT guided FNAC and the ZN staining showed plenty of AFB.

Once the diagnosis is made, antituberculous drugs should be started as early as possible. Majority of the patients show symptomatic improvement within two weeks. Because of the rarity of this disease, there are no specific treatment guidelines. The majority of cases of pancreatic tuberculosis respond well to 6-12 mo of anti-tubercular therapy and their prognosis is good (Table 1). In our case ATT was given for 12 mo with a repeat CT scan at 9 mo showing near complete resolution of the pancreatic mass.

In a conclusion, isolated pancreatic tuberculosis is rare, even in countries with a high incidence of tuberculosis. Radiologically, pancreatic tuberculosis presents typically as a solitary lesion located in the body or head with peripancreatic lymph nodes. Therefore, diagnosis is a challenge, calling for a team approach with the goal of making the diagnosis non-invasively. A more recent development includes endoscopic ultrasound-guided fine-needle aspiration for histological and microbiological tuberculosis diagnosis; thereby, major surgery may be avoided. Clinical awareness of pancreatic TB may guide clinicians to appropriate diagnostic studies and management; which may lead to alleviation of symptoms and possible resolution of pancreatic masses with ATT.

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Recurrent epithelial ovarian cancer and hormone therapy

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INTRODUCTION

Hormone therapy for ovarian cancer is not mentioned in the Treatment Guidelines for Ovarian Cancer 2010 Edition and the role of hormone therapy for treatment of ovarian cancer in Japan is not clear. In the NCCN guidelines (ver. 3 2012), hormone therapy is classified under “other drugs that are potentially effective” as “approved treatment for recurrent forms” of epithelial ovarian cancer, which include anastrozole (aromatase inhibitor), letrozole (aromatase inhibitor), leuporelin acetate (Gn-RH analog), megestrol acetate (synthetic progestin, not approved in Japan) and tamoxifen (antiestrogen). However, information on the efficacy of these drugs for recurrent ovarian cancer come from phase II studies or retrospective studies, and the evidence level is not very high. Recently, a phase III randomized comparative study of thalidomide and tamoxifen in patients who had marker recurrence after initial complete remission of stage III and IV ovarian epithelial cancer, fallopian tube cancer, or peritoneal cancer was conducted^[1]. However, due to the increased risk of death among the thalidomide group and the increased incidences of adverse events, the study was prematurely discontinued and the efficacy of tamoxifen was to be determined based on comparative studies with an untreated group or other drugs^[1]. Here, we review the antiestrogens (tamoxifen, fulvestrant) and aromatase inhibitors (letrozole, anastrozole) with relatively large amounts of data on their efficacy in recurrent ovarian cancer.

Abstract

The role of hormone therapy in the treatment of ovarian cancer is not clear. Data on the efficacy and safety of antiestrogens and aromatase inhibitors in recurrent ovarian cancer have been accumulated through phase II clinical studies. Most of these studies were conducted in platinum-resistant recurrent ovarian cancer, and although complete response rates were not high, reported adverse events were low. If administered to patients who are positive for estrogen receptors, hormone therapy may become a viable option for the treatment of recurrent ovarian cancer.

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Key words: Recurrent ovarian cancer; Hormone therapy; Letrozole; Anastrozole; Tamoxifen; Fulvestrant

Core tip: If administered to patients who are positive for estrogen receptors, hormone therapy may become a viable option for the treatment of recurrent ovarian cancer.

OVARIAN CANCER AND HORMONE THERAPY

Several risk factors are involved in the development of ovarian cancer. The most certain risk and preventive fac-

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tors are estrogen replacement therapy, obesity and oral contraceptives^[2]. The estrogen hypothesis assumes that ovarian cancer is caused by the exposure of ovarian surface epithelium to estrogen, which supports the identification of an increase in estrogen converted from androgen by increased aromatase in the adipocytes due to obesity as a risk factor. Since the use of oral contraceptives suppresses the production of estrogen, it is consistent as a preventive factor. In a nurse health study conducted between 1976 and 2002, 82905 post-menopausal women including 389 ovarian cancer patients were enrolled, and a prospective observational study was performed^[3]. Women who were receiving hormone replacement therapy with estrogen alone had a significantly increased risk by 1.25 fold-of developing ovarian cancer, and it was reported that coadministration with progesterone could reduce the risks^[3].

Estrogen stimulates tumor growth *via* estrogen receptor (ER). In a recent large-scale study, 36% of ovarian cancers were positive for ER^[4]. Antiestrogens such as tamoxifen block the ER pathway, and aromatase inhibitors inhibit the synthesis of estrogen itself. In theory, both antiestrogens and aromatase inhibitors should exhibit antitumor effects against ovarian cancer. ER activates expression of genes involved in cell survival and proliferation, thus promoting tumor growth and progression, while the function of ER has been found to be anti-proliferative and pro-apoptotic^[5]. Growth response to estrogen in hormone responsive ovarian cancer cell lines was shown to be mediated by ER and not by ER^[6,7]. A better understanding of ER signaling in ovarian cancer will permit refinement of combinations of targeted therapy with standard hormonal agents to improve treatment^[8].

ANTIESTROGENS (TAMOXIFEN, FULVESTRANT)

Tamoxifen is an antiestrogen for which many phase II studies in recurrent ovarian cancer have been conducted between 1980 and 2000. In the GOG study performed in 1991, 105 recurrent ovarian cancer patients including those with platinum-sensitive and resistant cancer received oral tamoxifen 20 mg/d as second line chemotherapy^[9]. The complete response (CR) rate was 17%^[9]. The disease control rate (DCR) including stable disease (SD) was 55%^[9]. The rate of ER detection was 59% in partial response (PR) and SD and 89% in CR, which demonstrated a correlation between ER expression and tamoxifen treatment response^[9]. Based on this study, the CR rate reassessed for platinum-resistant recurrent cancer patients was 13%^[10]. In a review by Tropé *et al.*^[11] that includes the results of their own studies, in 647 recurrent ovarian cancer patients, the CR rate of tamoxifen was reported to range from 0% to 56%, with a mean CR rate of 11%. There are inconsistencies between reports on the correlation between ER expression and tamoxi-

fen treatment response^[12,13]. Meanwhile, a phase II study was performed in which fulvestrant, a new antiestrogen approved for the treatment of postmenopausal hormone sensitive progressive/recurrent breast cancer, was used for the treatment of recurrent ovarian cancer^[14]. Twenty-six recurrent ovarian cancer patients who had received a regimen of, on average, 5 types of anticancer drugs received muscular injection of fulvestrant 500 mg on day 1, 250 mg on day 15, and 250 mg on day 29. When this was repeated over a 28-d cycle, the CR rate was 8%. However, DCR including SD was 50%, and the median time to progression was 62 d^[14].

AROMATASE INHIBITORS (LETROZOLE, ANASTROZOLE)

From 2000, there are reports of phase II studies on aromatase inhibitors in recurrent ovarian cancer. The first report is by Bowman *et al.*^[15] on a phase II study of letrozole. When 50 recurrent ovarian cancer patients received letrozole 2.5 mg/d orally, although there was no CR or PR, 10 patients maintained SD for 12 wk. ER was significantly higher in the tumors of SD patients than in the PD group^[15]. Another phase II study examined the effect of letrozole by accumulating only the cases of ER-positive recurrent ovarian cancer. In a study by Smyth *et al.*^[16], 42 ER-positive recurrent ovarian cancer patients received letrozole 2.5 mg/d orally. Of the 33 patients who had a measurable lesion, 3 patients (9%) achieved PR and 14 patients (42%) maintained stable disease state for 12 wk^[16]. The study showed a positive correlation between the level of ER expression and treatment response^[16]. In a similar study where ER-positive recurrent ovarian cancer patients received letrozole 2.5 mg/d orally, clinical benefit (PR or SD) was observed in only 26% of patients^[17]. Meanwhile in another study in which 27 recurrent ovarian cancer patients, regardless of ER expression, received letrozole 2.5 mg/d orally, 1 patient (4%) achieved CR, 3 patients (11.1%) had PR, and 5 patients (18.5%) had SD, with DCR in 33.6% of patients, although no correlation was found between ER expression and treatment response^[18]. In a phase II study in which 53 recurrent ovarian cancer patients received anastrozole 1 mg/d orally, only 1 patient had PR, and SD over 90 d was observed in 42% of patients^[19]. This study also could not find any correlation between ER expression and treatment response^[19].

Reasons for the inconsistencies in the correlation between DCR value/ER expression and treatment response in the reports of antiestrogens and aromatase inhibitors include the small numbers of enrolled patients, differences in patient backgrounds including past treatment histories, and differences in the method of measuring ER. Based on the DCR, antiestrogens and aromatase inhibitors may both become an option in the treatment of recurrent ovarian cancer. However, in the future, it is important to examine the efficacy of these

Table 1 Therapeutic effect of antiestrogens and aromatase inhibitors on relapsed ovarian cancer *n* (%)

Ref.	Agents	Dose and usage	The kind of study	No. of patients	CR
Schwartz <i>et al</i> ^[12]	Tamoxifen	Oral 20 mg daily, maximum is 3210 mg	Phase II	13	0
Weiner <i>et al</i> ^[13]	Tamoxifen	Oral 40 mg for 7 d, then 20 mg <i>po</i> daily	Phase II	31	1 (3.2)
Hatch <i>et al</i> ^[9]	Tamoxifen	Oral 20 mg daily	Phase II Platinum sensitive/resistant	105	10 (9.5)
Tropé <i>et al</i> ^[11]	Tamoxifen	Oral 30 mg or 40 mg daily	Phase II Platinum sensitive resistant	66	2 (3)
Argenta <i>et al</i> ^[14]	Tamoxifen	Day 1500 mg <i>im</i> day 15 250 mg <i>im</i> day 29 250 mg <i>im</i>	Phase II Platinum sensitive resistant	26	1 (4)
Bowman <i>et al</i> ^[15]	Letrozole	Oral 2.5 mg daily	Phase II	50	0
Papadimitriou <i>et al</i> ^[18]	Letrozole	Oral 2.5 mg daily	Phase II Platinum sensitive/resistant	27	1 (4)
Smyth <i>et al</i> ^[16]	Letrozole	Oral 2.5 mg daily	Phase II Platinum sensitive/resistant	33	0
Ramirez <i>et al</i> ^[17]	Letrozole	Oral 2.5 mg daily	Phase II Platinum resistant	31	0
del Carmen <i>et al</i> ^[19]	Letrozole	Oral 1 mg daily	Phase II	53	0

CR: Complete response.

drugs in hormone receptor positive ovarian cancers in a greater sample size with a more homogenous patient background.

ADVERSE REACTIONS IN HORMONE THERAPY

Very few adverse events have been reported in phase II studies. The number of serious adverse events (grade 3 and 4) is extremely small. In studies of antiestrogens, the only adverse events observed were deep vein thrombosis in 1.4% of patients, and grade 3 gastrointestinal symptoms in 1.4%^[1]. There were relatively greater occurrences of nausea, vomiting, hot flush, arthralgia and malaise; however, the symptoms were mild^[1]. In studies of aromatase inhibitors, there were no grade 3 or 4 adverse events, and adverse reactions, which included hot flush, sweating, malaise, queasy, and headache, were mild^[16-19]. The incidence of arthralgia was relatively low^[19].

INDICATIONS AND ADMINISTRATION OF HORMONE THERAPY IN OVARIAN CANCER

With antiestrogens and aromatase inhibitors, there are few occurrences of adverse events, and tolerability is high. Therefore, even if the general conditions are not favorable, unlike cytotoxic anticancer drugs, hormone drugs are beneficial in that they can be used over a relatively long period. In Japan, hormone therapy is not mentioned in the guidelines of ovarian cancer, however, it is likely to provide an option treatment which is not the treatment for cure but to prevent the progression of the disease for the recurrent ovarian cancer patients who have already been treated with various anticancer drugs and have no alternative treatment.

Evidence for hormone therapy for the treatment of ovarian cancer has been established from small-scale phase II studies (Table 1). In many of these clinical studies, patients were not selected based on the hormone receptors in their ovarian cancer, and since patient backgrounds were different, this may be affecting the response rate to hormone

therapy and masking its clinical benefits. It is desirable that prospective clinical studies in tumors with confirmed hormone receptors be planned to establish the effects and the role of hormone therapy.

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Infliximab for the treatment of pouchitis

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Core tip: Pouchitis represents the most frequent long term complication of the ileal pouch anal anastomosis and consists of an idiopathic nonspecific inflammation of the ileal mucosa of the pouch. Several studies show the effectiveness of treatment with anti-tumor necrosis factor- α in chronic forms in reducing the synthesis of pro-inflammatory molecules and in restoring the balance between pro-inflammatory and anti-inflammatory cytokines.

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Abstract

Pouchitis is not a rare complication that develops after an ileal-pouch anastomosis, performed after colectomy in patients refractory to treatment or with complicated ulcerative colitis. This condition may become chronic and unresponsive to medical therapies, including corticosteroids, antibiotics and probiotics. The advent of biological therapies (tumor necrosis factor- α inhibitors) has changed the course of these complications. In particular, in these cases, infliximab (IFX) may represent a safe and effective therapy in order to avoid the subsequent operation for a permanent ileostomy. This article reviews the therapeutic effects of one of the most widely used anti-tumor necrosis factor- α molecules, IFX, for the treatment of complicated pouchitis (refractory to conventional treatment and/or fistulizing).

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Key words: Ileal pouch-anal anastomosis; Infliximab; Pouchitis; Tumor necrosis factor- α ; Ulcerative colitis

INTRODUCTION

Approximately 10% to 30% of patients with ulcerative colitis (UC) refractory to conventional treatment, hemorrhage, perforation, dysplasia or cancer will require surgery^[1]. The ileal pouch-anal anastomosis (IPAA) is widely accepted as the procedure of choice for the majority of these patients^[2]. This procedure consists of an abdominal colectomy, rectal mucosectomy and construction of an ileal pouch that is anastomosed to the anus. Complications include pelvic sepsis, small bowel obstruction, strictures, incontinence and pouch inflammation^[3]. Pouchitis is the most frequent long term complication and is defined as a nonspecific, idiopathic inflammation of the ileal mucosa of the pouch. In fact, the IPAA procedure is associated with pouchitis in approximately 45%-60%^[4,5], of whom 60% will suffer from recurrent episodes and 5%-10% will develop chronic pouchitis^[5]. This condition was first described by Kock *et al*^[6] who noted the inflammation of the continent ileal reservoir. The histopathological changes seen in pouchitis are similar to those seen in UC, with acute inflammation characterized by neutrophil infiltrate, crypt abscesses formation and ulceration^[7]. The etiology of pouchitis remains

still unclear. Several risk factors for pouchitis have been investigated, such as extension and severity of UC, backwash ileitis, extraintestinal manifestations, pre-colectomy thrombocytosis, pANCA positivity, nonsmoking status and nonsteroidal anti-inflammatory drug use. All these factors have still not been demonstrated consistently^[8-12]. The increase of interest for this clinical entity is due to its manifestations. Symptoms are generally mild but in severe cases systemic ones may be present.

Infliximab (IFX), a fusion protein dimer of the human tumor necrosis factor- α (TNF- α) receptor (Remicade®, Centocor Incorporated, Horsham, PA, United States), is a chimeric monoclonal antibody to human TNF- α developed as a therapeutic agent to immune-mediated diseases^[13]. This drug specifically binds to TNF- α , blocking its biological activity, and has important effects on anergic regulatory T cells, restoring their capacity to inhibit cytokine production^[14,15]. IFX has been successfully used for the treatment of inflammatory and fistulizing Crohn's disease (CD), while its role for the treatment of UC remains controversial^[16].

The aim of this brief review is to evaluate the importance of treatment with IFX for pouchitis on the basis of a literature review.

IFX AND POUCHITIS

Reports of the incidence of pouchitis vary considerably. The incidence in UC patients varies from 6% to 50% and depends greatly upon the definition and length of follow up^[17]. The more important factor is probably the criteria of the definition of pouchitis. According to the literature, pouchitis is defined clinically as episodic or continuous symptoms severe enough to require treatment and the diagnosis has to be confirmed endoscopically^[18]. According to this definition, the frequency of pouchitis appears to be highest in the first 6 mo after closure of the ileostomy and then decreases greatly after 12 mo^[19].

The cause of pouchitis remains unknown. Several potential mechanisms have been investigated and include fecal stasis, bacterial overgrowth, dysbiosis, genetic susceptibility and immune alteration^[20]. However, it is generally accepted that bacterial overgrowth plays an important role and that symptoms and lesions are due to an overproduction of pro-inflammatory cytokines^[21]. Of these, TNF- α is maybe the most potent cytokine with direct tissue destructive power.

The treatment of pouchitis is above all empirical and based more on clinical experience than controlled clinical trials. Antibiotics continue to be the main therapy. In fact, most patients respond quickly to metronidazole and/or ciprofloxacin^[17]. Chronic pouchitis is more difficult to manage. New promising therapies include probiotics such as VSL#3^[22]. The data concerning other therapies are much more limited and include topical (rectal) budesonide^[23], oral and topical steroids, topical mesalamine, azathioprine and 6-mercaptopurine^[24].

More recently, IFX has been used in these patients.

Results of these studies are summarized in Table 1. Colombel *et al.*^[25] reviewed 26 patients with an IPAA and CD-related complications treated with IFX. The median time between the IPAA and the diagnosis of CD was 4.5 years (range 0.1-16 years). The main reasons for changing the original UC diagnosis to CD were complex: perianal or pouch fistulizing disease in 14 patients (54%), pre-pouch ileitis in five (19%), and both pre-pouch ileitis and complex fistula in seven (27%). Patients received one to three doses of IFX over 8 wk as induction therapy. Subsequently the patients received a variable number of maintenance infusions. At a short term follow up, 16/26 patients (62%) had a complete response, 6 of 26 (23%) had a partial response, and 4 of 26 (15%) had no response. Information regarding long term follow up was available in 24 patients. After a median follow up of 21.5 mo (range 3-44 mo), 8 patients (33%) either had their pouch resected or had a persistent diverting ileostomy. The pouch was functional in 16/24 (67%) patients, with either good ($n = 7$) or acceptable ($n = 7$) clinical results in 14/24 (58%). Of these 14 patients, 11 were under long term, on demand, or systematic maintenance treatment with IFX. The authors conclude that IFX is beneficial in both the short and long-term treatment of patients with an IPAA performed for a presumed diagnosis of UC who subsequently develop CD-related complications.

Viscido *et al.*^[26] evaluated the efficacy of IFX in the treatment of chronic refractory pouchitis complicated by fistulae following IPAA for UC. Seven patients (4 females, 3 males) with chronic refractory pouchitis complicated by fistulae were included in the study. Pouchitis was diagnosed by clinical, endoscopic and histological criteria. The sites of the fistulae were as follows: pouch-bladder in one, vaginal in three, perianal in two, and both vaginal and perianal in one. Extra-intestinal manifestations (erythema nodosum, arthralgia) were present in 4 patients. CD was carefully excluded in all patients after re-evaluation of the history, re-examination of the original proctocolectomy specimen and examination of the proximal small bowel. All patients had been treated with antibiotics and three with steroids. Patients received IFX, 5 mg/kg, at 0, 2 and 6 wk. Azathioprine (2.5 mg/kg) was also started for all patients as bridge therapy. Clinical response was classified as complete, partial or no response. Fistulae closure was classified as complete (cessation of fistulae drainage and total closure of all fistulae), partial (a reduction in the number, size, drainage or discomfort associated with fistulae) or no closure. The pouchitis disease activity index and quality of life were also used as outcome measures. Clinically, all patients improved. After a follow up of 10 wk, 6 of the 7 patients had a complete clinical response and five had complete fistulae closure. Moreover, the median pouchitis disease activity index decreased from 12 (baseline) (range 10-15) to 5 (range 3-8); the median quality of life decreased from 37 points (range 33-40) to 14 (range 9-18). Erythema nodosum and arthralgia showed complete remission soon after the first infusion of IFX. These preliminary

Table 1 Studies analyzing the use of infliximab in pouchitis

Ref.	No. of patients	Fistulae	Extraintestinal manifestations
Colombel <i>et al</i> ^[25]	26		
Viscido <i>et al</i> ^[26]	7	Perianal (2), vaginal (3), perianal-vaginal (1) pouch-bladder (1)	Arthralgia (3), erythema nodosum (3)
Kooros <i>et al</i> ^[27]	4	Perianal (2)	
Molnar <i>et al</i> ^[28]	1	Perianal (1)	Pyoderma gangrenosum
Semb <i>et al</i> ^[30]	3	Not specific (3)	-
Calabrese <i>et al</i> ^[31]	10	-	-
Yeates <i>et al</i> ^[29]	1	-	-
Ferrante <i>et al</i> ^[32]	28	Perianal (2), vaginal (5)	Not specific (11)
Barreiros-de Acosta <i>et al</i> ^[33]	33	Not specific (10)	Not specific (12)
Barreiros-de Acosta <i>et al</i> ^[34]	8	Not specific (7)	-
Viazis <i>et al</i> ^[35]	7	Perianal (2), pouch-bladder (1)	Arthralgia (2), Erythema nodosum (2)

results indicate that IFX may be recommended for the treatment of refractory pouchitis complicated by fistulae following IPAA for UC.

IFX has been also used in paediatric patients with CD and IPAA. In a retrospective review, Kooros *et al*^[27] studied patients originally diagnosed with UC who developed findings compatible with CD. Refractory pouchitis developed in all patients as well as protracted symptoms of diarrhea, abdominal pain, joint pain and incontinence. All patients received IFX. Four pediatric patients (2 males and 2 females) with mean age of 14.5 years (range 11-18 years) were studied. The development of perianal fistulas in 2 patients, granuloma on biopsy in 1 patient and perianal skin tag in 1 patient, led to a diagnosis change of CD. After failure to respond to antibiotics, aminosalicylates and immunomodulators such as azathioprine and 6-mercaptopurine, all patients were treated with IFX. Patients received IFX infusions at a dose of 5 mg/kg, initially at week 0, 2 and 6 and subsequently at 8 wk intervals in combination with an immunomodulator drug. All patients showed marked improvement clinically, endoscopically and histologically. The authors conclude that IFX can be used successfully for the treatment of pediatric patients with CD and IPAA who are refractory to conventional therapies.

In the literature we found other two pediatric cases. A 14-year-old girl with fistulising pouchitis (perianal fistula) associated with pyoderma gangrenosum and another young girl, 8-year-old, with refractory pouchitis, both treated successfully with IFX^[28,29].

Semb *et al*^[30] reported the use of IFX in three patients who developed pouch-related fistula after undergoing IPAA surgery for UC.

Calabrese *et al*^[31] evaluated the efficacy of IFX in treatment of chronic refractory pouchitis complicated by ileitis using a wireless capsule endoscopy (WCE). Ileitis was documented using WCE and pouchitis was diagnosed by clinical, endoscopic and histological criteria. Sixteen patients with chronic refractory pouchitis complicated by ileitis were enrolled. CD and intestinal infections were excluded in all patients. Patients were treated with IFX and WCE was repeated at week 10. Ten patients completed the study and clinical remission was achieved in nine patients. At WCE and pouch endoscopy, a com-

plete recovery of lesions was observed in 8 patients. One patient presented with four small lesions of the ileum at the 6th week of treatment and 1 patient did not show any modification. Clinical and endoscopic remission was maintained in these eight patients for at least 6 mo. The authors concluded that IFX may be recommended for the treatment of chronic refractory pouchitis complicated by ileitis^[31].

Ferrante *et al*^[32] studied 28 IPAA patients who received IFX for refractory luminal inflammation (pouchitis and/or pre-pouch ileitis, $n = 25$) and/or pouch fistula ($n = 7$). At week 10 following the start of IFX, 88% of patients with refractory luminal inflammation showed clinical response (14 partial, 8 complete), while 6 patients (86%) showed fistula response (3 partial, 3 complete). The modified pouchitis disease activity index (mPDAI) dropped significantly from 9.0 to 4.5 points ($P < 0.001$). After a median follow up of 20 mo (7-36 mo), 56% showed sustained clinical response while 3 out of 7 fistula patients showed sustained fistula response. Five patients needed permanent ileostomy^[32].

Barreiro-de Acosta *et al*^[33], in a retrospective, multicenter study, studied 33 patients with chronic refractory pouchitis treated with IFX (5 mg/kg). Short term IFX efficacy was evaluated at week 8 and mid-term efficacy at week 26 and 52. Complete response was defined as cessation of diarrhea and urgency and partial response as marked clinical improvement but persisting symptoms. The mPDAI without endoscopy was calculated when available. Thirty-three consecutive UC patients with chronic refractory pouchitis were included (18 male, mean age 45 years, range 21-67 years). At week 8, 21% of patients achieved complete response and 63% showed partial clinical response. At weeks 26 and 52, 33% and 27% achieved complete response and 33% and 18% showed partial clinical response, respectively. Thirteen patients (39%) withdrew from treatment (4 for lack of efficacy, 4 for loss of response and 5 for adverse events). None of the potential factors analyzed had an influence on response to IFX.

More recently, Barreiro-de Acosta *et al*^[34] analysed the use of adalimumab, a fully human monoclonal antibody to TNF- α (Humira®, Abbott Laboratories, Abbott Park, IL), in 8 chronic refractory pouchitis

previously treated with IFX. After 8 wk, 13% of the patients achieved remission and 62% showed a clinical response. At week 26, 13% achieved remission and 38% showed a clinical response. At 52 wk, 50% of the patients avoided a permanent ileostomy but only 25% achieved remission. The authors concluded that adalimumab may be an alternative for these patients who have chronic refractory pouchitis previously treated with IFX^[32].

Finally, Viazis *et al.*^[35] evaluated the long term benefits of one year administration of IFX in patients with chronic refractory pouchitis following IPAA for UC. Seven patients were included in the study and received IFX 5 mg/kg at 0, 2, 6 wk and thereafter every 2 mo for 1 year. Three patients had fistulae (1 pouch-bladder, 2 perianal) and 4 extraintestinal manifestations (2 erythema nodosum, 2 arthralgia). CD was excluded after re-evaluation of the history and small bowel examination with enteroclysis or capsule endoscopy. All patients were refractory to antibiotics and 3 to azathioprine. Clinical response was classified as complete, partial and no response. Fistulae closure was classified as complete, partial and no closure. The pouchitis disease activity index (PDAI) was used as an outcome measure. All patients were followed up for 3 years after discontinuation of IFX therapy. After 1 year of IFX administration, 5 patients had complete clinical response, 1 partial clinical response and 1 no response, while 2 out of the 3 patients with fistulae had a complete closure. The median PDAI dropped from 11 (baseline) (range 10-14) to 5 (range 3-8). Extraintestinal manifestations were in complete remission too. Three years after completion of therapy, all patients with complete clinical response at one year remained in remission^[35].

CONCLUSION

Pouchitis is an idiopathic inflammatory condition of the ileal reservoir in patients who have undergone a proctocolectomy. Ileal pouch-anal anastomosis has become the surgical treatment of choice. A subset of patients with ileal pouches can develop CD or a Crohn's-like condition of the ileal pouch after surgery. Diagnosis, differential diagnosis and management of CD of the ileal pouch have been challenging.

An overlap with UC is suggested by the frequency with which pouchitis affects patients with UC compared with familial adenomatous polyposis patients^[8]. There is significant clinical evidence implicating bacteria in the pathogenesis of pouchitis. Studies using culture and molecular methods demonstrate a dysbiosis of the pouch microbiota in pouchitis. Risk factors, genetic associations and serological markers of pouchitis suggest that the interactions between the host immune responses and the pouch microbiota underlie the etiology of this idiopathic inflammatory condition^[8]. Evidence suggests that pouchitis could result from a reactivation

of the immunological mechanisms that lead to UC. In these conditions, it has been observed that the ileal-pouch mucosa synthesizes a variety of pro-inflammatory molecules, including TNF- α , with an imbalance between pro-inflammatory and anti-inflammatory cytokines^[36-38]. Furthermore, patients who develop pouchitis show greatly increased levels of signal transducer and activator of transcription-1 (STAT1) activation in the pouch mucosa^[11]. STAT1 is a pro-inflammatory transcription factor similar to nuclear factor kappa B, which activates genes involved in inflammatory and immunological responses^[39].

Early recognition of this condition is very important for treatment. Although most of these patients show a good response to antibiotic therapy, there are a few cases in which other therapeutic options, such as topical and/or oral mesalamine, topical and/or oral steroids, and immunosuppressive and biological treatment, have to be used. The advent of biological response modifiers (anti-TNF- α inhibitors) represents a new and efficacious approach that is able to modify the clinical course of such patients.

Reading the literature, we found several studies included in this brief review that show for the first time that IFX may significantly contribute to the salvage of complicated pouchitis in patients after IPAA, both in patients with a diagnosis of UC and CD. In our opinion, the decision should be individualized, even if the administration of IFX seems to be safe in both short and long term treatment, and also in paediatric patients.

In conclusion, since the introduction of the biological agents, antibodies to cytokine TNF- α , the treatment of complicated pouchitis refractory to conventional treatment and/or fistulizing, has changed dramatically.

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Dynamic mechanical allodynia following finger amputation: Unexpected skin hyperinnervation

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been proposed as a mechanism of pain following nerve lesions, but the increased innervation described here could be also attributed to neuronal plasticity occurring in chronic inflammatory conditions. Independently from the uncertain cause of the epidermal hyperinnervation, in this patient we tried to reduce the elevated number of epidermal nerve fibres by treating the skin with topical capsaicin (0.075%) three times a day, and obtained a persistent pain relief. In conclusion, neurodiagnostic skin biopsy might represent an useful tool for detecting derangements of epidermal innervation in patients with dynamic mechanical allodynia and can help to select an individually tailored therapeutic strategy in such difficult clinical conditions. Further studies are needed to clarify this issue and try to gain better understanding of chronic pain mechanisms in patients who underwent finger amputation.

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Key words: Neuropathic pain; Hyperinnervation; Dynamic mechanical allodynia; Amputation; Skin biopsy

Abstract

The development of chronic pain after amputations is not an uncommon event. In some cases the most disabling problem is represented by the symptom called dynamic mechanical allodynia, characterized by the painful sensation evoked by gently stroking the skin. Despite the growing interest in understanding pain mechanisms, little is known about the mechanism sustaining this peculiar type of pain. We present here the case of a 53-year-old female patient who complained of severe tactile allodynia in the hand after amputation of her left second finger, resistant to several medical and surgical treatments. In order to gain information about the pain mechanism, two neurodiagnostic skin biopsies were obtained from the area of tactile allodynia and from the contralateral, normal skin area. Skin biopsies showed an unexpected increased innervation of the allodynic skin compared to the contralateral, normal skin area (+ 80.1%). Hyperinnervation has

Core tip: In some patients with post-amputation chronic pain dynamic mechanical allodynia (a painful sensation evoked by gentle stroking the skin) represents the most disabling problem. So far, little is known about the mechanism of this peculiar type of pain. We present here a patient who complained of severe dynamic mechanical allodynia in the hand after amputation of the left second finger. The neurodiagnostic skin biopsy showed an increased innervation of the allodynic skin compared to the contralateral, normal skin area (+ 80.1%), suggesting hyperinnervation as a possible pain mechanism. Interestingly, topical capsaicin (0.075%) relieved allodynia for a long period.

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INTRODUCTION

The development of chronic pain after finger amputation is not an uncommon event^[1-4]. In this context, one of the most disabling symptoms is dynamic mechanical allodynia (or brush evoked allodynia), which has been defined as the pain induced by a light moving mechanical stimuli on the skin^[5-7]. Although it has been described some decades ago, its mechanisms are far to be completely understood^[5,8].

We describe here the case of a 53-year-old female patient who complained of severe tactile allodynia in her hand after amputation of the left index finger at the metacarpal-phalangeal joint and discuss the possibility that the painful sensation was sustained by an hyperinnervation of the skin.

CASE REPORT

In 2001, following a minor trauma, the patient experienced acute pain in the tip of her left index finger. Surprisingly, the pain persisted, despite any efforts to relieve it by several analgesic drugs including paracetamol, non-steroidal antiinflammatory drugs and tramadol. In order to relieve the persistent pain, in the period 2002-2004, three operations for removal of neuromas of the digital nerves to the index finger were performed, but they provided only transient pain relief.

Due to the persistence of pain, on January 2006 the patient underwent amputation of her left second finger at the metacarpal-phalangeal joint. In particular, the palmar collateral nerves of the index were exposed and the radial one was found adherent to the underneath structures. It was isolated, resected and sutured end to end to the ulnar collateral nerve according to the principle of centro-central loop coaptation as described by Fourrier *et al.*^[9]. Skin suture was performed and a volar slab was applied and kept for 3 wk.

Following amputation the patient experienced a significant pain relief, but 4 mo later the pain reappeared in the hand with the characteristics of deep allodynia during flexion or extension of left middle finger. In the following weeks dynamic mechanical allodynia spread to the skin of both the palm and dorsum of the hand.

Since the pain relief was only transient and incomplete and because of the inefficacy of several pharmacological agents including gabapentin, pregabalin and amitriptyline, on October 2006 the patient presented at our hospital for the first time. In order to get more information on the possible mechanism of her pain, the patient underwent several diagnostic tests and a neurodiagnostic skin biopsy was proposed. The patient consented to skin biopsy and signed an informed consent approved by the

Ethics Committee of the "Salvatore Maugeri Foundation". On March 2007, after an intradermal injection of 2% lidocaine (0.5 mL), a 3 mm punch biopsy was obtained from the skin area more severely affected by dynamic mechanical allodynia (Figure 1). A second skin biopsy was obtained from the contralateral, normal skin area.

Epidermal nerve fibres (ENFs) were labelled with indirect immunofluorescence and the images of optical sections were collected with a fluorescence microscope system^[10].

According to recent guidelines of the European Federation of Neurological Societies^[11], the density of ENFs (ENFD) was calculated by counting only the ENFs crossing the basement membrane and expressed as the number of ENFs per millimetre of epidermis (ENFs/mm)^[11,12].

In the patient presented here, skin biopsy showed a marked asymmetry of ENFD with a significant higher value (+ 80.1%) in the allodynic skin (Figure 2). In particular ENFD was 23.6 fibres/mm in the allodynic skin and 13.1 fibres/mm in the contralateral, normal skin area, with an epidermal innervation symmetry ratio of 0.55 (normal value > 0.6)^[13].

DISCUSSION

In the case described here, the neurodiagnostic skin biopsy provided evidence for an increased innervation of the allodynic skin, suggesting it as a possible pain mechanism.

Hyperinnervation has already been proposed as a possible mechanism of pain^[14,15] and previous papers have documented an increased innervation in patients with painful conditions. For example, an increase in the innervation of the lateral retinaculum was correlated with anterior knee pain in a group of patients with symptomatic patellofemoral malalignment^[16,17]. Hyperinnervation has been also described in patients with inflamed appendix^[18], painful lumbar discopathy^[19] and vulvodynia^[20]. However, the relationship between hyperinnervation and allodynia has been rarely investigated. The presence of both hyperinnervation and allodynia has been described in an animal study where the injection of doxorubicin (an anti-cancer agent) into eyelids of adult rabbits produced inflammation, increased sensitivity to touch and hyperinnervation^[21].

Since the development of mechanical allodynia during inflammation has been widely described in literature both in animal^[22-24] and human studies^[25-27], a possible explanation of the increased innervation described in our case report is the neuronal plasticity occurring in inflammatory conditions. In fact, it has been reported that acute skin inflammation tends to induce neurodegeneration, while chronic inflammation leads to increased innervation^[28]. This seems to be confirmed by the increased number of nerve fibres observed in skin chronic inflammatory diseases such as prurigo nodularis^[29,30],



Figure 1 Area of severe dynamic mechanical allodynia from which the punch skin biopsy was taken. The area of tactile allodynia was actually larger than the illustrated one because it was partially diffused also in the dorsum of the hand.

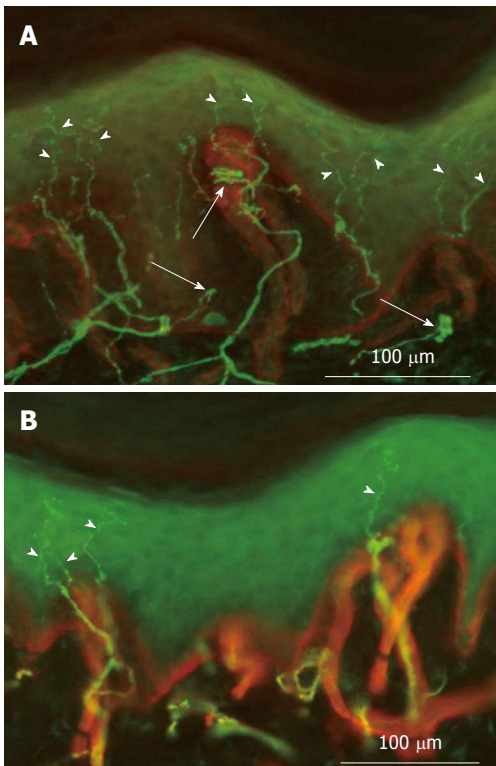


Figure 2 The figure illustrate the higher density of epidermal nerve fibres (arrowheads) in the allodynic skin (A), when compared to contralateral normal skin (B). It also shows some abnormal patterns of nerve fibre regeneration (arrows) in the dermis of the allodynic skin. Indirect immunofluorescence method: in green, protein gene product 9.5 staining of nerve fibres; in red, type IV collagen staining of basement membrane and blood vessels.

psoriasis^[31,32] and atopic dermatitis^[33].

Another possible explanation of the increased skin innervation is the excessive regeneration of amputated nerve axons. Although in humans neuropathic pain has been associated with poor nerve regeneration following traumatic nerve lesions^[34,35], mechanical allodynia is indeed strictly related to the well known development of mechanosensitivity in regenerating primary afferents^[35-38]. When some regenerating axons directly reach

the peripheral target tissues, non-neuronal cells synthesise growth factors which are able to induce the sprouting of the lesioned fibres towards the target tissues^[39,40].

All that considered, increased number of skin afferents with a reduced threshold for mechanical stimuli could explain the dynamic mechanical allodynia observed in this case.

According to this hypothesis, a targeted therapeutic strategy was carried out in this patient. Considering the ENFs degeneration after topical application of capsaicin^[41] we topically treated the patient's skin with capsaicin cream (0.075%) in the tactile allodynia area three times a day. In order to prevent the unbearable burning sensation, sometimes associated with capsaicin based therapies, we instructed the patient to a gradual dose titration. After 4 wk of treatment, the tactile allodynia was still present, but the patient reported a significant reduction in both its intensity and extension. Capsaicin treatment was then discontinued, but the antalgic effect was still present on a mid-term follow-up (3 mo).

In conclusion, the case described here seems to confirm, at least in some patients, the possible association between epidermal hyperinnervation and the clinical development of dynamic mechanical allodynia. Moreover, skin biopsy might represent an useful tool to better define the underlying pathology of allodynic conditions and can help to select an individually tailored therapeutic strategy in such difficult clinical conditions. Further studies are warranted in order to improve the knowledge about the mechanisms underlying the onset of dynamic mechanical allodynia after amputation.

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Cystic benign teratoma of the neck in adult

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Author contributions: Alimehmeti M wrote the article and made histological diagnosis; Alimehmeti R operated on the patient, prepared intraoperative photos and reviewed the manuscript; Ikonomi M performed literature research and prepared the histological photos; Saraci M operated on the patient; Petrela M reviewed the article for its intellectual content and approved the final version.

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Abstract

Teratomas are embryonal neoplasms that arise when totipotential germ cells escape the developmental control of primary organizers and give rise to tumors containing tissue derived from all three blastodermic layers. Teratomas have been reported to occur in various sites and organs. Teratoma of the cervical neck are relatively rare in adulthood. It usually extends from the neck to the thoracic cavity causing local mass effect. In most of the cases intrauterine diagnosis is possible by ultrasound. Because of dyspnea due to mass effect, this condition is treated promptly after birth. However cases of teratoma in adulthood with supraclavicular localization have been reported rarely in the literature. The presented case is of a 25-year-old female with a cervical mass. Histological examination revealed a benign mature teratoma. The patient has been disease free for more than nine years after surgical removal of a neck teratoma.

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Key words: Teratoma; Neck; Adult; Total surgical re-

section; Clinically disease-free

Core tip: Neck teratoma in adult is reported very rarely. We present a case of neck teratoma managed successfully with total surgical resection. The patient remains clinically disease-free more than nine years after surgery.

Alimehmeti M, Alimehmeti R, Ikonomi M, Saraci M, Petrela M. Cystic benign teratoma of the neck in adult. *World J Clin Cases* 2013; 1(6): 202-204 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i6/202.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i6.202>

INTRODUCTION

Teratoma of the neck is found mostly with extension to mediastinal space generally before birth through ultrasound or immediately after birth due to its evident mass effect. In some cases it can reach enormous size and cause airway obstruction making resuscitation maneuvers difficult. Adult neck teratoma is very rarely encountered^[1-4]. It is reported as situated in the thyroid, but also between cervical structures.

CASE REPORT

A 25-year-old female came to our attention for a right supraclavicular mass, that had shown slow progressive growing within 2 wk. At physical examination a retro-muscular mass was palpable behind and laterally the right sternocleidomastoid, not painful at digital pressure and without local discoloring of the overlying skin. Ultrasound had documented a heterogenic partially cystic lesion of approximately 4 cm diameter. The patient was claustrophobic and refused a proposed magnetic resonance imaging (MRI).

The patient underwent, under local anesthesia and intravenous sedation, a small incision of 5 cm over the

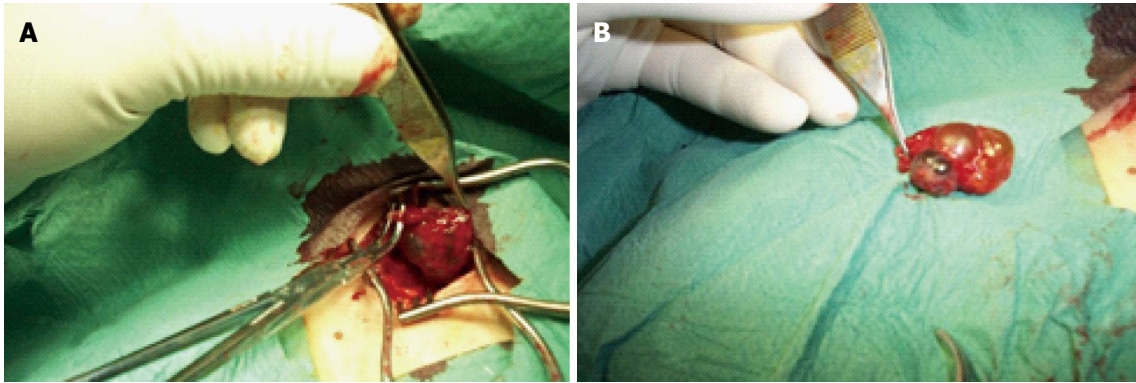


Figure 1 Intraoperative appearance of cystic lesion. A: Initial appearance of a cystic lesion separating fibres of cervical plexus from it; B: Intraoperative appearance of multicystic and solid lesion of different color.

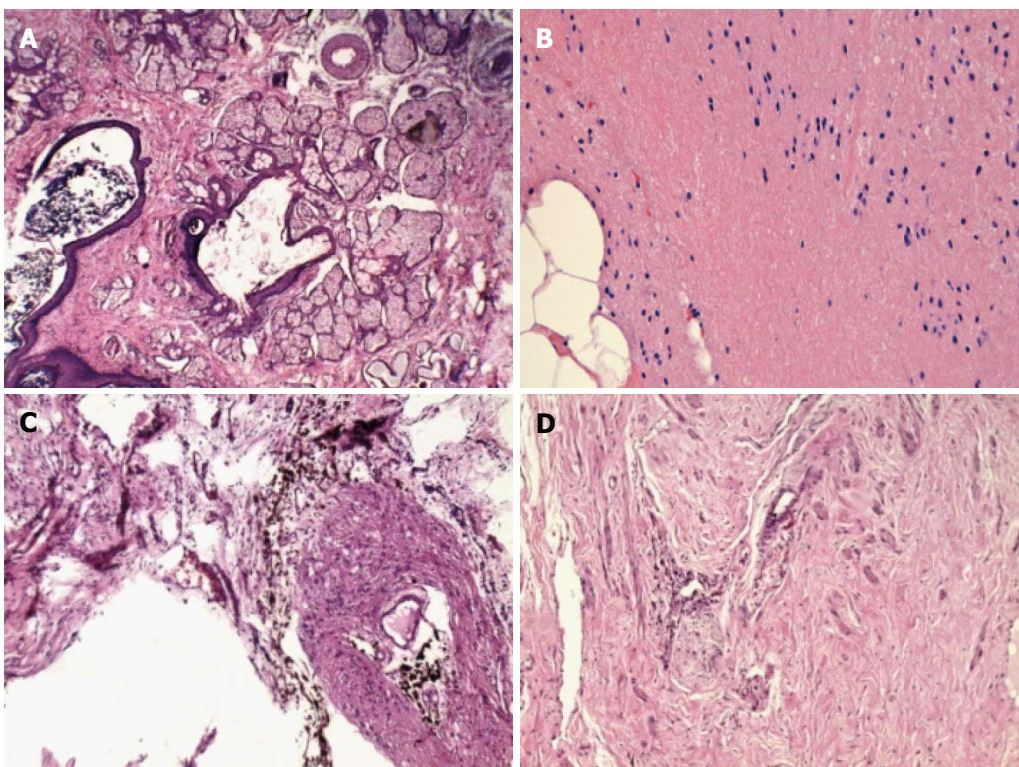


Figure 2 The cyst consisted of ectodermal derivatives with predominant keratinized squamous epithelium covering the wall of the cyst (HE stain, $\times 20$). A: With hair and other skin adnetik lesional structures; B: Mature glial tissue; C: Cartilage; D: Muscle and fat.

lamp parallel to the right clavicle. After dissecting the fibers of platysma a pluralistic lesion was discovered. The lesion was progressively detached from platysma and the adipose tissue under it. A sensitive branch of cervical plexus was preserved (Figure 1). The tumor was completely removed as the adjacent structures were not infiltrated and discernibly dissectible from the pluralistic tumor. The lady was discharged next day without any particular complaints. Uneventful recovery followed.

The histological examination showed ectodermal derivatives consisted of keratinized squamous epithelium covering the wall of the cyst, hair and other skin adnexal structures, mature glial tissue, cartilage, muscle and fat. The lesion was thus labeled as a mature cystic teratoma

on basis of these histopathological features (Figure 2). The patient was advised to undergo a computed tomography (CT) or MRI of the chest and neck that she regularly refused in phone interviews and consultations, with the excuse of claustrophobia and the stated feeling of being in the best of health. Nine years from surgery the patient leads a normal life without any signs or symptoms of the disease.

DISCUSSION

Teratomas are embryonal neoplasms that arise when totipotential germ cells escape the developmental control of primary organizers and give rise to tumors containing

tissue derived from all three blastodermic layers (ectoderm, endoderm, and mesoderm). They are histologically heterogenous with cystic or solid areas, mature or immature components. Hystologically teratomas are classified as mature (benign in 95% of cases), and immature with malignant transformation^[5].

They are rare tumours with a frequency of 1/40000 birth. The cervical localization represents 1.5% to 5% of all the localisations^[6]. They predominate in females (3/4 of the cases). The germinal cells or primary gonocytes migrate from the vitellin sac during the first week of the intrauterine life and colonize the sexual cord forming thus primitive undifferentiated gonads. During this migration they arrest and form a germinal tumor benign or malignant, being localised so from the head to the coxygeal of the infant^[6].

Teratomas are located more often in the sacrococcygeal region and in the ovary, but they may be also found in many other anatomic regions. Teratomas of the neck and mediastinum are particularly rare and may give rise to severe respiratory distress. Prenatal diagnosis may be the only opportunity for perinatal relief of the obstruction before spontaneous breathing is established.

The differential diagnosis is done with a metastasis from thyroid carcinoma, cystic squamous cell carcinoma of cervical lymph node arising in the oro/nasopharynx, follicular adenomas of the thyroid, lymphangiomas, and bronchial cysts^[7]. Approximately 5% of germ-cell neoplasms appear in one of several extracranial sites in the head and neck region. Cervical teratomas are rarely encountered in adults. The radiological diagnosis is supported by ultrasonography, computed tomography or magnetic resonance imaging that reveal pluralistic tumor.

Malignant transformation of cervical teratoma has been reported. Complete surgical removal is the elective treatment^[5]. Adjuvant radiotherapy or chemotherapy is generally considered ineffective.

In the presented case the surgical removal was deemed complete. The patient was advised to be checked with total body CT and MRI of the neck which she refused repeatedly. The clinical long term follow up has demonstrated no recurrence so far.

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Use of central venous saturation monitoring in a patient with pediatric cardiac beriberi

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nous oxygen saturation may be useful for the diagnosis.

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Key words: Cardiac beriberi; Central venous saturation; Pediatric

Core tip: When unexplained heart failure is observed in children, cardiac beriberi must be excluded as a differential diagnosis of myocarditis and cardiomyopathy. The measurement of the central venous oxygen saturation may be useful for the diagnosis. Although beriberi is a rare disease today, it is necessary to remember that it may still be caused by an unbalanced diet.

Abstract

The patient was a 1-year-and-4-mo-old boy. He had drunk about 1 L of an isotonic drink for infants daily since about 10 mo after birth. He was examined by a local doctor due to anorexia and vomiting, found to have cardiomegaly, and transported to our hospital with suspected myocarditis. After admission, the patient showed polypnea, a decreased level of consciousness, and marked metabolic acidosis and lapsed into circulatory insufficiency, requiring catecholamine administration, endotracheal intubation, and extracorporeal membrane oxygenation. Initially, low-output heart failure due to acute myocarditis was suspected, but the central venous oxygen saturation was high, at 82%. Considering high-output heart failure to be more likely, we evaluated its cause and noted, by urinary organic acid analysis, increases in lactate, pyruvate, 3-OH-butyrate, acetoacetate, metabolic products of branched-chain amino acids, 2-ketoglutarate, 2-OH-glutarate, 2-keto-adipate, and 2-OH-adipate. Since the vitamin B1 level was reduced to 12 ng/mL (normally 20-50 ng/mL), a diagnosis of cardiac beriberi due to vitamin B1 deficiency was made. When unexplained heart failure is observed in children, cardiac beriberi must be excluded as a differential diagnosis of myocarditis and cardiomyopathy. The measurement of the central ve-

Majima N, Umegaki O, Soen M. Use of central venous saturation monitoring in a patient with pediatric cardiac beriberi. *World J Clin Cases* 2013; 1(6): 205-207 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i6/205.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i6.205>

INTRODUCTION

The condition related to vitamin B1 deficiency is called beriberi or cardiac beriberi, which markedly decreased due to postwar improvements in the nutritional state. In the latter half of the 1970s, an unbalanced diet due to the excessive intake of instant foods in the young, alcohol intake, and overwork were recognized again as causes of beriberi. Subsequently, its incidence decreased due to improvements in the awareness of nutritional problems associated with instant foods and soft drinks and the addition of vitamins, but beriberi has yet to be eradicated^[1,2].

In this report, a child with cardiac beriberi due to excessive intake of an isotonic drink for infants, in whom the measurement of the central venous oxygen saturation was useful for the diagnosis, is presented.

Table 1 Blood test results on admission

WBC	10090/ μ L	AST	42 U/L
Neutro	41.50%	ALT	12 U/L
Lym	43.60%	LDH	399 U/L
Hb	12.5 g/dL	CK	206 U/L
Ht	37.90%	CK-MB	23 U/L
PLT	726×10^3 / μ L	BUN	5 mg/dL
Na	134 mEq/L	Cr	0.26 mg/dL
K	4.2 mEq/L	CRP	< 0.01 mg/dL
Cl	100 mEq/L	BNP	333 pg/mL
Ca	10.4 mg/dL	Rapid troponin T assay	Positive

WBC: White blood cells; PLT: Platelet count; CK-MB: Creatine kinase-MB; CK: Creatine kinase; BNP: Brain natriuretic peptide; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; ALT: Alanine amino transferase; CRP: C-reactive protein.



Figure 1 Chest X-ray on admission. Marked cardiomegaly with a cardiothoracic ratio of 66% was observed.

CASE REPORT

The patient was a 1-year-and-4-mo-old boy, with a height of 77 cm and a body weight of 11 kg. There was no particular history. He had had anorexia for about 1 wk before the consultation but showed no fever or cold-like symptoms. He started vomiting from 2 d before the consultation and was examined by a local doctor the next day, when he was suspected to have infectious enteritis and was prescribed an antiemetic. Since the symptoms were not alleviated, he was examined by the local doctor again, found to have cardiomegaly on a thoraco abdominal radiography, and transported to our hospital with suspected myocarditis. On admission, the body temperature was 36.8 °C, heart rate was 142/min, respiratory rate was 34/min, complexion was relatively poor, and vigor was reduced. The first and second heart sounds were both weakened, and the third heart sound or heart murmur was not heard. No hepatomegaly or splenomegaly was noted. Also, no clear generalized edema was noted. There was no clear abnormality in the sensory or motor nerves of the limbs. No decrease in the deep tendon reflex was noted. The blood test results on admission included: white blood cells: 10090/ μ L, C-reactive protein < 0.01, creatine kinase: 206/L, creatine kinase myoglobin band: 23/L, brain natriuretic peptide: 333 pg/mL, and rapid troponin T assay: positive (Table 1).

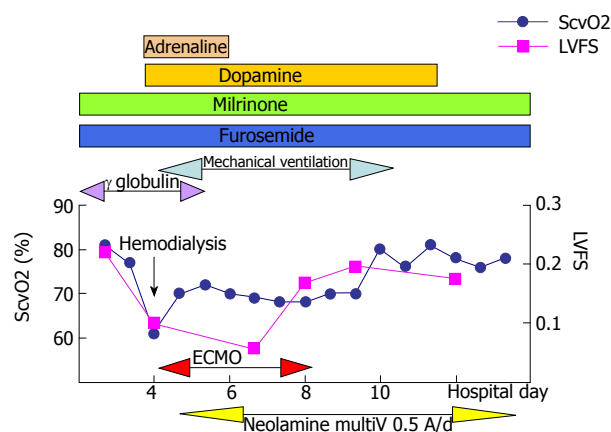


Figure 2 Course after admission. The central venous oxygen saturation was high. LVFS: Left ventricular fractional shortening; ECMO: Extracorporeal membrane oxygenation.

Chest X-ray showed marked cardiomegaly with a cardiothoracic ratio of 66% (Figure 1). On electrocardiogram, negative T waves were noted in V2-V5. Echocardiography disclosed depressed left ventricular contractility with a fractional shortening of 17%, cardiomegaly, and moderate circumferential pericardial effusion. From the history, physical findings, and laboratory results, heart failure due to acute myocarditis was suspected, and the administration of a diuretic and γ -globulin was initiated. On the 4th hospital day, polypnea and a decreased level of consciousness were noted, and marked metabolic acidosis was indicated by blood gas analysis (room air: pH 7.275, pCO₂: 7.5 mmHg, pO₂: 131 mmHg, BE: -23.1 mEq/L, lactate: 114 mg/dL). After the initiation of hemodialysis, the patient lapsed into circulatory insufficiency, and catecholamine administration, endotracheal intubation, and extracorporeal membrane oxygenation (ECMO) became necessary. Initially, low-output heart failure due to acute myocarditis was suspected, but the central venous oxygen saturation was high at 82%. Despite circulatory insufficiency, the central venous oxygen saturation remained generally high during the course and showed no marked decrease (Figure 2). We considered high-output to be more likely than low-output heart failure and searched for its cause, but no clear abnormality was shown by various viral, endocrine function, or immunological tests. On urinary organic acid analysis, increases in the lactate and pyruvate levels, marked increases in the excretion of 3-OH-butyrate and acetoacetate, increases in metabolic products of branched-chain amino acids, and increases in 2-ketoglutarate, 2-OH-glutarate, 2-keto-adipate, and 2-OH-adipate were observed, and the vitamin B1 level was reduced to 12 ng/mL (normally 20-50 ng/mL). From these findings, a diagnosis of cardiac beriberi due to vitamin B1 deficiency was made. Careful inquiry with the patient's family about his daily diet revealed that he had drunk about 1 L of an isotonic drink for infants daily from about 10 mo after birth. Central venous nutrition and the administration of vitamin preparations were initiated on the 5th hospital day, leading to marked improvements in the clinical condition. The patient was weaned from ECMO

on the 8th hospital day, extubated on the 10th hospital day, and recovered with no sequela.

DISCUSSION

In children with unexplained heart failure, cardiac beriberi must be considered as a differential diagnosis of myocarditis and cardiomyopathy. In vitamin B1 deficiency, resistance vessels, particularly arterioles, are dilated due to metabolic acidosis. High-output heart failure is often observed due to increases in the peripheral vascular bed and venous return^[3,4]. In adults, pulmonary artery catheterization or cardiac catheterization is performed for the differential diagnosis of heart failure, but such invasive procedures are often difficult to perform in children. The central venous oxygen saturation can be monitored continuously by placing a PediasatTM catheter in the superior vena cava, and can be determined from the arterial oxygen saturation, hemoglobin level, cardiac output, and systemic oxygen saturation^[5,6]. Since the balance of oxygen demand and supply in the body can be evaluated less invasively compared with pulmonary artery catheterization, the central venous oxygen saturation can be a useful index to differentially diagnose heart failure in children. In the case presented here, the central venous oxygen saturation showed no marked decrease and generally remained high despite heart failure, so we suspected high-output heart failure and, by searching for its cause, diagnosed the condition as cardiac beriberi.

In patients with cardiac beriberi, echocardiography has been reported to show right heart dilation by some^[7] but no characteristic change by others^[8], and the diagnosis of the condition by echocardiography alone is occasionally difficult. In our patient, echocardiography showed no clear right heart dilation and yielded no significant finding suggestive of cardiac beriberi, but the high central venous oxygen saturation was useful for the diagnosis. Despite high-output heart failure, the central venous oxygen saturation decreased for about 1 wk from hospital days 2-3, which may have been partly because venous return was impaired due to pericardial effusion, and the right atrial pressure increased, reducing the left ventricular contraction function^[9]. With improvements in the hemodynamics after vitamin B1 administration, the central venous oxygen saturation increased.

Cardiac beriberi is a serious disease with a rapid onset and course and causes lactic acidosis and cardiogenic shock but is clinically characterized by prompt resolution by the administration of a vitamin preparation^[7]. After early treatment, high-output cardiac failure rapidly improves. However, a rapid increase in systemic vascular resistance and a decrease in left ventricular contraction due to afterload mismatch occur during the course, requiring cardiotonic or diuretic

administration. In this patient, milrinone and a diuretic were used during the course.

Concerning hemodynamics associated with beriberi, a marked decrease in the diagnostic pressure and an increase in cardiac output are well known. It may be difficult to diagnose as it may be accompanied by low-output^[10] and not necessarily by high-output heart failure. Since the prognosis is favorable with early diagnosis and treatment, it is important to suspect the condition first by comprehensively evaluating indices including the history, echocardiography findings, and central venous oxygen saturation. Although beriberi is a rare disease today, it is necessary to remember that it may still be caused by an unbalanced diet.

In conclusion, when unexplained heart failure is observed in children, cardiac beriberi must be excluded as a differential diagnosis of myocarditis and cardiomyopathy. The measurement of the central venous oxygen saturation may be useful for the diagnosis.

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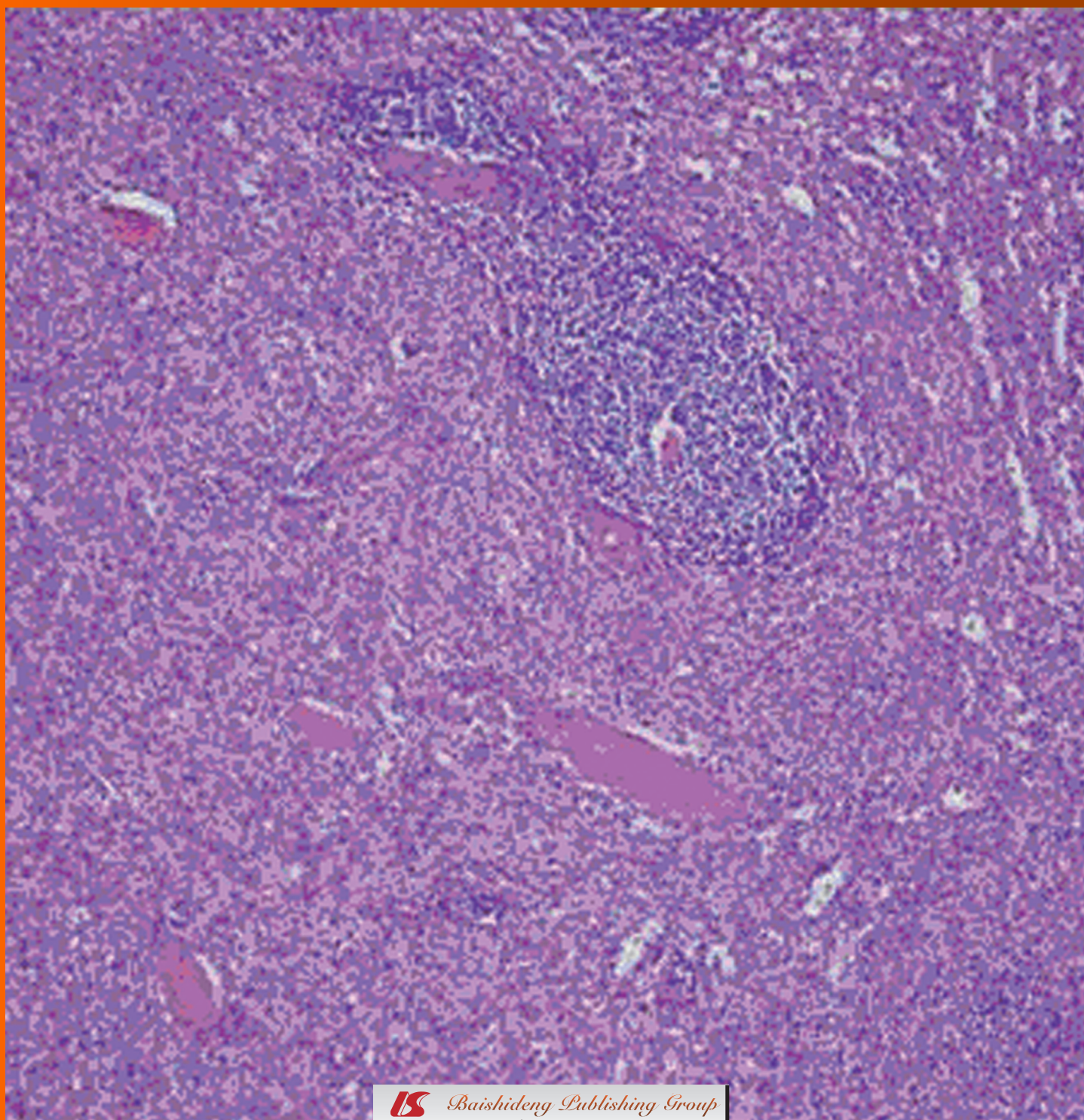
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Dermatology in the military field: What physicians should know?

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Abstract

In the civilian dermatological setting, the top 5 skin diseases usually seen are eczema/dermatitis, acne, benign skin tumors, viral infections and pigmentary disorders. In comparison, the top 5 skin conditions encountered in the military sector are usually fungal infections, eczema/dermatitis, insect bite reactions, bacterial infections and acne. This is not surprising as military personnel, due to the special environment and vocations they are in, are prone to getting eczema as heat, sweating and wearing of the military uniform aggravate the condition. Fungal infections are common in those who wear the army boots. Insect bite reactions are not an uncommon sight among those who have to go to the jungle regularly for outfield training. Grass allergy or intolerance, contact dermatitis or acneiform eruption due to the application of military camouflage cream on the face, contact dermatitis to insect repellents, and military uniform allergy and intolerance are amongst the commonest dermatological problems encountered in the military field, and physicians should recognize them, investigate and manage these problems accordingly. Lastly, a diagnosis not to be missed in the military field is cutaneous melioidosis, especially when a military personnel presents with a non-healing ulcer.

Key words: Dermatology; Skin diseases; Military

Core tip: In the civilian dermatological setting, the top 5 skin diseases usually seen are eczema/dermatitis, acne, benign skin tumors, viral infections and pigmentary disorders. In comparison, the top 5 skin conditions encountered in the military sector are usually fungal infections, eczema/dermatitis, insect bite reactions, bacterial infections and acne. This is not surprising as military personnel, due to the special environment and vocations they are in, are prone to getting eczema as heat, sweating and wearing of the military uniform aggravate the condition. Fungal infections are common in those who wear the army boots. Insect bite reactions are not an uncommon sight among those who have to go to the jungle regularly for outfield training. Grass allergy or intolerance, contact dermatitis or acneiform eruption due to the application of military camouflage cream on the face, contact dermatitis to insect repellents, and military uniform allergy and intolerance are amongst the commonest dermatological problems encountered in the military field, and physicians should recognize them, investigate and manage these problems accordingly. Lastly, a diagnosis not to be missed in the military field is cutaneous melioidosis, especially when a military personnel presents with a non-healing ulcer.

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INTRODUCTION

In the year 2012, the most common top 5 dermatoses seen at the tertiary dermatological center, the department of dermatology, National Skin Center (NSC), Singapore were eczema/dermatitis, acne, benign skin tumors, viral

Table 1 Top 5 skin diseases seen in the civilian and military dermatology patients

Skin disease	Civilian ¹	Skin disease	Military ¹
Eczema/dermatitis	24%	Fungal infections	28%
Acne	12%	Eczema/dermatitis	20%
Benign skin tumors	8%	Insect bite reactions	7%
Viral infections	7%	Bacterial infections	6%
Pigmentary disorders	6%	Acne	5%
Total	57%	Total	66%

¹NOTE: % refers to proportion of all skin diseases seen in each category of patients.

infections and pigmentary disorders. In contrast, the top 5 skin conditions encountered in the military sector, the Singapore Armed Forces (SAF) during the same period were fungal infections, eczema/dermatitis, insect bite reactions, bacterial infections and acne. The proportions of civilian and military top 5 skin diseases are illustrated in Table 1. This is not surprising as military personnel, due to the special environment and vocations they are in, are prone to getting eczema as heat, sweating and wearing of the military uniform aggravate the condition. Fungal infections are common in those who wear the army boots. Insect bite reactions are not an uncommon sight among those who have to go to the jungle regularly for outfield training.

In one study analyzing medical conditions that affected the Australian troops deployed for peacekeeping missions in East Timor from 1999-2000, it was found that as high as 25% of all medical conditions seen were dermatologically related^[1]. Infections (bacterial, viral and fungal) alone accounted for more than 50% of all skin conditions seen during that time.

OCCUPATIONAL DERMATOSES IN THE MILITARY

There was a study done looking at the occupational skin diseases in national servicemen and military personnel in Singapore from 1989 to 1999^[2]. A total of 1059 patients were diagnosed to have occupational skin diseases at NSC, out of which 77 (7.3%) were national servicemen and regulars. Personnel included 44 from the Army (57%), 16 from Air Force (21%), 7 from Navy (9%), 6 from Civil Defense (8%) and 4 from Police Force (5%). The most common vocations associated with occupational skin diseases were vehicle repairs/maintenance (48%) and food handling (19%).

Irritant contact dermatitis accounted for 61 (80%) cases, allergic contact dermatitis 10 (13%) cases and contact urticaria 4 (5%) cases. The most common irritants were oil/grease (66%), wet work (23%) and solvents (18%). Other irritants found included acids/alkalis (lime burns in a Civil Defense serviceman), cement (in a Civil Defense serviceman), coolant (in an Army mechanic), uniform dye, fiber glass (in an Army technician), food (papaya in an Army cook), friction, pesticide (in an Army hygiene as-

sistant) and resin (in an Air Force aircraft technician).

The most common allergens were food (40%) and chromate in cement (20%). One Army cook was patch tested positive to garlic, and 3 other cooks had positive prick tests to prawns, chicken, fish, squid and salted vegetables. Other allergens observed included nickel (in a Police Force personnel's uniform buttons), epoxy (in an Air Force flying instructor's mask), grease and kerosene. In conclusion, irritant contact dermatitis was found to be much more common than allergic contact dermatitis and contact urticaria in military personnel, outnumbering by 4.4:1.

GRASS ALLERGY

It is not uncommon to see military personnel who regularly go for outfield training complaining of itch and rash appearing after contact with grass. The difficulty on the physician's part is to determine whether this is truly grass allergy or malingering. There are 2 studies done locally which attempted to address this issue.

The first is a study looking at 23 military personnel referred to the contact clinic at NSC for the investigation of grass allergy from 1989-1990^[3]. As *Axonopus compressus* (cow grass) is the most common grass species found locally in the training field, patch test was done to standard series and *Axonopus compressus* as whole plant (leaves, flowers and stem) and prick test to the crushed grass was also performed. Twenty controls were also prick and patch tested to grass as well.

It was found that only 8 (35%) were atopic and the majority 19 (83%) did not present with any skin rash in the clinic. Prick test was positive to the grass in only 2 (9%) patients and patch test was positive in 3 (13%), making a total of 5 (22%) who were tested positive to prick/patch tests. All controls were tested negative to prick and patch tests.

Grasses, grains (maize, oats, rice), sugar cane and bamboo belong to the *Gramineae* family. Contact dermatitis to grasses is mainly due to mechanical irritation. However, the importance of grass testing in military personnel is really 2-fold. Firstly, it is potentially medico-legal as dermatologists need to certify a patient fitness for field training. Secondly, it is vital to determine whether the reaction is truly allergic, or just irritant, or the personnel is malingering. It is really not possible to predict which patient would give a positive reaction to prick or patch test based on history and physical examination. This study also shows that a history of atopy does not increase the chance of positive prick or patch test.

In conclusion, grass allergy is mostly an irritant contact dermatitis and atopic patients are not more likely to get it. Only a minority of patients are truly allergic to grass. But as only 1 grass species was utilized in testing, a "grass mix" would be more appropriate.

Subsequently, another study analyzing grass allergy was published, this time utilizing a total of 6 common local grass species (found in lawn and training field) instead

of just 1 for patch test^[4]. Out of 46 patients who were investigated for grass allergy, 5 were tested positive (11%) to the various grass species in different combinations.

However, the real problem with grass testing is that a negative test reaction does not totally exclude a true allergy to grass as some patients might have been allergic to grass species that were not tested. Besides, contact allergy to non-grass plants should be considered in patients who did not react to grass. Plants such as Compositae (Asteraceae), for instance *Vernonia cinerea*, *Emilia sonchifolia*, *Mikania cordata* and *Mikania micrantha* are also found in this region. Other phytophotodermatoses and Type I reaction to pollens could also cause symptoms as well.

Patients who are grass-tested negative should probably be more appropriately labeled as having grass intolerance than allergy.

MILITARY CAMOUFLAGE

A 20-year-old Chinese army recruit was referred in 1999 for rashes on 2 occasions after applying camouflage with camouflage stick^[5]. Pruritic vesicular eruption over the neck, chin, face and hands appeared 1 d after applying the camouflage, associated with eyelid swelling. The rash lasted 3 to 4 d. Diagnosis of an allergic contact dermatitis to the military camouflage was made and patch test was performed to the standard series, camouflage stick and suspected substances in it, including ricinoleic acid.

A 2+ reaction was observed for both the camouflage stick and ricinoleic acid (30% in petrolatum). The main component of the camouflage stick was found to be castor oil (47.1% w/w). Other ingredients were iron oxide (black, red, yellow, green pigments), chromium oxide (green), beeswax, distilled oleyl alcohol, ozokerite wax, carnauba wax and 2-bromo-2-nitropropane-1,3-diol. Ricinoleic acid is the main constituent of castor oil, extracted from seeds of the castor oil plant *Ricinus communis*. It is also commonly found in lipsticks and make-up remover.

However, the current camouflage cream has totally different ingredients, including water, mineral oil, talc, propylene glycol, glyceryl stearate, magnesium aluminium silicate, stearic acid, cetyl alcohol, triethanolamine, kaolin, methylparaben, propylparaben, iron oxide, chromium oxide and titanium dioxide. It appears to be less sensitizing and less likely to cause an allergic contact dermatitis.

Nevertheless, it is not uncommon to see military personnel who already suffer from moderate to severe acne vulgaris complaining of a flare of acne when such camouflage cream is being applied to the face during outfield training. This can be due to the irritating and comedogenic effects of the ingredients such as mineral oil in the camouflage cream. But more likely, the flare of acne is a manifestation of an occlusion folliculitis, resulting from thick application of the camouflage cream, which has to be left on the face for a long time throughout the outfield exercise. It is analogous to acne cosmetica when comedogenic cosmetics are being applied to the face; when camouflage cream causes acne, the condition is probably

more appropriately called “acne camouflagacea”.

INSECT REPELLENT

The military insect repellent contains DEET (N,N-diethyl-M-toluamide, 75% w/w) in an inert gel base. It commonly gives a hot, burning sensation when applied to the skin. An irritant contact dermatitis is most often associated with the use of such insect repellent, but contact urticaria has been reported as well. Other adverse effects are erythema, blistering and skin necrosis. Neurotoxicity and cardiotoxicity have been reported as well when a large amount is applied.

A survey carried out on soldiers in SAF studying the perception, use and acceptability of the insect repellent showed that although over 80% of the servicemen knew the proper use of the insect repellent and brought along the army-issued repellent in the field, less than half used this repellent frequently while on exercise^[6]. Eighty three percent felt that the army repellent was only effective sometimes and that it lasted 4 h or less. Skin irritation was a common side effect when using the repellent. Thus the army-issued insect repellent currently used is not totally acceptable to the servicemen.

UNIFORM ALLERGY

Many military personnel complain of itch and rash on the body after wearing the Army uniform, which is made of thick, non-porous material. This is most often due to irritation rather than a true allergy—a more appropriate term is probably uniform intolerance. However, the potential allergens include the textile dyes, azo dyes, formaldehyde resins and chromate. Purpuric contact dermatitis to the Navy blue uniform has been reported as well.

Two cases with allergic contact dermatitis from chromate in green military uniform sweater and pants have been reported^[7]. Chemical analysis showed that water-soluble chromate was released from the uniform even after repeated washings.

FUNGAL FOOT INFECTIONS

In a study carried out among Algerian military personnel, it was found that 18.3% of the patients who attended the department of dermatology of the Army Central Hospital had fungal foot infections, with tinea pedis and Candida intertrigo being the most common forms (68%)^[8]. *Trichophyton rubrum* (20.9%) and *Candida parapsilosis* (18.7%) were shown to be the major causal agents isolated.

When subjects were grouped according to military rank, fungal foot infections were prevalent in troop soldiers; when grouped according to years of service in the army, the infections were frequent in military recruits.

CUTANEOUS MELIOIDOSIS

Melioidosis is a rare tropical disease caused by infec-

tion with the bacterium *Burkholderia pseudomallei*, which is widely distributed in water and soil of the tropics, especially in rice paddies^[9]. Humans become infected by contact (*via* direct or cutaneous inoculation) with contaminated water or soil, presenting with a non-healing ulcer or ulcerated plaque, also known as cutaneous melioidosis. Inhalation or ingestion of contaminated materials occurs less frequently. Melioidosis occurs endemically in parts of Southeast Asia, such as Malaysia, Thailand, Vietnam and Myanmar, Northern Australia, Africa, Central and South America.

The disease may be localized or disseminated with multi-organ involvement. Any organ may be affected especially the lungs (causing acute fulminant pneumonia or an indolent cavitary disease), skin and subcutaneous tissues, bones and joints, liver, spleen, kidneys and brain. Subacute disease can potentially progress to cause severe systemic multi-organ involvement, leading to severe morbidity and mortality.

Between 1987 and 1994, 23 cases of melioidosis were diagnosed in persons serving in the SAF^[10]. There were 4 deaths resulting from complications of the infection. Unlike the situation in the general population, where the affected are mainly the elderly with underlying illness, the majority of cases in the SAF were otherwise fit and healthy young servicemen. Serological surveys have shown the prevalence of the infection in Singapore to be 0.2% in the military as well as civilian population. As physical contact with soil is an unavoidable part of military training, military personnel continue to be at risk of exposure to this soil-related disease.

Therefore, in any military personnel who has gone for outfield training and complains of a non-healing ulcer or ulcerated plaque, cutaneous melioidosis must be borne in mind as a differential diagnosis.

CONCLUSION

This paper aims to offer readers insights to aid understanding of the development and impact of dermatological diseases in a military population in a tropical environment. Compliance to treatment can be a practical

issue to deal with as many military personnel are too busy involved in various military exercises and outfield training, resulting in suboptimal response to treatment. This is certainly an important point to be borne in mind whenever a clinician encounters military personnel seeking treatment. Understanding differences between the civilian and military populations of patients would allow clinicians to better recognize them, investigate and manage these problems accordingly and appropriately with due empathy.

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Ingested bone fragment in the bowel: Two cases and a review of the literature

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Core tip: The ingested bone fragment may cause bowel perforation at any site from the jejunum to anal margin, obstruction and fistula formation. An experienced clinician should suspect such conditions in the presence of some predisposing factors, such as rapid eating and the use of dentures in the elderly, and should consider various surgical options. We report herein two cases, one of bowel perforation and another of anal impaction, both caused by ingested bone fragments. Complications due to ingested bone fragments are not common and preoperative diagnosis remains a challenge and therefore it must be considered in susceptible cases.

Emir S, Özkan Z, Altınsoy HB, Yazar FM, Sözen S, Bali İ. Ingested bone fragment in the bowel: Two cases and a review of the literature. *World J Clin Cases* 2013; 1(7): 212-216 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i7/212.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i7.212>

Abstract

Generally, ingested foreign bodies are excreted from the digestive tract without any complications or morbidity. In adults, ingestion of foreign bodies frequently occurs in alcoholics and elderly individuals with dentures. The most commonly ingested foreign bodies are food stuffs or their parts, such as fish bones or fragments of bone and phytobezoars. Sharp foreign bodies like fish and chicken bones can lead to intestinal perforation and peritonitis. We report herein two cases, one of bowel perforation and another of anal impaction, both caused by ingested bone fragments. Complications due to ingested bone fragments are not common and preoperative diagnosis remains a challenge and therefore it must be considered in susceptible cases.

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Key words: Bone fragment; Bowel perforation; Anal pain

INTRODUCTION

The majority of ingested foreign bodies (IFB) are excreted from the digestive tract without any complications or morbidity; however, occasionally they may lead to serious clinical problems, such as obstruction, perforation or bleeding^[1-3]. Although IFB are a common problem in children, they are infrequently encountered in adults but are seen in elderly people wearing dentures, alcoholics and/or patients with learning difficulties^[4]. IFB, such as chicken bones, fish bones, toothpicks and dentures, rarely require surgical intervention (5%). Patients are not usually aware of the IFB which is usually detected either during laparotomy or at the time of pathology examination of the surgical specimen^[5]. Less than 1% of IFB, especially large, sharp and/or pointed objects, cause bowel perforation. Perforation usually occurs at the narrowest parts of the bowel, either at the ileocecal valve or at the recto-

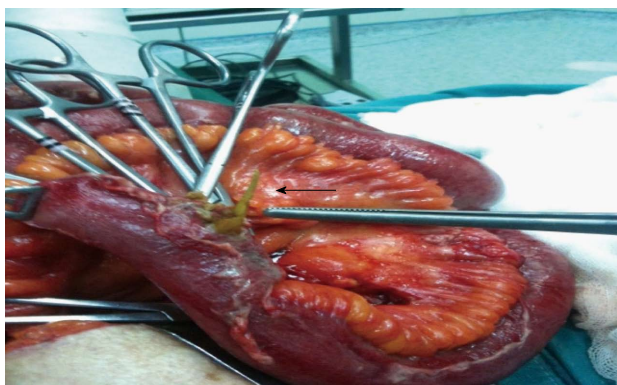


Figure 1 A sharp-pointed bone fragment perforated the ileum and protruded from this area. The arrow shows sharp pointed bone fragment.

sigmoid junction^[6]. In the literature, there are reports of ingested bone causing intestinal perforation, enterovesical fistula and perianal abscesses^[4-7].

We report herein two patients who presented with different complications caused by an ingested bone fragment; we also review the existing literature on IFB in the gastrointestinal (GI) tract.

CASE REPORT

Case 1

An 87-year-old woman was admitted to the emergency department with complaints of abdominal pain and vomiting for 2 d. Her past medical history included chronic obstructive pulmonary disease, cardiac failure and renal failure. On physical examination, she was conscious and alert, with a mild pyrexia. Abdominal examination revealed generalized rebound tenderness. Her white blood cell count, BUN and creatinine levels were out of the normal range; 13.500/ μ L, 79.5 mg/dL and 2.5 mg/dL respectively. Apart from free intra-abdominal fluid, no other abnormality was detected on abdominal X-ray, abdominal ultrasound (US) and computed tomography (CT). As the reason of the acute abdominal pain was not clear, a laparotomy was performed. At laparotomy, 500 cc of a purulent fluid collection in the right paracolic region and a perforation caused by a protruding sharp-pointed bone fragment, 15 cm proximal of the ileocecal valve, were noted (Figure 1). Partial ileal resection and end ileostomy were performed. She was discharged on the postoperative 8th day. Ileostomy closure was successfully performed after three months. After surgery, her abdominal CT scan was re-evaluated by the radiologists and a lesion with bone density was identified at the terminal ileal region (Figure 2).

Case 2

A 27-year-old female was admitted to the general surgery outpatient clinic complaining of severe anal pain for 3 d. Previous medical history revealed no significant pathology. Anal inspection in the knee-chest position was normal; at anal digital examination a hard, flat object lodged

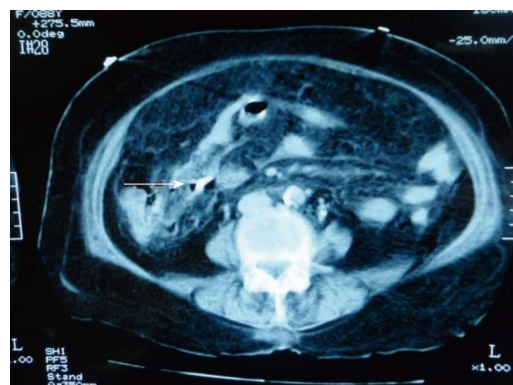


Figure 2 There is a lesion in bone density at the right hypogastric region on the abdominal computed tomography (arrow).

in the anal canal 4 cm above the anal margin was identified. Abdominal CT confirmed the presence of the foreign body in bone density. In the operation room under sedation and analgesia, a 2 cm bone fragment that was lodged at the lateral rectal wall was removed by a Kelly clamp with anoscopy. The patient was discharged 6 h after the intervention.

DISCUSSION

Accidentally ingested foreign bodies are a common problem. Most of the IFB pass uneventfully through the gastrointestinal tract and are excreted in the stool within 1 wk^[4]. Foreign body ingestion generally occurs in childhood but may also be seen in adults. In adults, IFB are usually seen in alcoholics, elderly individuals with dentures, drug abusers, prisoners, individuals with mental disorders or learning difficulties, people with fast eating habits and workers such as carpenters and dressmakers who tend to hold small sharp objects in their mouths^[4,8]. Elderly people may have trouble using dentures and as the sense of feeling in the palate is decreased, they may become prone to FB ingestion. Generally patients do not recall ingesting a foreign body and this is usually detected on radiological imaging studies, during surgery or in the pathological examination of the surgical specimens^[5,7]. Both patients presented herein did not recall any FB ingestion. Although the first case was an elderly individual who wore dentures and had comorbidities, the second case was a young woman with no prior mental or physical disorders. However, she eventually admitted to being a fast eater.

The American Society for Gastrointestinal Endoscopy classifies IFB as: (1) food bolus impactions, usually meat; (2) blunt objects, such as coins; (3) long objects, longer than 6-10 cm such as toothpicks; (4) sharp-pointed objects, such as fish bones or small bones; (5) disk batteries; and (6) narcotic packets, wrapped in plastic or latex. The types of IFB vary according to regional differences and feeding habits. For example, fish bone ingestion is more common in eastern countries while meat bolus impactions are mostly seen in western countries^[4,9]. The

most common IFB are food stuffs or their parts, such as fish bones, bone fragments or vegetable bezoars and toothpicks^[4]. Although generally the ingested bones are digested or uneventfully pass through the gastrointestinal tract within 1 wk, complications such as impaction, perforation or obstruction may rarely occur^[7,10-13]. Gastrointestinal perforation occurs in less than 1% of all patients. The possibility of perforation is associated with the length and sharpness of the swallowed object^[14]. Ingested sharp bones, fish and chicken bones can lead to intestinal perforation and peritonitis^[15]. Goh *et al*^[16] state that most of the foreign bodies causing gastrointestinal tract perforation were of a food origin, such as fish bones, chicken bones, bone fragments or shells. Another study on IFB found that a fish bone was the most frequently encountered foreign body causing GI tract perforation^[17]. In some cultures or religions, people prefer to eat all parts of the fish and thus fish bone ingestion and related complications are common in these populations^[18]. GI perforations caused by a chicken bone are less frequently reported. Also, different GI complications were defined as caused by poultry bones, duck bones, rabbit bones and meat bone fragments in the literature^[19,20].

Although bowel perforations may occur at any part of the intestinal tract, the most common site is at an acute angulation or physiological narrowing, such as the ileocecal region and rectosigmoid junction^[7,11]. It is reported that the ileum was the site of perforation in 83% of cases^[21]. Goh *et al*^[16] recorded the most common site of intra abdominal perforation as the terminal ileum in 38.6%. Perforation of the jejunum is less frequent and its incidence is approximately 14.3%^[4]. Predisposing factors for perforation or other complications are bowel disease, adhesions, diverticular disease, inflammatory bowel disease, bowel tumors, abdominal wall hernias and a blind loop of bowel^[16]. Glasson *et al*^[11] reported a case with perforated sigmoid diverticulum caused by a chicken bone. Akhtar *et al*^[12] reported 3 cases with bowel perforation caused by chicken bones, two cases had a hernia and the other case had diverticulitis. In their case report and review of literature, McGregor *et al*^[13] presented a case in whom clinical diagnosis of previously undiagnosed carcinoma was established based on colonic perforation resulting from ingested chicken/poultry bone and they also reported 3 such cases in the literature.

There were no intestinal or abdominal disorders in our cases but they said they experienced constipation from time to time. Bowel perforations can present with different clinical manifestations, such as intra abdominal abscesses, anal fistula or rectal abscess, coloenteric, colovesical or rectocutaneous fistulas, and acute abdomen. A very interesting clinical presentation reported in the literature is an aortocolic fistula^[8,22-24]. Although generally anal or rectal FB engage transanally and are possible causes of anal pain, ingested fish bone has been reported to lead to perianal abscesses, anal fistulae and severe anal pain. Adufull^[10] reported that ingested chicken bones and fragments of meat bone can also cause anal pain, abscess

formation and anal fistula^[10]. Cash *et al*^[8] also reported anorectal abscess and fistula caused by ingested chicken bones; they stated that a partially closed anal sphincter against rectal contractions might lead to these disorders.

IFB usually present with non-specific symptoms and different clinical symptoms may occur in patients. Abdominal pain is the most common complaint (95%), followed by fever (81%) and localized peritonitis (39%). The other symptoms that may occur are nausea, vomiting, hematochezia and melena. Bowel perforation and acute surgical abdomen can lead to misdiagnosis with other conditions causing surgical abdominal diseases, such as acute appendicitis, diverticulitis or perforated peptic ulcer^[7,25]. The most common preoperative diagnosis is acute abdomen of uncertain origin^[18]. Gastric, duodenal or colonic perforations can present as more chronic events, such as abdominal mass or abscess^[14]. Usually physicians cannot establish a preoperative diagnosis as the patient cannot recall a foreign body ingestion.

Our first case presented with acute abdominal pain and the second with severe anal pain, particularly during defecation. Generally, no specific image is detected by imaging methods. Free abdominal gas due to pneumoperitoneum, abdominal fluid collection, gas-fluid levels due to bowel obstruction, or a chicken bone image facilitates the preoperative diagnosis^[15].

Free gas is rarely detected on abdominal X-rays; it was present in only 20% of cases with perforation^[7]. According to the studies, the degree of radiopacity of ingested fish bones varies according to the species of the fish^[16]. A prospective study of 358 patients with fish bone ingestion revealed that a plain radiography had a sensitivity of only 32%^[26]. Ingested fish bones are overlooked on plain films as they are minimally radiopaque and adjacent inflammatory tissue or fluids interfere with the image of the fish bone^[22].

Ultrasound can detect even non radiopaque FB, such as fish bones and toothpicks, based on their high reflectivity and variable posterior shadowing. There are reported cases of ingested FB defined by US^[17]. Intra abdominal fluid and adjacent tissue changes can be seen using US.

Abdominal CT scan can detect even more details, such as intestinal obstruction, pneumoperitoneum, a thickened intestinal wall or foreign body^[16]. Goh *et al*^[17] reported, in their study of seven patients with fish bone perforations, that a correct diagnosis was made in five of the seven original radiology reports. However, on retrospective review of the scans, the fish bones could be identified in all cases, typically appearing as a linear calcified lesion surrounded by an area of inflammation.

In this report, the abdominal X-ray of the first case was evaluated as normal, ultrasound and CT scan only showed intra abdominal fluid and therefore the preoperative evaluation was non diagnostic. However, in the postoperative evaluation of the CT scan, the radiologists detected a radiopaque lesion at the terminal ileum. In the second case, no X-ray examination was performed

as X-ray examination was insufficient in revealing non radiopaque FBs and other intra abdominal complications. We preferred only CT scan for imaging methods. The CT scan revealed no pathology except a bone density lesion in the rectum.

Only 1% of the complicated ingested FB in the gastrointestinal tract requires a surgical operation; 10% to 20% of them are successfully removed by non operative methods such as endoscopy^[11]. If the foreign body is at the anorectal region, it is easily removed *via* proctosigmoidoscopy or digitally^[27]. Watanabe *et al*^[28] detected a fish bone stuck in the sigmoid colon wall by sigmoidoscopy and removed it with a sigmoidoscopy snare^[28].

In recent years, laparoscopy has been used for intraperitoneal and intraluminal foreign body removal with success. Laparoscopy is less invasive than laparotomy and thus it can be a good choice for FB removal^[29]. Hur *et al*^[15] reported two cases of peritonitis caused by sharp bones perforating the intestinal tract and the bones were successfully removed by laparoscopy. Surgery treatment is based on removal of FB and peritoneal lavage. The appropriate surgical intervention is decided according to the anatomical location of the perforation or other clinical pathological findings, such as primary suture of a perforated bowel segment, bowel resection and a Hartman procedure. Antibiotic treatment should also be added to the surgical treatment^[7,27]. Generally, surgeons prefer resection; the use of primary sutures is rare in the literature. In the presence of any accompanied surgical disorders, such as abdominal wall hernias, diverticulitis or sigmoid tumor, appropriate treatment is performed^[13,21].

When a perianal fistula or abscess or a colovesical fistula is caused by a FB, after removal of the FB, abscess may be drained and the fistula can be operated on. Aduful^[10] also reported two cases of swallowed bones that caused anal pain and anal fistula.

Our first case was an acute surgical abdomen; she was an elderly patient with cardiac, respiratory and renal disorders. The anesthesiologists evaluated the patient using the American Society of Anesthesiologists (ASA) classification, ASA-4, and thus a laparotomy was preferred, which was a fast surgery and a well-known method. Laparoscopy was not preferred because of technical conditions. During the operation, ileum perforation by a bone fragment and intra abdominal diffuse purulent fluid was observed. The case was not suitable for primary repair, we considered anastomosis may pose a risk and therefore resection and end ileostomy was performed. In the second case, as a FB was suspected and a careful rectoscopic examination under sedation was done, the impacted bone fragment was seen and removed.

Complications due to ingested bone fragments are not common and preoperative diagnosis remains a challenge. The patient's medical history can be misleading and the clinical symptoms are not specific. They can present with different clinical manifestations in the bowel. The ingested bone fragment may cause bowel perforation at any site from the jejunum to anal margin, obstruction and fistula

formation. An experienced clinician should suspect such conditions in the presence of some predisposing factors, such as rapid eating and the use of dentures in the elderly, and should consider various surgical options.

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Splenic hamartoma: A case report and review of the literature

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Abstract

Splenic hamartoma is a rare benign malformation, composed of an anomalous mixture of normal splenic elements, often found incidentally while working up other complaints or at autopsy. A splenic mass was incidentally found while evaluating the effects of a traffic accident in a 63-year-old woman. Abdominal computed tomography revealed a well-defined splenic mass with rim enhancement. The patient underwent splenectomy. The resected spleen contained a well-defined mass lesion measuring 3.5 cm × 3.0 cm. Microscopic examination revealed disorganized slit-like vascular channels lined by plump endothelial cells without atypia. The cells lining the vascular channels were positive for CD8, CD31, CD34 and vimentin. Endothelial cells that are positive for CD8 are a key feature that differentiates hamartoma from other vascular lesions of the spleen. Although this tumor is very rare, it must be included in the differential diagnosis of splenic mass-forming lesions.

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Key words: Hamartoma; Malformation; Spleen; Splenoma

Core tip: It is important to consider that splenic hamar-

toma is included in the differential diagnosis of splenic mass-like lesions, although it is a benign and very rare.

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INTRODUCTION

Splenic hamartoma is a rare benign vascular proliferative neoplasm characterized by CD8 immunopositivity of the vascular endothelial lining cells^[1]. It is composed of an anomalous mixture of normal splenic elements, such as red and white pulp^[2]. Since the first case of splenic hamartoma was described by Rokitansky^[3], more than 150 cases have been reported, with an incidence of 0.024% to 0.13% given in a review of autopsies^[4]. Most cases are often discovered incidentally at autopsy or when evaluating images for other reasons^[1]. Splenic hamartoma has also been called splenoma, accessory spleen in spleen, congenital malformation and hyperplastic nodule^[1,5]. Although splenic hamartoma is benign, it is important to differentiate it from splenic malignancies, including metastatic tumors^[1,6]. We report a rare case of splenic hamartoma found incidentally while evaluating the effects of a traffic accident in a 63-year-old woman.

CASE REPORT

A 63-year-old woman visited our hospital for further evaluation of a splenic mass found incidentally during the evaluation of the consequences of a traffic accident. She had a ten year history of diabetes mellitus. Laboratory examinations were unremarkable. On physical examination, there was no palpable mass in the abdomen. Abdominal computed tomography (CT) revealed a homogeneous

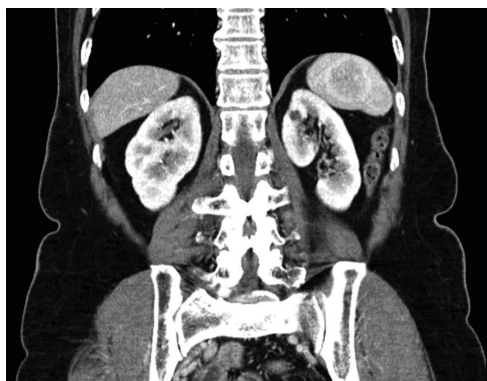


Figure 1 Abdominal computed tomography scan revealing a homogeneous round splenic mass with rim enhancement.

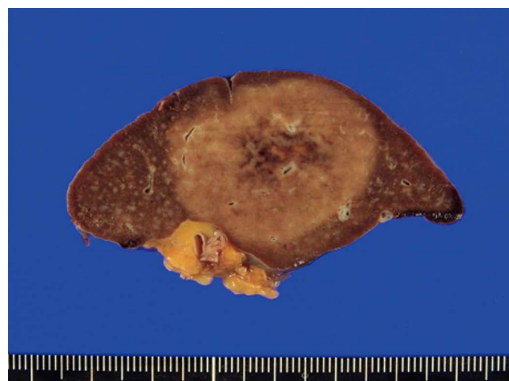


Figure 2 A well-defined homogeneous red-tan mass can be seen on the cut surface compressing the adjacent normal splenic parenchyma.

round mass with rim enhancement in the splenic parenchyma (Figure 1). Radiologically, the possibility of a metastatic cancer of unknown origin or splenic hemangioma was suspected. However, there was no evidence of primary malignancy on gastroscopy, colonoscopy, abdominal ultrasonography and positron emission tomography (PET)-CT. PET-CT findings suggested a benign splenic tumor. The patient underwent a laparoscopy-assisted splenectomy.

The resected spleen measured 8 cm × 5 cm and the outer surface was unremarkable. The cut surface revealed a well-defined homogeneous red-tan mass of 3.5 cm × 3.0 cm. The mass was a round, well-circumscribed, unencapsulated bulging nodule compressing the adjacent normal splenic parenchyma (Figure 2). There was no evidence of hemorrhage or necrosis. Microscopically, the vague nodular tumor contained haphazardly arranged small slit-like vascular spaces enclosing red blood cells. The vascular spaces were lined with plump endothelial cells without atypia and the intravascular areas enclosed focal lymphoid aggregates with a connecting network of fibrosis. The tumor was well demarcated from the adjacent normal spleen and the surrounding normal parenchyma was focally compressed. There was no fibrous capsule and the histology of the surrounding spleen was unremarkable, consisting of red and white pulp. Immunohistochemically, the lining endothelial cells of the vascular channels were positive for CD8, CD31, CD34 and vimentin (Figure 3). The scattered stromal macrophages were CD68-positive, whereas the cells lining the vascular spaces were CD68-negative. The final pathological diagnosis was a splenic hamartoma. After the operation, the 7 mo follow-up period was uneventful.

DISCUSSION

In this report, we describe a rare and interesting case of splenic hamartoma, which was found incidentally during the evaluation of a traffic accident. More than 80% of such cases are asymptomatic and found incidentally at autopsy or during image evaluation for other reasons^[5]. Approximately 20% of the cases present with primary

or systemic symptoms. The common presenting clinical manifestations are splenomegaly, palpable mass, spontaneous rupture, anemia, thrombocytopenia and digestive symptoms, including loss of appetite and abdominal pain^[1,7]. A strong association between splenic hamartomas and solid and hematological malignancies, including thymomas, squamous cell carcinomas and renal cell carcinomas, has been reported and rare cases of splenic hamartoma also occur, associated with tuberous sclerosis^[1,5].

Recently, Wang *et al*^[7] described the radiological features of splenic hamartomas on ultrasonography (US), color Doppler imaging, CT and magnetic resonance imaging (MRI). Most are hyperechoic solid masses relative to the adjacent normal splenic parenchyma on US. On color Doppler imaging, there is evidence of increased blood flow resulting from hypervascularity. On CT imaging, the hamartomas appear as isodense or hypodense solid masses relative to the adjacent normal splenic parenchyma. Cystic changes and combined calcification are regarded as the characteristic CT findings. MRI findings differ depending on whether the tumor is fibrous or non-fibrous. Most splenic hamartomas are isointense in T1-weighted MRI and heterogeneously hyperintense in T2-weighted MRI.

According to the review literature^[1,7], splenic hamartomas present as solitary or multiple lesions forming round, well-circumscribed, unencapsulated bulging nodules compressing the adjacent normal splenic parenchyma. The tumors vary in size with a median size of 5 cm and a maximum of 20 cm. They are of two histological types: a white pulp type and a red pulp type. The white pulp type is composed of lymphoid tissue and the red pulp type is composed of an aberrant complex of sinuses. Most tumors are a mixture of the two subtypes. The characteristic histological features are disorganized vascular channels lined by plump endothelial cells. The lining cells of the vascular channels are typically positive for CD8, CD31, CD34, factor VIII-related antigen and vimentin^[5,8].

The origin of splenic hamartomas is still controversial. Some consider them to be congenital malformations of the splenic red pulp, others to be neoplasms of the

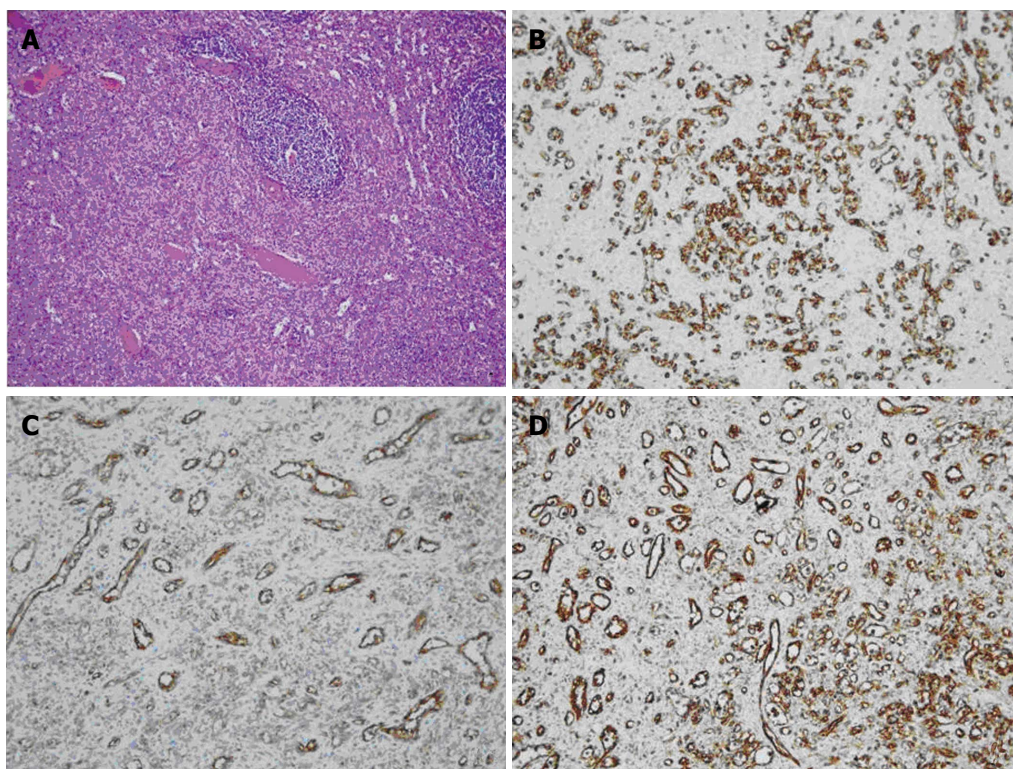


Figure 3 Pathological findings: Hematoxylin-eosin staining and immunohistochemical stainings. A: The tumor contains haphazardly arranged small slit-like vascular spaces lined by plump endothelial cells; B: The endothelial cells lining the vascular channels are positive for CD8; C: CD31; D: Vimentin.

splenic red pulp or post-traumatic reactive lesions^[2,9]. They have also been seen as acquired proliferative processes, with documented cases associated with hematological malignancy^[6]. The main differential diagnosis includes other vascular tumors and solid mass-forming lesions of the spleen. Hemangioma, littoral cell angioma, lymphangioma, hemangioendothelioma, sclerosing angiomatoid nodular transformation and angiosarcoma are included in the pathological differential diagnosis^[1]. The radiological differential diagnosis includes inflammatory myofibroblastic tumor, lymphoma and metastatic tumors^[7]. Splenectomy is also important in patients with an incidentally discovered mass in the spleen when a malignant tumor cannot be ruled out. Splenic hamartoma with systemic or primary symptoms is rare but often associated with hematological disorders, which can be cured by splenectomy^[10].

In conclusion, splenic hamartoma is a benign vascular proliferative lesion with the characteristic CD8 positive immunophenotype of the lining endothelial cells. Although this tumor is very rare, it must be included in the differential diagnosis of splenic mass-forming lesions.

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Cytomegalovirus enteritis with jejunal perforation in a patient with endometrial adenocarcinoma

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with a jejunal perforation.

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Key words: Cytomegalovirus; Enteritis; Jejunum; Perforation

Core tip: Small bowel involvement with gastrointestinal cytomegalovirus (CMV) infection is very rare. However, CMV enteritis should be included in the differential diagnosis of the ulcerative lesion of a small bowel segment when abdominal pain, vomiting, diarrhea and perforation develop in patients with a history of cancer.

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Abstract

Cytomegalovirus (CMV) infection of the gastrointestinal tract has been reported most frequently in the setting of immunodeficiency. The whole gastrointestinal tract can be affected; however, the small bowel is rarely affected. We report a case of CMV enteritis with jejunal perforation in a 53-year-old woman with a history of chemoradiation therapy for endometrial cancer 8 years previously. At follow-up evaluation, lower abdominal pain, diarrhea and vomiting appeared. Abdominal computed tomography showed intra-abdominal free air in the subphrenic space and porta hepatis. The jejunal segment revealed serosal purulent exudates with a perforation. The resected jejunal segment showed a large geographic ulcerative mucosal lesion. The microscopic findings revealed a diffuse ulcerative mucosal change with a prominent granulation tissue formation and many large atypical vascular endothelial cells and stromal fibroblasts with intranuclear or intracytoplasmic inclusion bodies. These cells were positive for CMV antibody. The final diagnosis was CMV-associated jejunitis

INTRODUCTION

Cytomegalovirus (CMV) infection commonly develops in immunocompromised patients and is a major cause of morbidity and mortality^[1]. Most cases occur in patients with human immunodeficiency virus infection, undergoing cancer chemotherapy, receiving long-term corticosteroid treatment, and organ transplant recipients^[2,3]. It may affect the gastrointestinal tract anywhere from the mouth to the anus. The site most commonly affected is the colon, followed by duodenum, stomach, esophagus and small intestine^[4,5]. Esophagitis, gastritis, duodenitis and enterocolitis are induced by CMV infection in the gastrointestinal tract. However, intestinal perforation is relatively rare^[6]. The most common site of perforation with CMV infection of the gastrointestinal tract is the colon,



Figure 1 Abdominal computed tomography revealed intra-abdominal free air in the right subphrenic space (arrows).

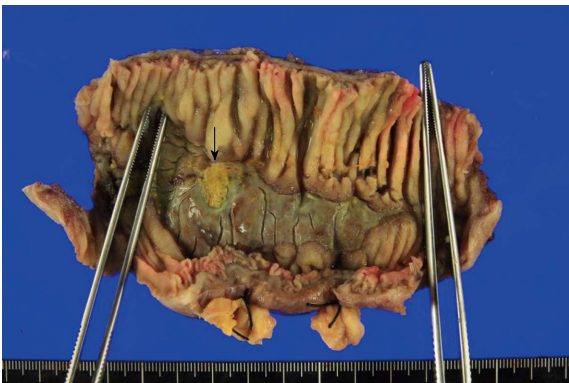


Figure 2 The resected jejunal segment showed a large geographic ulceration with a perforation site (arrow).

followed by the ileum and appendix^[7]. Jejunal perforation due to gastrointestinal CMV infection is extremely rare. Only five cases have been reported in the English literature^[8-12]. Here, we report a case of CMV enteritis with a jejunal perforation in a patient with endometrial adenocarcinoma.

CASE REPORT

A 53-year-old woman with a history of endometrial cancer surgery visited the emergency room with left lower abdominal pain. She had a one week history of diarrhea and vomiting. She had undergone an extended abdominal hysterectomy with bilateral salphingo-oophorectomy and pelvic lymph node dissection for endometrial adenocarcinoma and received chemotherapy and radiation therapy 8 years previously. On physical examination, she complained of abdominal distension and generalized abdominal tenderness with muscle guarding. Clinically, generalized peritonitis was suspected. Simple X-ray and computed tomography of the abdomen demonstrated free intraperitoneal air in the right subphrenic space and porta hepatis (Figure 1). Radiologically, the possibility of intestinal perforation was suspected. She underwent an emergency laparotomy and a perforation was found in a segment of the jejunum with a serosal grayish white exudative covering. The affected

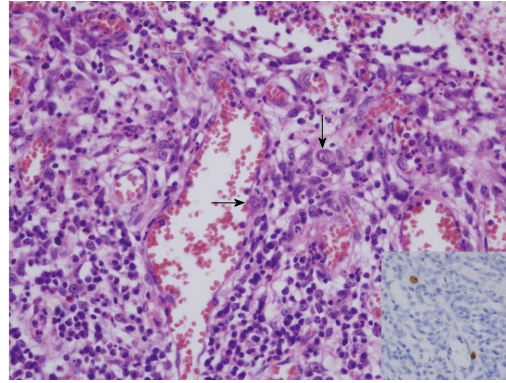


Figure 3 The ulcer bed was composed of granulation tissue with abundant vascular proliferation. Many large atypical endothelial cells and stromal fibroblasts with the formation of intranuclear inclusion bodies were noted (arrows). These cells were positive for cytomegalovirus antibody (Inset).

jejunal segment was resected.

The resected jejunal segment measured 10 cm in length and 7 cm in circumference. The outer surface showed a perforation site with serosal purulent exudates. The mucosal surface of the jejunal segment revealed a diffuse geographic ulcerative lesion which measured 9.5 cm × 3.5 cm in size. The ulcerative lesion showed an irregular, dirty mucosal surface and a perforation site was noted (Figure 2). Microscopically, the jejunal wall showed a diffuse ulceration with exuberant granulation tissue formation and heavy inflammatory cell infiltration. Many large atypical vascular endothelial cells and stromal fibroblasts with intranuclear or intracytoplasmic inclusion bodies were found in the granulation tissue area (Figure 3). The features of vasculitis were combined. The immunohistochemical staining using monoclonal anti-CMV antibody revealed many positive nuclear reactions of large atypical cells with or without intranuclear inclusion bodies (Figure 3, inset).

DISCUSSION

In this report, we have described a rare case of CMV enteritis with a jejunal perforation in a patient with a history of endometrial cancer surgery and chemoradiation therapy. To the best of our knowledge, only five cases of CMV enteritis with a jejunal perforation have been reported^[8-12]. The reported five cases are summarized in Table 1. Four cases were male and one case was female. The mean age was 42.4 years (range: 28 to 60 years). The clinical presentations were lower abdominal pain, diarrhea, fever, nausea, loss of appetite, intermittent epigastralgia and emesis. The underlying diseases were acquired immunodeficiency syndrome (AIDS) in three patients, adult T-cell leukemia-lymphoma in one patient and no underlying disease in one patient. Our case was a 53-year-old woman with a clinical presentation of left lower abdominal pain, diarrhea and vomiting and a history of endometrial adenocarcinoma.

Cytomegalovirus infection is a well-known opportunistic viral infection that frequently occurs in im-

Table 1 Summary of reported five cases of cytomegalovirus enteritis with jejunal perforation.

Cases	Sex	Age	Perforation sites	Clinical presentation	Underlying disease	Ref.
1	M	50	Jejunum	Lower abdominal pain, nausea, emesis, diarrhea	AIDS	[7]
2	M	34	Jejunum and ileum	Loss of appetite, intermittent epigastralgia	Adult T-cell leukemia-lymphoma	[8]
3	M	28	Jejunum and ileum	Chronic diarrhea, fever, abdominal pain	AIDS	[9]
4	M	40	Jejunum	Lower abdominal pain, fever	AIDS	[10]
5	F	60	Jejunum	Diarrhea, fever	None	[11]
Our case	F	53	Jejunum	Left lower abdominal pain, diarrhea, vomiting	Endometrial adenocarcinoma	

M: Male; F: Female; AIDS: Acquired immunodeficiency syndrome; Ref.: Reference number.

munocompromised patients, including patients with AIDS, those who have received bone marrow or organ transplants, those who received long-term corticosteroid treatment and those who have received chemotherapy or radiation therapy^[2,6]. CMV is a member of the herpes viral group and is a DNA virus. More than 90% of healthy adults are seropositive for CMV^[3,6]. Pulmonary infection is the most frequently recognized type of CMV infection. However, CMV infection of the gastrointestinal tract is also common^[13]. It can affect the gastrointestinal tract anywhere from the mouth to the anus. In CMV infection of the gastrointestinal tract, the site most commonly affected is the colon (47%), followed by the duodenum (21.7%), stomach (17.4%), esophagus (8.7%) and small bowel (4.3%)^[4]. Intestinal perforation as a complication of gastrointestinal CMV infection is a rare finding. The most common site of perforation is the colon (53%), followed by the ileum (40%) and appendix (7%)^[7]. The jejunum, as a perforation site in gastrointestinal CMV infection, is an extremely rare location. In our case, the patient presented with a gastrointestinal CMV infection manifested as jejunitis which led to a jejunal perforation.

CMV-associated enteritis appears to be related in part to up-regulation of the production of local pro-inflammatory cytokines, potentially by altering resident intestinal macrophages to express human immunodeficiency virus proteins^[14]. The CMV-induced ulceration is thought to involve ischemic mucosal injury secondary to the infection of the vascular endothelial cells^[5,15]. CMV may infect various gastrointestinal cells. The most commonly affected cells are the vascular endothelial cells and stromal fibroblasts. CMV infection in the vascular endothelial cells leads to abnormal cellular swelling and enlargement, vascular luminal compromise, fibrin thrombus formation, local vasculitis and tissue damage in the intestinal segment supplied by the affected vessels^[3,15]. Finally, intestinal ulceration is developed in the infected intestinal segment. Our case showed a large geographic ulceration with exuberant granulation tissue formation. CMV infection is frequently found in the vascular endothelial cells and stromal fibroblasts, which is supportive of the reported pathophysiology of CMV-induced ulceration.

In conclusion, the small bowel is a rare site of involvement by gastrointestinal CMV infection and CMV enteritis with jejunal perforation is extremely rare. However, CMV enteritis should be considered as a possible di-

agnosis in the ulcerative lesion of a small bowel segment when abdominal pain, vomiting, diarrhea and perforation develop in patients with a history of endometrial cancer.

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Pneumomediastinum, pneumorachis, subcutaneous emphysema: An unusual complication of leukemia in a child

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Key words: Pneumomediastinum; Leukemia; Pneumorachis; Subcutaneous emphysema; Chemotherapy

Core tip: Pneumomediastinum, pneumorachis, subcutaneous emphysema is an unusual complication in leukemia. Although not mentioned in literature, this case may be an eye opener to look for this complication in this scenario. Acute lymphoblastic leukemia (ALL) is not mentioned as a cause of this condition but medical science has always made us learn from case to case. This case may be an index for this complication as all mentioned secondary causes were ruled out by all available investigations. Whether it is related to chemotherapy or not, it is definitely a case of ALL with this complication.

Abstract

Pneumorrhachis (PR), or epidural emphysema, denotes the presence of air in the spinal epidural space. It can be associated with a variety of etiologies, including trauma; recent iatrogenic manipulations during surgical, anesthesiological and diagnostic interventions; malignancy and its associated therapy. It usually represents an asymptomatic epiphenomenon but also can be symptomatic by itself, as well as by its underlying pathology, and rarely can be fatal. The pathogenesis and etiology of PR are varied and can sometimes be a diagnostic challenge. As such, there are no standard guidelines for the management of symptomatic PR and its treatment is often individualized. Here, we present a case of a 14-year-old boy treated for leukemia who developed this complication and whether chemotherapy related or not, it proved to be fatal for him. To our knowledge, this is the first case in the literature of this complication with acute lymphoblastic leukemia.

Showkat HI, Jan A, Sarmast AH, Bhat GM, Jan BM, Bashir Y. Pneumomediastinum, pneumorachis, subcutaneous emphysema: An unusual complication of leukemia in a child. *World J Clin Cases* 2013; 1(7): 224-226 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i7/224.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i7.224>

INTRODUCTION

Pneumomediastinum or air in the mediastinum may originate from the esophagus, lungs or bronchial tree. As suggested by a handful of small case series in the literature^[1-4], spontaneous pneumomediastinum is an uncommon, self-limiting condition. It results from alveolar rupture, otherwise known as the Macklin phenomenon. Alveolar rupture results from high intra-alveolar pressures, low peri-vascular pressures, or both. Air escaping from the alveoli tracks into the mediastinum during the breathing cycle as the pressure in the mediastinum de-

Table 1 Investigation chart

Hb (g%)	TLC	PLT	Neutrophil/lympho	KFT urea/creat	PO ₂	SPO ₂	Ca ²⁺ (mg/dL)	Blood culture	Urine culture
11.2	4.2	68	73/21	33/0.98	77	95	9.8	Sterile	Sterile
10.5	3.7	63	69/26		68	91			
11.3	3.4	61	77/20	39/1.1	64	92	8.9		
10.9	3.2	58	78/19		67	94			
11.2	3.3	57	66/22	31/0.78	69	90	9.1	Sterile	Sterile

TLC: Total leucocyte count; PLT: Platelet count; KFT: Kidney function test.

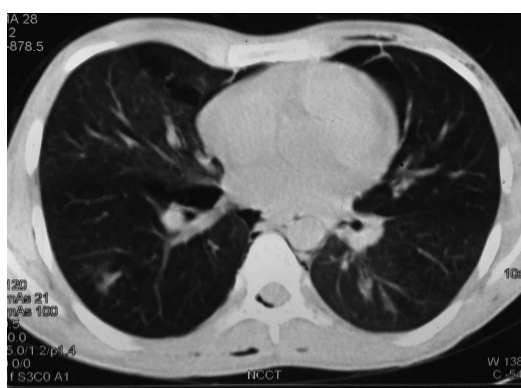


Figure 1 Computed tomography showing pneumomediastinum and pneumorachis and subcutaneous emphysema.

creases relative to the pulmonary parenchymal pressure. From there, air may track into the cervical subcutaneous tissues, epidural space^[5], pericardium^[6] and/or peritoneal cavity^[7,8]. A handful of small case series in the literature have suggested the benign course of this condition^[1-4] but there are still no clear guidelines regarding the diagnostic and therapeutic interventions needed.

CASE REPORT

A 14-year-old male with a case of precursor B cell acute lymphoblastic leukemia (ALL) (Bcr-Abl-negative), who was on chemotherapy (as per UKALL-XII protocol), developed a cough for 5 d which was non-productive, brassy and with no nocturnal worsening. In addition to antibiotic policy as per IDS guidelines, he also received nebulisation and antitussives. Over a period of time, he developed pain and swelling of the chest and face, had crepitus on the chest wall and parotid area and complained of neuropathic pain of the lower limbs. Examination showed a pulse of 102 beats/min, blood pressure 110/72 mmHg, respiratory rate 18/min and temperature 99°F. Crepitus was noticed on the anterior chest wall, parotid area bilaterally and neck. The chest showed an occasional wheeze in the right infrascapular area. Neurological examination showed that the neuropathic pain and reflexes were exaggerated in the lower limbs only. Computed tomography showed pneumomediastinum, pneumorachis and subcutaneous emphysema (Figure 1). The patient was managed in consultation with the cardiovascular and neurosurgery team who preferred a conservative line of management in the form of high flow oxygen, respira-

tory care and monitoring blood gases and electrolytes. Investigations showed hemoglobin 11.2 g%, total white cell count $3.3 \times 1000/\text{mm}^3$ and platelets $57000/\text{mm}^3$. Oxygen saturation was 90% on room air. Kidney and liver functions were normal, as shown in Table 1. Blood and urine cultures were sterile and no sputum was possible even after giving mucolytic nebulisation and chest physiotherapy by an expert. The patient was managed conservatively but after 7 days of conservative management he developed respiratory arrest, was intubated and moved to the intensive care unit, but expired 2 d later. No apparent or definite cause could be ascertained.

DISCUSSION

The presence of pneumomediastinum implies that there is or has been a breach of an air-containing mediastinal structure. Air in the mediastinal tissues may originate from the respiratory tract, such as after blunt or penetrating trauma to the facial bones, pharynx, hypopharynx, trachea and main stem bronchi. Dental procedures using compressed air may result in facial and neck subcutaneous emphysema and pneumomediastinum. Severe straining, the Valsalva maneuver and free perforation of the gastrointestinal tract may be responsible for the appearance of pneumomediastinum and subcutaneous emphysema^[9]. Surgical emphysema was reviewed in 1957 by Shovelton^[10] who reported 13 cases after endodontic treatment. Epidural space pneumorrhachis usually occurs by the two following mechanisms: atmospheric air passes through a spinal needle into the epidural space or air moves through the posterior mediastinum into the epidural space. Air may unintentionally enter the epidural space during a lumbar puncture or may enter intentionally during lumbar epidural anesthesia to locate the epidural level. These conditions are self-limited^[11]. If air is present in the posterior mediastinum, it may dissect along fascial planes from the posterior mediastinum (or retropharyngeal space), through the neural foramina and into the epidural space. No true fascial envelope protects the epidural space. Mediastinal air moves into the epidural space behind the driving pressure of a tension pneumothorax or pneumomediastinum. In case reports, there are associated causative factors, such as trauma^[12,13], strenuous exercise^[14], asthma and violent coughing^[15,16].

Spontaneous pneumomediastinum is a self-limiting and benign condition that is frequently over-investigated and overtreated^[17,18]. However, clear guidelines regarding

the diagnostic and therapeutic interventions are currently unavailable. The management of these patients has to be decided on an individual basis and often requires an inter- and multi-disciplinary approach. There is little literature showing any direct relationship between pneumomediastinum or pneumorachis and leukemia but there are a few case reports showing mediastinal necrosis of a mass causing mediastinal emphysema and pneumorachis can happen later, as already discussed, through fascial planes through the neuro foramina to the epidural space^[19].

Unusual complications like this must be kept in mind in leukemic patients and treated with a multidisciplinary approach as we did, but unfortunately even although the literature says this is a treatable condition, we lost the patient without any apparent cause. More work needs to be done on this condition and a helpful working plan needs to be charted out. Autopsy could have solved many issues but because of religious reasons and policies in this part of world, it was not possible for this case. ALL is not mentioned as a cause of this condition but medical science has always made us learn from case to case. This case may be an index for this complication as all mentioned secondary causes were ruled out by all available investigations. Whether it is related to chemotherapy or not, it is definitely a case of ALL with this complication.

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Unusual case of insitu (intracystic) papillary carcinoma of breast

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Abstract

The term "intracystic papillary ductal carcinoma *in situ*", has recently changed and is now more appropriately referred to as "intracystic papillary carcinoma" constituting only 0.5% to 1% of all breast cancers. Herein, we discuss an unusual case of intracystic insitu papillary carcinoma of breast in a postmenopausal woman, the diagnosis of which was made on histopathology and confirmed by immunohistochemistry. Patient responded well to postoperative adjuvant radiotherapy without any recurrence, thereby preventing further morbidity and mortality related to invasion or tumor progression. So careful histopathological evaluation is the mainstay to arrive at the correct diagnosis to avoid untoward complications related to under diagnosis and /over diagnosis.

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Key words: Insitu papillary carcinoma; Histopathology

Core tip: The onco surgeon and onco pathologist should keep in mind this rare type of insitu carcinoma as a dif-

ferential diagnosis in palpable breast lumps as it often mimics a benign lesion clinically. However, careful histopathological evaluation superadded by immunohistochemistry is an effective tool to arrive at the correct diagnosis to avoid untoward complications related to under diagnosis and/over diagnosis.

Ingle SB, Hinge(Ingle) CR, Murdeshwar HG, Adgaonkar BD. Unusual case of insitu (intracystic) papillary carcinoma of breast. *World J Clin Cases* 2013; 1(7): 227-229 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i7/227.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i7.227>

INTRODUCTION

Intracystic papillary carcinoma (IPC) is an uncommon breast cancer constituting only 0.5% to 1% of all breast cancers^[1]. Benign and malignant papillary lesions of the breast can be very difficult to distinguish on cytology^[2,3]. It is said to occur more frequently among whites and postmenopausal women^[2]. Papillary lesions of breast have been evaluated in a wide spectrum ranging from intraductal papilloma to insitu papillary carcinoma of breast and invasive papillary carcinoma^[3,4]. Herein, we discuss an unusual case of IPC of breast in a postmenopausal woman in sharp contrast with the clinicoradiological diagnosis.

CASE REPORT

A 49-year-old female presented with a well-circumscribed swelling in the upper outer quadrant of left breast measuring 3 cm in diameter. The lump was freely mobile and not fixed to skin and deeper tissue. Mammography showed a circumscribed mass in breast with partially obscured margins. Sonography showed a cystic mass with internal echoes without posterior acoustic shadowing. All hematological parameters were within normal limits.

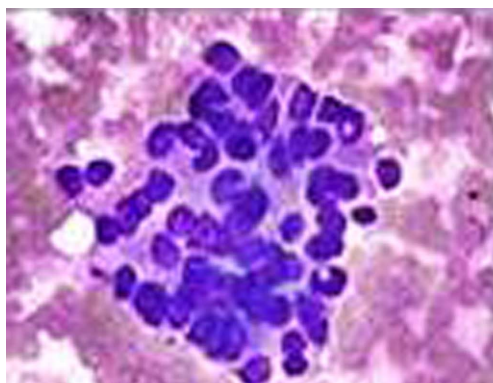


Figure 1 Fine Needle Aspiration Cytology confirmed the presence of atypical cells.

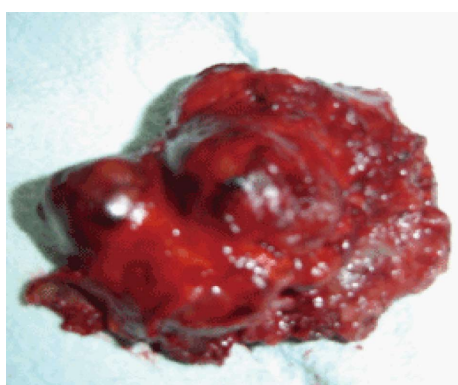


Figure 2 The cut surface was grey white and firm with focal areas of hemorrhages, necrosis.

On examination there was no palpable axillary lymphadenopathy. Fine Needle Aspiration Cytology confirmed the presence of atypical cells (Figure 1). A core biopsy of the lesion revealed atypical ductal hyperplasia, but no evidence of malignancy. In view of the atypical cells and the residual swelling, the lesion was excised. Gross examination revealed a lesion 3 cm × 2 cm × 2 cm in size. The cut surface was grey white and firm with focal areas of hemorrhages and necrosis (Figure 2). Histology showed an intracystic tumor composed of papillary, adenoid and cribriform structures lined by columnar cells exhibiting features of marked cytological atypia, *i.e.*, nuclear hyperchromasia, pleomorphism, abnormal mitosis and increased N:C ratio (Nucleocytoplasmic ratio) with fibrovascular cores (Figure 3). The myoepithelial layer was intact. On immunohistochemical staining 3+ nuclear staining was obtained by estrogen and progesterone, whereas a negative result was obtained by cerB2. The case was finally diagnosed as insitu papillary carcinoma of breast (IPC). Left simple mastectomy with sentinel lymph-node mapping was performed. There was no evidence of tumor in the mammary tissue and the sentinel node. Adjuvant radiotherapy (40 Gy in 25 fractions) was advised due to tumor extension close to deep margin and patient is doing well since last one year without any recurrence.

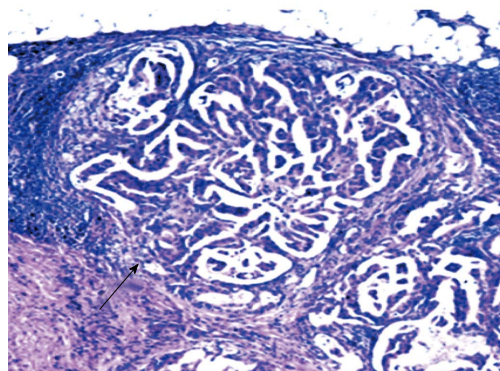


Figure 3 Showing intraductal malignant cells arranged in papillary fronds exhibiting features of malignancy (Insitu Papillary Carcinoma of Breast), × 10.

DISCUSSION

The terminology applied to describe papillary breast lesions in the literature is relatively confusing. The traditional term “intracystic papillary carcinoma” generally refers to a localized *in situ* lesion, in a cystically dilated duct. In view of the desmoplasia often surrounding these lesions, the distinction between *in situ* and invasive papillary carcinoma can be very difficult to make. Therefore, IPC had been divided into three subgroups which seem to correlate with the prognosis: IPC alone, IPC plus DCIS and IPC with invasion^[5]. In this manner, the term “papillary DCIS” would refer to a more diffuse process that involves multiple ducts as opposed to a localized lesion^[5].

Recently, Hill *et al.*^[6] using myoepithelial cell staining, suggested a spectrum of progression from *in situ* disease to invasive disease, signifying that what appears to be DCIS on histology may potentially cause distant metastases. The lack of an intact basal myoepithelial cell layer can be identified by calponin, smooth-muscle myosin heavy chain cytoplasmic stains and by p63 nuclear stains. This “gold standard” method has a relatively high sensitivity and denotes the invasiveness of the tumor cells in malignant papillary breast lesions^[7].

The diagnosis of IPC of the breast should be made carefully. Triple assessment is essential and the goal is to achieve a preoperative diagnosis prior to surgery. The radiological diagnosis of IPC is relatively challenging. The typical appearance of IPC on sonography is a hypoechoic area with soft tissue echoes projecting from the wall of the cyst^[6,8]. However, variations exist on ultrasounds from intraductal lesions associated with ductal dilatation and a predominantly solid pattern with the intraductal or intracystic mass totally filling the duct^[9]. Importantly, IPCs are vascular tumors demonstrating a characteristic flow pattern on color-flow studies, which are sensitive to identifying even very small IPCs. A distinct vascular pedicle can be identified within the central core with branching vessels arborising within the mass^[9].

The mammographic appearance of IPCs is less specific. Small IPCs are often negative on mammography, while larger lesions may resemble any other focal well-circumscribed dense mass^[9]. Both can cause minimal to

moderate duct dilatation in a tapering band-like density pattern from the nipple towards the parenchyma. In addition, one report suggested the use of pneumocystography^[10], and another MRI^[11], in combination with mammography and ultrasound to diagnose IPC.

Fine Needle Aspiration Cytology and core biopsy are usually performed. However, false negative results with cytology are relatively frequent^[12]. Therefore, excisional biopsy should be carried out in all cystic lesions of the breast, which are suspicious on any of the above diagnostic modalities.

There are no clear guidelines about the management of IPC, which is due to various factors. On one hand IPC is a rarity, on the other hand, the histopathological classification and detection of invasiveness in IPC is rather confusing^[5]. Since the prognosis of IPC is excellent with low loco regional and distant recurrence rates, mastectomy is usually not necessary, unless it is technically unavoidable^[13]. Axillary node metastasis can occur in up to 14% of the cases^[13] therefore, an axillary staging procedure or clearance is recommended by most authors^[9,13]. Others argue that IPC should be generally regarded as an *in situ* disease, therefore axillary surgery is not recommended by these authors^[6,8]. There has been no clear indication for adjuvant endocrine therapy, even for patients with estrogen-receptor-positive tumors. The addition of hormonal treatment does not appear to have influenced the outcome^[13]. On the contrary, Fayanju *et al*^[14] recently reviewed the usual adjuvant treatment applied for IPC and found that patients with DCIS or micro invasive disease in association with IPC were more likely to receive radiotherapy and tamoxifen

In a conclusion, the oncosurgeon and oncopathologist should keep in mind this rare type of carcinoma as a differential diagnosis in palpable breast lumps as it often mimics a benign lesion clinically. In such a scenario triple assessment, *i.e.*, clinical examination, radiology and histological assessment with a high level of clinical suspicion, is necessary to diagnose insitu papillary carcinoma due to its rarity.

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Mongolian spots: How important are they?

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Author contributions: Gupta D collected the articles and wrote the manuscript; Thappa DM initiated the idea for this article, and in addition, edited, revised and provided crucial critical inputs to the manuscript.

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Key words: Mongolian spot; Inborn errors of metabolism

Core tip: Though earlier considered to be benign birthmarks, it has been shown now that Mongolian spots (MS) are often associated with co-existent anomalies like inherited disorders of metabolism, vascular birthmarks and occult spinal dysraphism. Babies with extensive MS should be screened for the same.

Abstract

Mongolian spots (MS) are congenital birthmarks seen most commonly over the lumbosacral area. They are bluish-green to black in color and oval to irregular in shape. They are most commonly found in individuals of African or Asian ethnic background. Although these lesions resolve by one to two years of age, widespread, extrasacral and dark colored MS sometimes persist into adulthood. Aberrant MS over occiput, temple, mandibular area, shoulders and limbs may be confused with other dermal melanocytoses and bruises secondary to child abuse, thus necessitating documentation at birth. Although traditionally believed to be benign in nature, they have now been shown to co-exist with inborn errors of metabolism, most commonly GM1 gangliosidosis and mucopolysaccharidosis type I (Hurler's disease), followed by mucopolysaccharidosis type II (Hunter's syndrome), mucopolisidosis, Niemann-Pick disease and mannosidosis. They have also been seen to co-exist with various vascular or other pigmented birthmarks like café-au-lait macules. Co-existing Mongolian spots and vascular birthmarks like nevus flammeus, nevus anemicus or nevus spilus is termed as phakomatosis pigmentovascularis. This review focuses on the important associations of Mongolian spots and stresses upon the importance of screening babies with extensive MS.

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INTRODUCTION

Mongolian spots (MS) are non-blanching hyperpigmented patches over the gluteal region that usually present at birth or in the first few weeks of life. These lesions are most prominent at the age of one year and start regressing thereafter, with most of them disappearing by early childhood.

The blue color of MS is secondary to the Tyndall effect, a phenomenon where light is scattered by particles of matter in its path. Dermal pigmentation appears gray, grayish-blue or grayish black because these colors have a shorter wavelength and are reflected to the skin surface. Colors with a longer wavelength, such as yellow, orange or red, are not reflected and continue into the deeper parts of the skin. The amount of melanin in the dermal melanocytes, the number of dermal melanocytes and their depth in the dermis, are important determinants of color^[1,2].

A unique feature of MS is the ethnic difference with regards to prevalence in different racial communities, which has been the subject of much research. They are

most commonly seen in Asians and Africans, and less commonly so in the Caucasians. On average, prevalence of MS is around ten percent in White infants, 50% in Hispanics and 90%-100% in Asians and Africans^[3]. Kikuchi observed that although racial differences were present in the expression of MS, microscopically, dermal melanocytes were found in the buttocks of all the newborns, irrespective of race. According to him, the only difference was in the number of melanocytes, which was less in normal appearing bottoms, as compared to pigmented bottoms. Also melanocytes in the white children contained inactive, incompletely melanised melanosomes. Kikuchi^[1], in his paper, mentioned an earlier hypothesis of Morooka that the difference might also be due to the duration of dermal melanocyte production, which was longer in Asians as compared to Caucasians. As a result of this, the birthmark would still be present at birth in the former, but would have disappeared in the latter, thus giving rise to a higher prevalence at birth in Asians.

Historically, MS have been regarded as benign and parents are reassured that they will eventually fade away with time. Recent data, however, suggest that MS may be associated with other conditions like various inborn errors of metabolism and neurocristopathies. The term “neurocristopathy” refers to a disorder characterised by abnormalities in neural crest migration, growth and differentiation. A close relationship between central nervous system and melanocyte population, due to their common origin from neural crest, is well known. This explains why these conditions sometimes occur together^[4].

Inborn errors of metabolism

Weissbluth was the first to recognize an association between generalized MS and various storage disorders but termed it as being co-incidental^[5]. Given the high prevalence of MS in Asians and Africans, the association of these two conditions may be a chance occurrence, but over the last thirty years numerous case reports have been published linking the two^[6]. The most common lysosomal storage disorder associated with MS is Hurler's disease followed by GM1 gangliosidosis^[4]. Apart from GM1 gangliosidosis and mucopolysaccharidosis type I (Hurler's disease), MS have been reported in association with mucopolysaccharidosis type II (Hunter's syndrome), mucopolipidosis, Niemann-Pick disease and mannosidosis^[7,8].

Human keratinocytes and dermal fibroblasts express nerve growth factor (NGF), which is an important signal for transdermal melanocyte migration. NGF exerts its action *via* the Trk protein (tyrosine kinase-type receptor) as well as *via* receptors present on melanocytes. In inborn errors of metabolism (IEMs), accumulated metabolites bind to the Trk protein *via* glycosylation, resulting in an abnormal increase in NGF activity. Since melanocytes also have receptors for NGF, metabolite-Trk binding will lead to abnormal melanocyte migration. Also, metabolite-Trk binding acts as a trigger for melanin-synthesizing pathways in dormant melanocytes^[4,9].

MS in IEMs show a generalized distribution involv-

ing dorsal and ventral trunk in addition to sacral region and extremities. These lesions are persistent and may also progress over time. The pigmentation is deeper as compared to the common MS^[10].

Recognition of extensive MS can help a physician identify these related serious disorders early. The mucopolysaccharidoses respond well to stem cell transplantation or enzyme replacement therapy if instituted at an early stage, before irreversible organ damage occurs. Early palliative care decisions can be made for gangliosidoses. It also helps in identification of at risk families and prevention of complications^[9].

Vascular birthmarks

Co-existing MS (a type of pigmented birthmark) and vascular birthmarks have been described. The term “phakomatosis pigmentovascularis (PPV)” has been coined to denote the association of widespread, persistent and aberrant nevus flammeus and pigmentary abnormalities. PPV has been classified into four types^[11]: (1) Type I, Nevus flammeus plus nevus pigmentosus et verrucosus; (2) Type II, Nevus flammeus plus MS with or without nevus anemicus; (3) Type III, Nevus flammeus plus naevus spilus with or without nevus anemicus; and (4) Type IV, Nevus flammeus plus MS and nevus spilus with or without nevus anemicus. Each condition is further divided into type a and b, denoting a co-existing cutaneous and systemic disease respectively. PPV is due to “twin-spotting”, a phenomenon in which there are two genetically different clones of neighboring cells in a background of normal cells, thus giving rise to paired nevoid skin lesions occurring in close proximity to each other. This results in homozygous cell populations in different body areas, which lead to MS and nevus flammeus. The above defect may also be caused by abnormal neural crest migration of melanocytes and angiogenic cells adversely affecting each other^[12].

MS have been described in association with non-involting congenital hemangioma, Sturge-Weber syndrome, Klippel-Trenaunay syndrome, cutis marmorata telangiectatica congenita and segmental café-au-lait macules^[12-14]. In these cases persistent MS carry a worse prognosis and may be associated with underlying neurological defects^[12].

Child abuse

In recent years, documentation of the MS has assumed medico-legal importance, as they can sometimes be confused with bruises, especially if present over atypical sites. This leads to a mistaken diagnosis of child abuse or battered child syndrome. MS can be distinguished from a bruise in that it is not tender, does not change color or evolve with time and may take several months to disappear^[15].

Miscellaneous

MS have been reported to occur with Sjögren-Larsson syndrome and leptomeningeal melanocytoma involving

the spinal cord^[16,17]. They may also represent a marker of occult spinal dysraphism. Whether these represent true or chance associations remains to be seen.

CONCLUSION

MS can no longer be considered as always benign congenital birth spots. A possible relationship between these birthmarks and IEMs has led to renewed interest in MS. A recent study has shown that extrasacral spots, diameter > 10 cm, dark color (blue/blue-black) and multiple patches are markers of persistence of MS beyond one year^[18]. Further research is needed to establish the association between these markers and presence of inborn errors of metabolism.

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Non-pharmacological cognitive intervention for aging and dementia: Current perspectives

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Abstract

In recent years, cognitive difficulties associated with normal aging and dementia have been receiving increased attention from both public and scientific communities. With an increase in overall lifespan, promoting healthy cognition has become a priority and a necessity for minimizing and preventing individual and societal burdens associated with cognitive dysfunctions in the elderly. The general awareness concerning the efficacy of preventive (*e.g.*, lifestyles) and palliative treatment

strategies of cognitive impairments, related to either healthy or unhealthy trajectories in cognitive aging, is continuously rising. There are several therapeutic strategies which can be broadly classified as either pharmacological or non-pharmacological/psychosocial. In face of the modest evidence for success of pharmacological treatments, especially for dementia related impairments, psychosocial interventions are progressively considered as a complementary treatment. Despite the relative spread of psychosocial interventions in clinical settings, research in this area is rather scarce with evidence for success of these therapies remaining controversial. In this work we provide an evidence based perspective on cognitive intervention(s) for healthy aging, pre-dementia (mild cognitive impairment), and dementia populations. Current evidence and future directions for improving cognitive functions in the elderly are discussed as well.

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Key words: Dementia; Aging; Cognitive intervention; Cognition; Non-pharmacological therapies

Core tip: Cognitive intervention (CI) may provide a viable option for improving cognition in healthy aging, as well as in mild cognitive impairment and dementia. Although current evidence regarding the efficacy of CI is modest, therapeutic strategies for mitigating the effects of aging on cognitive decline and early stage dementia, should be integrated into mainstream clinical practice.

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DEMENTIA - DEFINITION, DIAGNOSIS, EPIDEMIOLOGY

Dementia can be defined as a decline in cognition and/or behavioral impairment coupled with progressive deterioration of daily functionality which cannot be explained in terms of delirium or major psychiatric disorders^[1].

The worldwide prevalence of dementia for individuals who are 60 years and older is estimated to be between 5%-7% in most regions of the world^[2] with estimated worldwide costs of \$604 billion (in 2010), the majority of which (70%) incurred in western Europe and North America^[3]. Moreover, dementia's contribution (11.2%) to the years lived with disability (YLD) in people aged 60 years and over is higher than that of stroke, cardiovascular disease or cancer^[4]. Dementia presents a considerable burden both at the micro (individual/patient, family, formal and informal caregivers) and macro levels (societal, governmental).

While several etiologies can lead to dementia, Alzheimer's disease accounts for around 60% of all cases, and consequently is considered the leading cause of dementia^[5]. Besides disabling behavioral and motor disturbances, cognitive dysfunctions are considered to be a major source of difficulties for patients, caregivers and practitioners. Moreover, cognitive impairments are not only observed in early stages of Alzheimer's disease (AD) but also in a number of other dysfunctions such as vascular dementia, frontotemporal dementia (FTD) and even Parkinson disease (PD).

Currently, options for treating dementia include pharmacological and non-pharmacological therapies. At present, pharmacological treatments provide viable but rather modest symptom control^[6,7]. Also, disease-modifying therapies are currently under clinical testing (*e.g.*, vaccination, passive immunization for AD; for a review please refer to Galimberti and Scarpini^[8]) or in preclinical phases (*e.g.*, compounds aiming to interfere with tau^[9] or synuclein^[10] deposition in tauopathies and synucleinopathies, respectively).

Non-pharmacological approaches have also been used to manage behavioral problems and compensate for cognitive impairments. However, evidence of their effectiveness and use remain scarce and controversial. In the following sections, we aim to provide a balanced evidence-based perspective of cognitive intervention (CI) approaches to cognitive impairments in elderly populations with no cognitive pathology as well as with pathological cognitive decline.

CI FOR DEMENTIA - FROM HEALTHY TO PATHOLOGICAL TRAJECTORIES OF COGNITIVE AGING

Conceptual framework/background

The conceptual framework introduced by Clare *et al.*^[11] will be adopted in this review. The framework consists of

3 main approaches in CI: cognitive training (computer-based or paper-and-pencil cognitive exercises); cognitive stimulation (cognitive and social group activities); and cognitive rehabilitation (individualized interventions addressing patients' key difficulties and goals).

Cognitive training delivered in individual or a group format focuses on specific cognitive functions. Health professionals deliver paper-and-pencil as well as computer-based exercises with different difficulty levels (additionally, if not stressful to the patient, caregivers might participate in the intervention sessions or assist with exercise delivery at home). Traditionally, in older adults this intervention mostly focuses on memory training, but it can also target or include other cognitive functions aiming primarily at improving the trained functions/skills and/or learning compensatory techniques and secondary generalized gains to other tasks as well as to daily life. While there is some evidence for cognitive improvements resulting from training cognitive functions in all populations (*i.e.*, healthy adults^[12], pre-dementia^[13], and mild-to-moderate dementia^[14]), generalization of effects is not yet evident^[15].

Cognitive stimulation, instead, adopts a more global and contextualized perspective on cognitive functioning, and assumes that cognitive functions work together and should be stimulated accordingly in a social setting. There is some evidence that this approach can benefit cognitive functioning in dementia patients^[16]. However it is not yet clear whether the observed effects are due to cognitive or social components, since both are integral parts of cognitive stimulation.

Cognitive rehabilitation aims to identify and work on personally relevant difficulties and goals. These difficulties may include memory or performance in daily tasks. For this method, a holistic approach is adopted with health professionals working with the patient as well as a family member or caregiver if needed. Although there are only few studies investigating intervention in age related cognitive impairment with the holistic approach, there is initial evidence that people in fact do benefit from cognitive rehabilitation^[17].

It is noteworthy that not only these non-pharmacological cognitive approaches have been explored as a complementary therapeutic approach to medication^[18], but also other non-pharmacological multicomponent approaches such as combining different CIs (*e.g.*, cognitive stimulation plus computer-based cognitive training^[19]), physical exercise and cognitive training^[20], and more recently transcranial magnetic stimulation with cognitive training^[21] have been employed as well.

A selective narrative review was performed while recurring to representative articles, which were identified by authors and complemented with literature searches in PubMed/MEDLINE and ScienceDirect. Searches were performed for reviews (from which relevant references were extracted also) and trials of non-pharmacological CIs in healthy aging as well as several types of dementia. In our search, we used the expression "CI" and related

terms (*i.e.*, cognitive stimulation/training/remediation/rehabilitation) which were combined with the terms aging, mild cognitive impairment, AD, vascular dementia, PD, FTD, and Lewy body dementia. Relevant articles were selected following abstract inspection.

Healthy aging

Cognitive functioning and aging: A large number of scientists believe that aging does not have to encompass severe loss of memory or prevent healthy functioning. Many have spent their devoted life-long efforts on trying to understand how cognitive functioning changes across the human developmental span. A still popular theory, proposed nearly 30 years ago, assumes that the origin of differences between young and aged healthy humans lies in the speed of processing^[22]. Indeed, reduced speed of processing could compromise many cognitive processes, such as overall memory and in particular working memory which is commonly found to be affected with increasing age^[23]. Regardless of the origins of age-related cognitive decline, it is important to outline some of these specific age dependent changes. Besides memory and attention, language, and components of executive functioning may also be compromised with increasing age^[24]. Deficits in perception are also reported but these could simply be due to functional decline of sensory organs.

Often times it is rather difficult to disentangle whether a certain patient's complaint is part of a specific underlying disease process or if it is merely an age-normative complaint. Therefore, neuropsychological assessments are utilized as useful tools in assisting with diagnosis of disorders that imply cognitive impairment^[25] and help with distinguishing a subjective complaint from cognitive dysfunction.

CI in healthy elderly: To overcome age-related cognitive decline several non-pharmacological approaches^[26] have been developed. Exercise, for example, has been extensively studied with current evidence suggesting benefits for cognitive functioning and the promotion of functional mobility in healthy aging^[27,28]. Moreover, to explore the hypothetical additive or synergistic effects of several interventions, exercise has been combined with other techniques. Up until now, findings suggest that interventions targeting multiple domains may be more effective than those that treat each domain independently^[29]. These researchers believe that cognitive training should be offered in conjunction with physical activity^[30] since findings point to greater effects of combined approaches than either intervention alone^[29,31]. For instance, in a 4-mo randomized controlled trial (RCT), the combined training group (physical and cognitive) showed improvements in cognitive speed both immediately and at three months after intervention^[20]. Notwithstanding these findings, the present work will strictly focus on evidence of various CIs.

Cognitive training has been extensively studied in healthy elderly individuals^[12,32,33]. To quote Martin and

colleagues^[34], cognitive training is “an intervention providing structured practice on tasks relevant to aspects of cognitive functioning, using standardized tasks” and “intended to address cognitive function and/or cognitive impairment directly”. Building on these works, Gates and Valenzuela^[32] have stated that cognitive training implies repeated practice and use of standardized tasks that target specific cognitive domains. Similarly, cognitive training teaches theoretically-driven strategies and skills aiming to improve cognitive functioning^[35]. In order to determine if this approach is effective for healthy elderly, we briefly review current evidence from the literature.

In the ACTIVE study (Advanced Cognitive Training for Independent and Vital Elderly) large-scale RCTs were conducted to compare training in different cognitive domains^[12]. They studied the effects of memory, reasoning, and speed-of-processing training while comparing these groups with no-training controls. When compared to baseline assessment, each of these interventions improved the cognitive domain of interest with sustained improvements visible at a 2-year post-intervention follow-up^[12]. Furthermore, five years after training, it was observed that the groups with reasoning and memory training still maintained improvements in the targeted cognitive abilities^[36].

Another example of this line of research includes reading aloud and solving simple arithmetic calculations, such as the one in an ongoing trial study by Nouchi *et al.*^[37].

Due to limited evidence of transfer effects of this training approach to everyday life functions, some have adopted a multimodal strategy^[36]. Typically, these approaches involve lifestyle changes and social interactions. Quite different from standard cognitive training, multimodal programs engage older adults in “enjoyable or socially meaningful” activities. The underlying assumption is that this approach would increase the possibility of older adults maintaining their activity and skill levels even long after completing an intervention^[36] (for an example of this approach see Tranter and Koutstaal^[38]).

Several review studies have summarized the evidence in favor of CI. A review paper from Tardif and Simard^[39] states that CI can result in improvements in at least one outcome in each of the studies they have analyzed. In a more recent systematic review^[40], authors gathered evidence from thirty-five studies (most of them RCTs). Despite the diversity among employed interventions as well as methodological differences, their review presented evidence stating that cognitive training can be beneficial in improving several domains of cognitive functioning namely attention, memory, speed of processing and executive functioning. In a different review^[41] with clinical trials comparing the effects of CIs between older adults and a wait-and-see control group, the authors found a strong effect size. The longitudinal RCTs included in this review presented relative effect sizes pointing to protective effects of CI. When authors computed these values for meta-analysis they found an integrated effect size estimated to be 1.07 (95%CI: 0.32-1.83; $\bar{z} = 2.78$; $n = 7$; $P =$

0.006). Furthermore, the same review also noted that the effects of RCTs were maintained even at longer follow-up intervals. The authors conclude that CI in healthy older adults “produces strong and persistent protective effects on longitudinal neuropsychological performance” which might play a role in preventing the development of dementia^[41]. Hence, there is some evidence that CI can boost cognitive functioning in healthy older adults.

Even though the debate over the generalization of the effects of CI to everyday life activities remains to be fully addressed^[40], some have found evidence in support of this contention. For instance, improvements in cognitive outcomes were evident after CIs and were accompanied by more favorable scores of self-reported Instrumental Activities of Daily Living^[42] and the Useful Field of View test. These benefits lasted for at least 2 years and were reflected in everyday activities including in safer driving performance^[43].

Research has shown that adult brains preserve mechanisms that permit flexible change, such as neurogenesis and functional recruitment of neurons in the presence of a lesion^[44]. Whether older human brains have these capabilities or not, needs to be further explored to potentiate successful aging while preventing cognitive decline. One such strategy involves training and exposure to novelty, which has been associated with human cortical reorganization and grey matter volumetric changes (*e.g.*, changes in hippocampus^[45]; for a review see Greenwood and Parasuraman^[44]). Even short but yet intensive memory training, using for example the Method of Loci, yielded regional increases in cortical thickness (right fusiform and lateral orbitofrontal cortex), which were positively correlated with improvements in memory performance outcomes^[46].

Mild cognitive impairment/pre-dementia

The “mild cognitive impairment” (MCI) concept has been traditionally most closely related to AD with the amnesic variant of MCI being the most common in patients progressing to a diagnosis of dementia of the Alzheimer type. However, current guidelines^[47] explicitly include non-amnesic presentations in MCI (*e.g.*, executive functioning, attention, language, and visuospatial skills; either with single or multi-domain deficits), whether due to AD or other etiologies. The National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for AD^[47] refer to the following core criteria as features of MCI: evident change in cognition from a previous level of cognitive functioning; cognitive impairment in one or more domains (1 to 1.5 standard deviations below the mean for age and education matched peers); autonomously daily life functioning; no dementia. Biomarkers are also currently available (*e.g.*, cerebrospinal fluid amyloid and tau, structural and functional imaging, *etc.*) for aiding in the differentiation of MCI due to AD or due to other causes (pseudodementia or other dementias)^[47].

In order to ameliorate or reverse cognitive deficits characteristic of MCI and/or to prevent its progression

to an overt stage of dementia, new CIs have been steadily developing. Currently, there is positive evidence from individual studies, such as described by Belleville *et al.*^[13] displaying improvements in memory after an episodic memory training program of 120 min per session for 6 weekly sessions (4-5 participants per group) focusing on mnemonic techniques. The latter mentioned training included psychoeducational information regarding memory and ageing, and also memory techniques promoting encoding and retrieval (*i.e.*, imagery, the method of loci, face-name associations, hierarchical organization and semantic organization techniques), delivered by trained neuropsychologists.

In another randomized controlled trial study with amnesic mild cognitive impairment patients and family partners, Kinsella *et al.*^[48] found beneficial effects after a 5 wk intervention training program in everyday memory, namely in prospective memory performance, use of memory strategies, as well as in patient and family knowledge of memory strategies.

In a study of a 6-mo long CI program that included a comparison with a late active control group (receiving intervention after 8-mo), Buschert *et al.*^[49] found a stable intervention effect on the primary outcome Alzheimer Disease Assessment Scale - Cognitive subscale (ADAS-Cog) in the early-intervention group. Additionally, only the later-intervention group participants (6 out of 12) progressed into AD during an entire 28 mo period of the study.

A recent systematic review concerning CI in amnesic MCI individuals^[50], pointed out that evidence of improvements in neuropsychological measures after CI is in fact limited. However, the authors did state that patients were able to learn as well as benefit from memory strategies.

Moreover, aside from efficacy, feasibility parameters have rarely been evaluated, although there is evidence of CI being well received while meeting the needs of MCI patients^[51]. Considering the fact that the latter opinion is from the patient’s perspective (*i.e.*, whether their needs are being met) it should be regarded as an important future area of research that has thus far received little attention. MCI patients similarly show improved subjective perception of memory capacity after CI^[52].

Recently, neuroimaging has also been incorporated as an outcome measure assessing potential brain changes related to CI. Clare *et al.*^[53] provide evidence from a case report where a patient with MCI underwent a cognitive rehabilitation program showing post-treatment reduction in activation of areas such as fusiform gyrus and increased activation in prefrontal areas as well as the temporal-parietal junction. Furthermore, when using verbal encoding and retrieval tasks, Belleville *et al.*^[13] report increased post-intervention activation in MCI patients’ large fronto-temporo-parietal network, while at the same time healthy controls show decreased activation. Interestingly, the authors note the activation of specialized areas (already activated in pre-intervention) and “new” alterna-

tive areas, which we could interpret both as restorative or compensatory processes resulting from CI. However, despite the observed changes, only right inferior parietal lobule activation correlated with performance.

Dementia

AD: As AD is the most prevalent cause of dementia, and since research on CI is comparatively abundant for this cause of dementia, the present section will largely focus on AD. Moreover, cognitive deficits are one of the key features of AD dementia and are a relevant target for pharmacological as well as non-pharmacological therapies. While memory deficits have been traditionally considered the hallmark of AD, it is now widely accepted that other deficits are present even during early stages^[54], with AD pathology often leading to quite different symptomatic presentations such as prominent language or visual deficits^[1,55]. Due to the progressive and unstoppable nature of AD, interventions complementing pharmacological treatments have also been developing worldwide. One of these psychosocial approaches is CI. In 1982 Brinkman *et al*^[56] conducted one of the first trials of cognitive training in Alzheimer patients. In this lecithin trial study, using a double-blind crossover, patients received memory training in addition to the lecithin condition, and “placebo training” during the placebo drug condition. Follow-up trials suggested that memory training may have led to small immediate improvements in list-learning ability. More recently, Tárraga *et al*^[57] conducted a randomized controlled trial with 3 arms, comparing standard treatment (stable treatment with cholinesterase inhibitors) *vs* psycho-stimulation *vs* combined psycho-stimulation and internet-based cognitive training. The authors found that both CI programs lead to improvements in ADAS-Cog and Mini Mental State Examination (MMSE) after 12 wk of intervention, which were maintained at 24 wk post-intervention. Also, Clare *et al*^[17] conducted a cognitive rehabilitation trial for people with AD or mixed AD and vascular dementia, comparing an 8 weekly individual cognitive rehabilitation session program *vs* relaxation program *vs* no treatment (all participants were receiving a stable dose of acetylcholinesterase inhibitors). The individual cognitive rehabilitation program consisted of eight weekly 1-h sessions tackling personal relevant goals and including learning (*e.g.*, face-name learning), attention and concentration maintaining techniques. In the end, the cognitive rehabilitation group did in fact display improvements in goal performance and satisfaction. A subgroup of patients in this study also performed pre and post-intervention functional Magnetic Resonance Imaging face-name association task, exhibiting increased brain activity at the right fusiform face area, right parahippocampal cortex, right temporal parietal junction, and right medial prefrontal cortex. The authors interpreted these changes as being related to deeper encoding of faces and functional restoration of this face-name association learning network.

Despite these promising findings and the steady

increase of research in this area (Figure 1), a recent systematic review^[58] states the need for additional well-controlled and high-quality trials. Despite the limited amount of evidence, the aforementioned review suggests that CI for AD might lead to improvements in global cognitive functioning (*i.e.*, 0.83 points in MMSE, as estimated). Moreover, high rates of completion and adherence to the intervention procedures were observed which point to the feasibility of this approach for AD patients (and caregivers) and health professionals. Interestingly, when examining costs associated with treatment, we found preliminary evidence in support of cost-effectiveness of CIs in dementia. Importantly, we should note that over a 4-mo period, a 1-point decline in the MMSE is estimated to add £56 (£74.74 as of 2011) to direct health and social care costs^[59].

Although CIs in non-AD dementias are comparatively scarce, some of these studies will nonetheless be reviewed in the following sections.

Vascular dementia: Being the second cause of dementia and accounting for about 30% of dementia cases^[60], Vascular Dementia is the center of a considerable amount of research that includes its characterization and etiology. Still, there are only a few trial studies that are directed at investigations of the efficacy of CI for this type of dementia. One of these studies^[61] has specifically investigated the possible role of CI in vascular dementia. The authors addressed this issue in a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and found post-intervention improvements in processing speed as well as executive functioning and functionality. Nonetheless, given potentially conflicting findings, more detailed and comprehensive evidence concerning the efficacy of CI in this area is warranted. For example, although a recent systematic review^[62], including both vascular dementia and AD, reported no effect of cognitive training, a cognitive rehabilitation trial, including people diagnosed with AD, mixed AD or vascular dementia^[17], found improvements in goal performance and satisfaction.

PD: Although CI research in PD is scarce, a cognitive remediation study^[63] for attention skills with non-demented PD patients showed this type of intervention to be feasible and well accepted by patients. Another cognitive-motor intervention (including computer-based cognitive training) study with early stage non-demented PD patients^[64] found verbal fluency, memory (logic memory) and reasoning (Raven's matrices) improvements.

In addition, a neuroimaging study^[65] of a 6 mo daily cognitive training program found post-intervention improved performance in reaction time and hit rate in a fMRI modified Stroop task. The authors also observed a reduction in cortical activation when making comparisons with untrained patients.

FTD: To the best of our knowledge, despite CI being

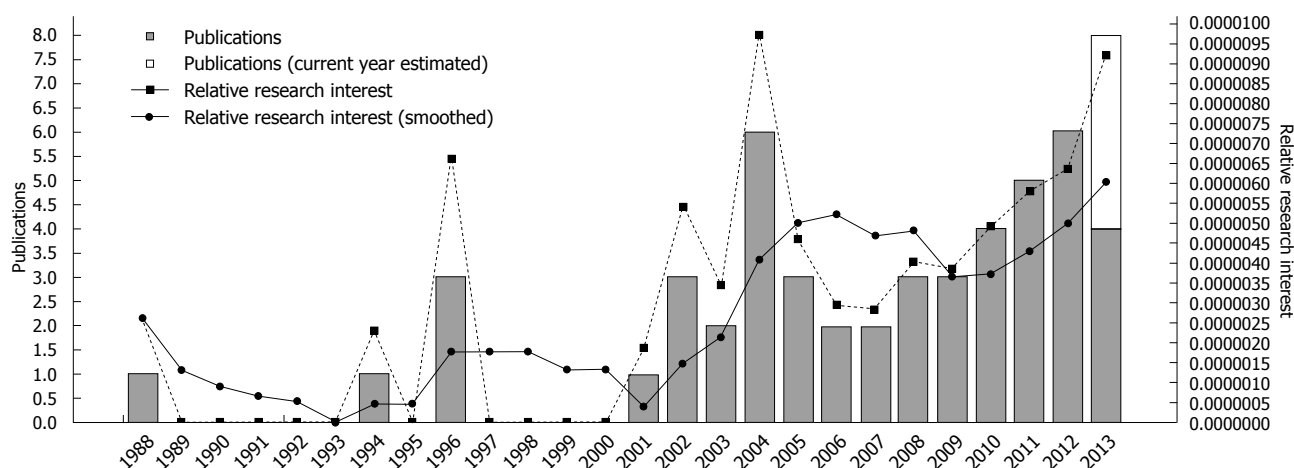


Figure 1 Temporal evolution of cognitive intervention research in Alzheimer's disease (Source: GoPubMed).

considered a therapeutic option for FTD^[66], such intervention trials in FTD are almost nonexistent. However, a speech therapy pilot trial, for Primary Progressive Aphasia, showed beneficial effects in language performance and naming skills^[67], providing preliminary evidence that additional studies in this area are warranted.

Other types of dementia: So far, research on CI has not focused on other types of dementias, such as Lewy bodies', for which we found no studies during our literature search.

One should consider the sensorial or perceptive (cortical) disruption and severe behavioral disturbances that make the implementation of CI approaches in some of these dementia patients difficult (*e.g.*, FTD) which somewhat explains the scarcity of practice and research in some of these types of dementia.

CONCLUSION

General conclusion and future directions

In the present manuscript, we narratively reviewed the current state of CI approaches for healthy aging, pre-dementia, and different types of dementia.

Taken as a whole, studies show evidence for small but consistent effects of CI in improving cognition in both healthy and unhealthy populations of aging adults. Preliminary studies also point to the feasibility, adequacy, patient involvement, and cost-effectiveness of these approaches.

Although research on aging and dementia in general is a dynamic and a rapidly changing field^[68], the CI sub-field of this research is still in its infancy and in spite of the growing evidence of its effectiveness, is still lacking recognition among health professionals as well as caregivers. With disease-modifying therapies still in preclinical or clinical trial stages, research in this field warrants a well deserved attention. While we hope for the development and assessment of new pharmacological therapies for cognitive deficits^[69], the positive role of non-pharmaco-

logical approaches should be considered more carefully, both in research and in practice.

To establish high quality evidence-based standard practices in the field, research on various CI approaches needs to increase considerably. In this regard, the following systematic steps may be considered: (1) Expert meetings should provide a comprehensive perspective ranging from healthy to impaired cognitive aging and allow standardization of methods of practice and research (*e.g.*, defining whether or not, if and when, Randomized Controlled Trials should be the gold standard for CI research, and establishing what constitutes a clinically significant change for a dementia patient); (2) Affirmation of the importance of multidisciplinary clinician/practitioner-researcher roles in the field of CI, as facilitators of advances in the field by rapid translation between research and practice and vice-versa; (3) Establishment of the optimal (the most efficacious and most cost-effective) intervention parameters such as frequency (*i.e.*, which is the most cost-effective number of sessions per week and per month?), duration (*i.e.*, which is the optimal session duration and program duration taking into account patient fatigue, costs and benefits?), and intensity (which is the optimal level of difficulty? What are the effects of different interval schedules?), which are still unclear, and in need of systematic evaluation by researchers; (4) Clarification of what constitutes an "active substance" in CI, and identification of global *vs* specific effects. For example, CI might exert its effects through tackling cognitive deficits related to brain dysfunction (*e.g.*, hippocampal atrophy), or it might improve overall activity and arousal levels; (5) Exploring the existence of secondary negative effects for each type of dementia, such as fatigue, depression, frustration, "burnout"/overtraining which could hypothetically lead to faster progression of cognitive decline; (6) Standardization of outcome protocols taking into account different types and stages of dementia, including neuropsychological, non-cognitive (*e.g.*, quality of life, subjective experience), and neuroimaging measures. Clarification of the relation between cognitive, experi-

ential and neuroimaging outcomes is also needed. For example, should we focus on cognition or on experiential components of the intervention? What is the meaning of brain activation changes? - Is it a possible restoration of function^[70]? Are neurophysiological markers more sensitive than behavioral ones? Can and should biomarkers (e.g. CSF) be incorporated as an outcome measure? (7) Although, there is some evidence for the immediate effects of CI in healthy and impaired cognitive aging, long-term effects and a possible preventive or protective role^[41] of systematic CI needs to be thoroughly assessed (either in the progression from healthy aging to MCI, or from MCI to different types of dementia). Can it delay or slow disease progression? Can it delay or prevent dementia for people with genetic risks? These are critical issues since efficacious preventive interventions might considerably lower the incidence of dementia^[2] with positive repercussions for individuals, and a reduced burden on society; (8) Focus on macro-issues (e.g., systemic, organizational and societal issues); allowing one to assess and modify the variables hindering the adoption and implementation of CI by different professionals and in different settings (e.g., hospital, health centers, clinics); and (9) Awareness of the comparative relevance, importance, efficacy and cost-effectiveness of new technologies (*vs* traditional approaches) not only as a mean of intervention delivery but also for an interaction between professionals, scientists and the public (see for example, the International Non-pharmacological Therapies Project - <http://nphtherapies.org/>). New technologies not only can facilitate the delivery of interventions but may also help in scientific research, allowing maximization of resources and sharing of ideas/protocols, as well as dividing tasks in an organized way. For example, it may facilitate the concerted, effective, and timely translation of neuropsychological instruments into several languages.

In summary, we hope that tackling the aforementioned issues will allow the field of CI to move into an evidence-based and patient-centered multidisciplinary personalized approach. However, before this goal is accomplished there is a need for additional evidence concerning the efficacy of these approaches for each type of dementia and each of its deterioration stages. This information may then be implemented based on individual patterns of dysfunction. Attaining this goal would positively impact cognitive functioning of healthy and impaired elderly and mitigate individual and societal impact of cognitive decline.

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Spinal pedicle subtraction osteotomy for fixed sagittal imbalance patients

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Key words: Sagittal imbalance; Pedicle subtraction osteotomy; Clinical outcome; Proximal junctional kyphosis; Complication

Core tip: In this review article, the literature focusing on pedicle subtraction osteotomy for fixed sagittal imbalance patients is reviewed. The long-term overall outcomes, surgical tips to reduce the complications and suggestions for their proper application are also provided.

Hyun SJ, Kim YJ, Rhim SC. Spinal pedicle subtraction osteotomy for fixed sagittal imbalance patients. *World J Clin Cases* 2013; 1(8): 242-248 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i8/242.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i8.242>

Abstract

In addressing spinal sagittal imbalance through a posterior approach, the surgeon now may choose from among a variety of osteotomy techniques. Posterior column osteotomies such as the facetectomy or Ponte or Smith-Petersen osteotomy provide the least correction, but can be used at multiple levels with minimal blood loss and a lower operative risk. Pedicle subtraction osteotomies provide nearly 3 times the per-level correction of Ponte/Smith-Petersen osteotomies; however, they carry increased technical demands, longer operative time, and greater blood loss and associated significant morbidity, including neurological injury. The literature focusing on pedicle subtraction osteotomy for fixed sagittal imbalance patients is reviewed. The long-term overall outcomes, surgical tips to reduce the complications and suggestions for their proper application are also provided.

INTRODUCTION

Disruption of normal sagittal alignment resulting in global sagittal imbalance can cause significant pain and impair ambulation directly and indirectly through compensatory mechanisms. When global sagittal imbalance arises because a long spinal segment is fixed or fused in a hyperkyphotic and/or hypolordotic position, the patient is said to have fixed sagittal imbalance. The causes of sagittal deformity are myriad, but most commonly include post-traumatic kyphosis, iatrogenic flat back syndrome, postlaminectomy kyphosis, degenerative lumbar kyphosis, and ankylosing spondylitis^[1-3]. For many years, posterior column osteotomies, such as Smith-Petersen osteotomy and Ponte osteotomy, with or without release of the anterior aspect of the spine, were the procedure of choice to shorten the posterior column and thereby reduce fixed kyphosis^[4]. A surgeon can usually achieve 5°-10° of sagit-

tal correction with each Smith-Petersen osteotomy; additional correction is limited by anatomical constraints of the anterior column.

In 1985, Thomasen^[5] first described the three-column posterior wedge osteotomy for the management of fixed sagittal plane deformities in patients with ankylosing spondylitis. The pedicle subtraction osteotomy (PSO) is typically performed at L3 as these vertebrae are the normal apex of lumbar lordosis. It is also safer to perform the osteotomy at one of these levels, as they are caudad to the conus medullaris^[6]. The technique involves a transpedicular vertebral wedge resection extending from the posterior elements through the pedicles and into the anterior cortex of the vertebral body. A PSO can usually produce 30°-40° of lordosis at each level at which osteotomy is performed and, when complete, results in bone-on-bone contact throughout all three columns of the spine^[7-9]. Unfortunately, the procedure is technically much more demanding than the posterior column osteotomies, so PSO is not commonly performed despite the fact that PSO can better restore lumbar lordosis and improve sagittal balance. Several studies have reported outcomes and complications associated with the procedure^[10-14]. The literature focusing on PSO for fixed sagittal imbalance patients is reviewed. The long-term overall outcomes, surgical tips to reduce the complications and suggestions for their proper application are also provided.

Normal sagittal balance and imbalance

In a patient with normal sagittal balance, the center of the C7 vertebral body is in line with the posterior superior corner of S1 and the longitudinal axis of the femur. This normal relationship is demonstrated by the C7 plumb line, also known as the sagittal vertical axis (SVA), which is extended from the center of the C7 body down to the posterosuperior corner of the sacrum at the L5-S1 disc, and the longitudinal axis of femur. In patients with positive sagittal imbalance, the C7 center is shifted forward in relationship to the femoral axis line.

There are two general types of spinal imbalance in the sagittal plane: type 1 and type 2^[1]. A type 1 imbalance refers to a condition in which the patient has a segmental or regional imbalance in the sagittal plane of the spine but still has a balanced spine as defined by a plumb line from C7 that falls over the L5-S1 disc. These patients typically have a short segment that is hyperkyphotic and results in the more cephalad or caudad vertebrae having to compensate with lordosis.

A type 2 imbalance refers to a global imbalance whereby the plumb line falls > 5 cm in front of the L5-S1 disc. A spine with a type 2 imbalance is unable to compensate for the deformity and the patient tends to flex the hips and knees to maintain a proper balance and horizontal gaze (Figure 1). Therefore, during an examination, it is important for these patients to stand with the hips and knees straight so that the uncompensated spinal deformity can be assessed.

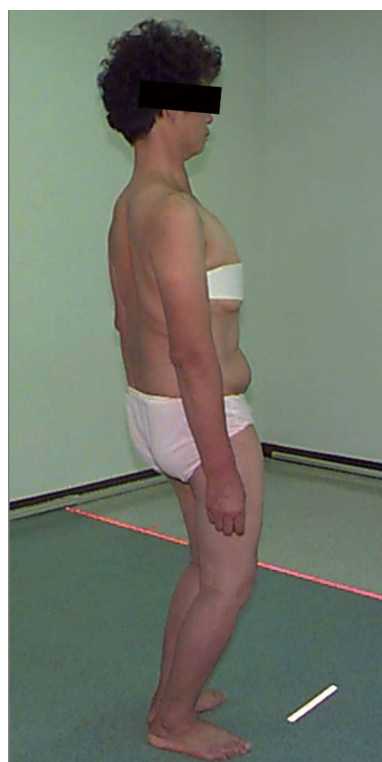


Figure 1 A clinical photograph of a 62-year-old woman who presented with severe lower back pain. To compensate for the lumbar kyphotic deformity, the patient tends to flex the hips and knees to maintain a proper balance and horizontal gaze.

PSO

Surgical decision making for PSO

The PSO is useful for treating patients with ankylosing spondylitis and an imbalance in the sagittal plane of the spine^[5,6,14-16]. Unlike the Smith-Petersen osteotomy, the PSO is mainly useful for deformities with an apex in the lumbar spine. The PSO is historically performed at L2 or L3 and an ideal candidate for the procedure typically has a positive sagittal imbalance of > 12 cm^[6,14-17]. The PSO is also indicated for patients who have had a circumferential fusion along multiple vertebrae, which prevents the performance of a Smith-Petersen osteotomy since osteoclasts cannot be obtained through a fused intervertebral disc.

Surgical decision making for PSO includes: (1) thoracic *vs* lumbar PSO at L2 *vs* L3 *vs* L4 *vs* L5; (2) stop at upper thoracic *vs* thoracolumbar junction; (3) interbody fusion or not for virgin spine *vs* PSO through previous fusion; and (4) consideration of operating table: OSI *vs* Maquett.

Operative technique

Our decision policy of PSO level depended on the site of the most significant pathological entity. For instance, lumbar PSO was indicated for the treatment of iatrogenic lumbar flat back syndrome and degenerative global sagittal imbalance, whereas thoracic PSO was indicated for isolated thoracic kyphosis such as posttraumatic kyphosis. The PSO was performed on patients for whom pos-

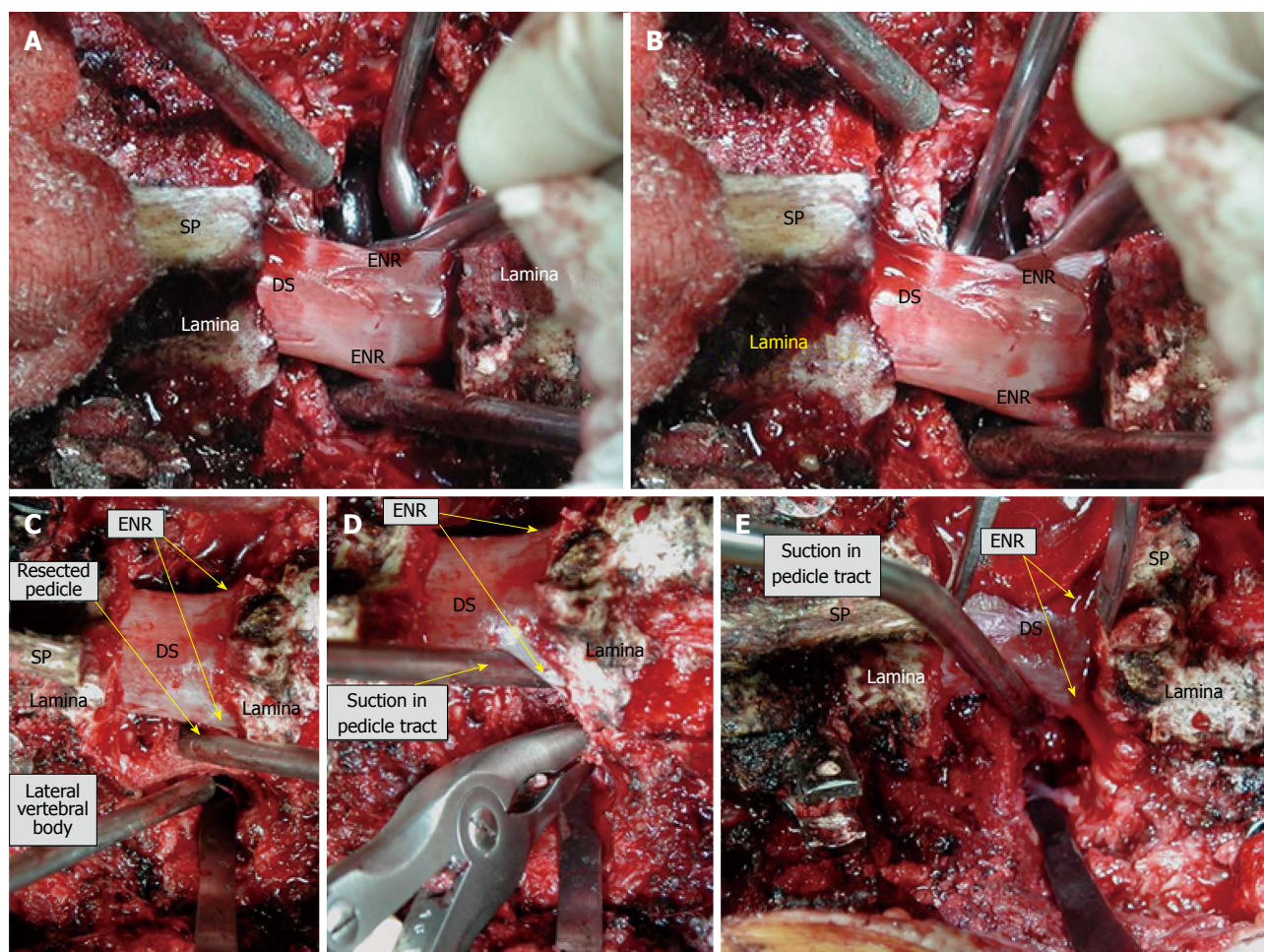


Figure 2 Intraoperative photographs of pedicle subtraction osteotomy. To summarize, exposure transverse to transverse/laminectomy/resection of transverse process/pedicle resection (A and B)/decancellation through pedicle or osteotomy of the pedicle after exposure of the lateral border (C and D)/resect the posterior vertebral body wall (E) and lateral wall if you did not take it/check the mobility and closure using gravity/instrument/operation table. SP: Spinous process; DS: Dural sac; ENR: Exiting nerve root.

terior column osteotomies such as Ponte/Smith-Petersen osteotomies alone would be inadequate, as at least 30° of corrective lordosis was required to correct their sagittal imbalances. Osteotomy was performed on the lumbar spine in most cases, typically at L3. The osteotomy size was based on preoperative standing radiograph measurements of sagittal imbalance, with the surgical goal being restoration of normal sagittal balance with the C7 plumb line falling at or within 5 cm of the posterior-superior corner of S1. A multi-segmental pedicle screw technique was used for posterior spinal instrumentation. All patients were positioned prone on a Jackson frame and were neurophysiologically monitored using somatosensory and motor evoked potentials^[18].

Although various descriptions of PSO exist, the first step in the technique consisted of removing all posterior elements at the level of planned correction, including the spinous process, the lamina, and the superior and inferior facets adjacent to the pedicle. In addition, the cephalad and caudal laminae were undercut to avoid iatrogenic canal stenosis or neural impingement during osteotomy closure. Next, pedicles were taken down to the level of the posterior vertebral body. The vertebral

body was then decancellated through each pedicle. In most instances, a temporary rod was placed across the osteotomy site to prevent sublaxation or premature osteotomy closure. A wedge-shaped portion of the lateral vertebral body walls was removed through the pedicle (Figure 2). A reverse-angled curette or Woodson elevator was used to thin and fracture the posterior cortex of the vertebral body underlying the spinal canal into the wedge-shaped defect. A posterior compression force was applied to the spine facilitating spinal hyperextension across the osteotomy site hinging on the anterior margin of the vertebral body. Typically, this maneuver was performed by changing the bolsters on the Jackson frame to allow extension across the osteotomy, with further compression and correction obtained using compression techniques across the posterior instrumentation. In this step, a central hook/rod construct can be helpful^[19]. It not only adds fixation strength to the overall construct but avoids placement of undue stress on pedicle screws that can lead to screw loosening and potential fixation failure. When the middle and posterior column bone defects are closed, the length of the anterior vertebral cortex remains unchanged (Figure 3).

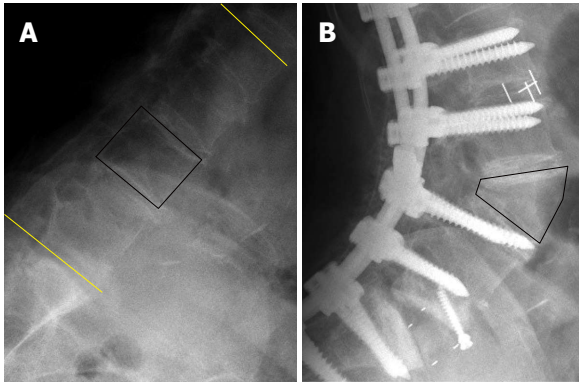


Figure 3 Pre- and post-operative lateral plain radiographs of a 70-year-old woman who underwent pedicle subtraction osteotomy at the L3 vertebra. Kyphotic lumbar spine (A) and hyperlordotic lumbar spine after pedicle subtraction osteotomy (B). Note that the length of the anterior vertebral cortex remains unchanged even after the shortening of the middle and posterior spinal columns.

With every step of correction/compression, careful attention was paid to ensure the central canal and exiting nerve roots were not compressed. After ensuring that exiting nerve roots were free, the final spinal contour was maintained with segmental rod fixation for which cantilever forces were employed. After completing the fixation procedure, autografts and allografts were placed over the laminae, facet joints and transverse processes. Anterior-column support is known to decrease the pseudarthrosis rate associated with long-segment posterior fusions. In all cases where fusions extended to the sacrum, anterior column support was provided at L5-S1 by a transforaminal lumbar interbody fusion or an anterior lumbar interbody fusion (Figure 4). In patients with severe osteopenia/osteoporosis or in those with histories of pseudarthrosis, a demineralized bone matrix or bone morphogenetic protein was considered to supplement fusion. A 3-6 mo course of thoracolumbosacral orthosis or lumbosacral orthosis with a thoracic extension pad was typically prescribed for any patient in whom the PSO was supported only by segmental posterior instrumentation.

Sagittal rebalancing after PSO

For ideal preoperative surgical planning, spine surgeons should consider sagittal spinopelvic alignment change after lumbar PSO. Kim *et al.*^[20] reported the change with an analysis of 114 patients who had undergone lumbar PSO. The authors found a single level lumbar PSO 34° increase in lumbar lordosis, 15° contribution on thoracic kyphosis, 9° increase in sacral slope, 8° decrease in pelvic tilt and 8.9 cm shortening in SVA at 4.4 years after surgery. Because sagittal rebalancing such as an increase in thoracic kyphosis occurs after lumbar PSO, spine surgeons usually need more correction angle to achieve optimal sagittal balance.

Clinical outcomes of PSO

The PSO is advantageous in that it can produce substantial correction at a single level, it results in successful bone union due to the three columns of bony contact,

and it can be done without the use of a supplemental anterior approach^[21]. In a prospective study in which thirty patients underwent a Smith-Petersen osteotomy and forty-one patients underwent a PSO, only 39% of the patients treated with the PSO required a concomitant anterior arthrodesis compared with 87% of those treated with the Smith-Petersen osteotomy^[17]. Kim *et al.*^[16] retrospectively analyzed their results at a minimum of five years following PSOs in thirty-five patients. Between two and five years postoperatively, the authors did not see any significant radiographic changes in thoracic kyphosis or lumbar lordosis ($P = 0.38$ and 0.84 , respectively). Eight patients (22.8%) subsequently underwent revision procedures for treatment of pseudarthrosis. The Oswestry Disability Index (ODI) and Scoliosis Research Society outcome scores between two and five years postoperatively also did not change significantly. A sagittal vertical axis of < 8 cm at the time of final follow-up was significantly associated with a better Scoliosis Research Society outcome score ($P = 0.038$). The authors concluded that PSO can provide satisfactory clinical and radiographic outcomes at a minimum of five years postoperatively.

In a retrospective study comparing anterior-posterior circumferential fusion to PSO in twenty-six patients with posttraumatic kyphosis who were followed for a mean of 3.5 years, Suk *et al.*^[22] found that the PSO had a shorter operative time (215 min compared with 351 min), less intraoperative bleeding, and more correction of the kyphosis between the preoperative and postoperative examinations (25.7° compared with 11.2°). In our recent study with a long-term follow-up data, we analyzed 13 consecutive PSO-treated patients presenting with fixed sagittal imbalances from 1999 to 2006^[14]. The median follow-up period was 73 mo (range 41-114 mo). The average preoperative ODI score was 55.4 ± 13.6 , and the mean postoperative ODI score 30.2 ± 16.5 . Improvement after surgery was statistically significant ($P < 0.001$). Subjective evaluation of back pain showed that nine patients perceived improvement, three no change, and one an aggravation. Outcome of leg pain demonstrated that seven patients perceived improvement, five no change, and one an aggravation. The patients who experienced suboptimal outcome of leg pain had arthralgic rather than neuralgic pain. Subjective assessment of stooping symptoms showed that no patient perceived a result as aggravated even if the patient experienced proximal junctional kyphosis (PJK) or rod fracture. Statistical analysis revealed that ODI score reduction was significantly related to the postoperative C7 plumb line value ($P = 0.003$), but not to lumbar lordosis, thoracic kyphosis or PJK.

Complications of PSO

Postoperative sagittal decompensation following PSO is a problematic event. Kim *et al.*^[23] found that the prevalence of sagittal decompensation following PSO for adult patients with sagittal imbalance was 29% and associated risk factors were immediate postoperative SVA > 8 cm, the sum of TK, LL and pelvic incidence Cobb angles $> 45^\circ$,

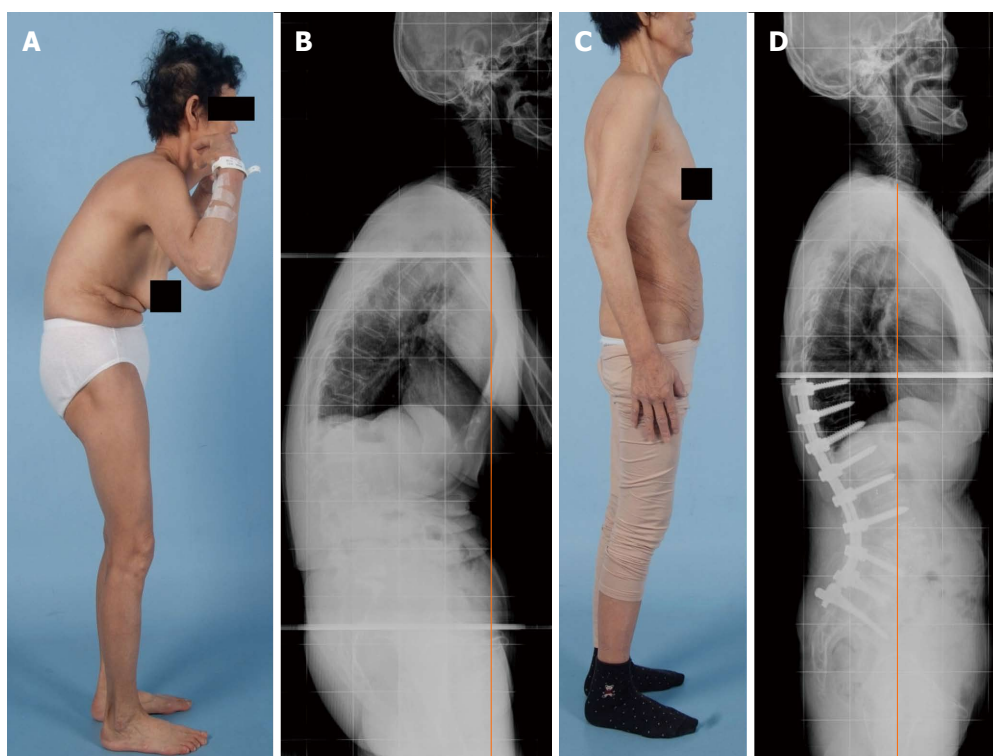


Figure 4 Pre- and post-operative clinical photographs (A)/radiographs (B) of a 65-year-old woman, revealing degenerative lumbar kyphosis with global sagittal imbalance. The patient presented with intolerable lower back pain and stooping symptoms. She underwent L4 pedicle subtraction osteotomy with anterior column support, and the plain film obtained at her most recent follow-up examination shows dramatic improvement in global sagittal alignment as well as the lumbar kyphosis (C and D).

the sum of TK and LL Cobb angles $< 25^\circ$, T12 horizontal angle $> 15^\circ$, LL Cobb angle increase $\geq 40^\circ$, associated comorbidities, age at surgery > 55 years, uppermost instrumented vertebra below T8, and preoperative SVA > 15 cm. Multiple factors should be considered to obtain optimal correction while minimizing the risk of developing sagittal decompensation.

Pedicle subtraction osteotomies are technically demanding and involve substantial mobilization of the neural tissue, and the blood loss is greater than that associated with the Smith-Petersen osteotomy^[24,25]. A retrospective analysis of data obtained prospectively in a study of forty-six patients who were sixty years of age or older showed that patients who underwent a PSO were seven times more likely to have at least one major complication compared with patients who underwent a different spinal procedure (OR = 6.96; 95%CI: 1.10-79)^[26]. Major complications included neurological deficits, deep wound infection, pulmonary embolus, pneumonia and myocardial infarction. Increasing age was a significant predictor of a complication ($P < 0.05$). The researchers concluded that the age at which patients are able to tolerate a major procedure such as a PSO may be lower than the age at which they can tolerate other common spinal procedures. Buchowski *et al*^[27] reported the prevalence of intraoperative and postoperative neurological deficits to be 11.1% and the prevalence of permanent deficits to be 2.8% in a study of 108 patients who had undergone a PSO. In a study by Bridwell *et al*^[11], five (15%) of thirty-three patients who had undergone a PSO for the treatment of

an imbalance in the sagittal plane experienced a transient neurological deficit. In another study, Yang *et al*^[13] found the prevalence of intraoperative or postoperative neurological deficits to be 4% (one of twenty-eight patients) after lumbar or thoracic PSO for the treatment of an imbalance in the sagittal plane. This single deficit was thought to be most likely due to nerve root compression.

In our recent investigation, no patient died or became permanently paraplegic as a result of surgery^[14]. The incidence of perioperative transient neurological deficits was 7.6% (1 of 13 patients). Surgery was associated with 16 complications in 8 patients (61%); there were 3 intraoperative complications (dural tear, massive bleeding > 5000 mL), 3 perioperative complications (hypotension, cerebrospinal fluid leakage and spinal cord compression) and 10 late-onset postoperative complications (PJK with or without adjacent segment collapse, pseudoarthrosis including rod fracture and screw loosening). Complication frequencies were significantly higher in patients who rated clinical outcomes as aggravated or unchanged than in patients who rated outcomes as improved ($P = 0.012$).

Surgical tips to reduce the complications

Surgical and medical complications in earlier reports have included hypotension resulting from intraoperative massive bleeding, cerebrospinal fluid leakage, neurological injury, wound-related problems and nosocomial infections^[13,27]. In our series, massive bleeding occurred in two patients with preoperative normal laboratory findings. An option to reduce the large blood loss known to be

associated with all PSOs is vertebral body embolization or intraoperative administration of tranexamic acid, but this strategy awaits further clinical validation^[28]. For safe and uneventful surgery, intraoperative neurophysiological monitoring should be performed by an experienced neurophysiologist or technician. Nevertheless, in our practice, one patient experienced transient paraplegia because a bone fragment caused spinal cord compression that was not detected by intraoperative neuromonitoring. In a previous analysis of 45 patients with ankylosing spondylitis, Kim *et al.*^[29] found transient postoperative radiculopathy in four patients and spinal cord compression caused by a bone fragment at T12 in one patient. Although it is unclear what mechanisms were responsible for development of neurological deficits in most previous reports, the problems were thought to arise from a combination of subluxation, residual dorsal impingement, dural buckling and spinal cord ischemia^[10,13,27]. To reduce the risk of intraoperative or postoperative neurological deficits, some authors recommend central canal enlargement, careful osteotomy closure to prevent subluxation across the osteotomy site, limited osteotomy at the level of the spinal cord or conus medullaris, a wake-up test after osteotomy closure, and examination of all motor groups following surgery^[10,11,13,27].

Most late-onset complications are related to kyphosis progression, pseudarthrosis and instrumentation failure. There was a higher incidence of complications in patients with compression fractures, caused mainly by osteoporosis, compared with patients with degenerative changes. Correcting kyphosis after a compression fracture is associated with a high risk of additional compression fractures in adjacent vertebrae. Some researchers have studied complications after PSO using the combined anterior-posterior approach and have emphasized the need for anterior reconstruction^[11]. We found the PJK prevalence on median 6 year follow-up to be 23% and clinical outcomes were not adversely affected by PJK^[14]. Kim *et al.*^[30] reported that 62 (39%) of 161 adult spinal deformity patients with segmental posterior spinal instrumented fusions were diagnosed with PJK at an average of 7.8 years postoperative follow-up. Concordant to our results, self-reported patient satisfaction was not adversely affected by PJK.

Several investigators have noted that titanium rods have the advantages of magnetic resonance imaging compatibility and tolerable rigidity, but are prone to microfracture propagation and are notch-sensitive in bending^[13,31]. Stainless steel or cobalt chrome rods are thus used in most patients with spinal deformities, except for those with infections or tumors. Recently, we found that the use of a multi-rod construct is a safe, simple and effective method to provide increased stability across 3-column osteotomy sites in order to significantly prevent implant failure and symptomatic pseudarthrosis *vs* a standard 2-rod construct^[32]. Thus, we strongly recommend using a multi-rod construct to stabilize 3-column osteotomy of the thoracic and lumbar spine.

CONCLUSION

PSO is used to treat sagittal imbalance of the spine in patients with a variety of spinal pathologies. It is important to be able to recognize the type and underlying cause of the deformity so that the most appropriate osteotomy can be chosen. Pedicle subtraction osteotomies are typically used in patients with greater imbalances in the sagittal plane of the spine and when a minimum of 30° of correction is needed. Intraoperative or postoperative neurological deficits are relatively common following PSO. Obtaining optimal spinal balance with minimal operative complications seemed to lead to better clinical outcomes. An understanding of the relative merits of each of the osteotomy techniques is imperative so that the spine surgeon can use these methods to greatest effect. Based on the review of the literature, PSO is considered effective, relatively safe and imperative for the correction of kyphotic spinal deformity.

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Priming the tooth surface with chlorhexidine and antibacterial activity of resin cement

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Abstract

AIM: To evaluate the effect of priming the tooth surface with 2% chlorhexidine gluconate on antibacterial activity of resin cement.

METHODS: Ten patients in whom a single missing tooth was present on both the right and left side in the upper or lower arch were selected. Two fixed partial dentures (FPDs) in each patient on the right and left side were planned. Each FPD was assigned either to the control or test group. In the control group, FPD was luted with resin cement and in the test group, the tooth surface was primed with 2% chlorhexidine gluconate before luting with resin cement. Bacteriological samples were collected at base line level, as the patient came to the outpatient department before the start of any treatment, 5 wk prior to cementation of FPD and at 13 wk (8 wk after final cementation). Microbiological processing of all samples was done and the results were statistically analyzed.

RESULTS: In the test group, a predominance of aerobic/facultative gram positive cocci rod was seen which indicates a healthy periodontal site, whereas in the

control group, a predominance of anaerobic gram negative rods was present which indicates an unhealthy periodontal condition. This is evident by the fact that the anaerobic bacteria percentage in the control sample is 57% and 15% in the test sample after 13 wk, whereas the aerobic/facultative bacteria percentage is 43% in the control sample and 85% in the test sample after 13 wk. The percentage of gram negative bacteria in the control sample is 61% and in the test sample is 20% after 13 wk, whereas the percentage of gram positive bacteria in the control sample is 39% and in the test sample is 80% after 13 wk. The shift from anaerobic gram negative bacteria to aerobic gram positive bacteria is clearly seen from the control to test sample after 13 wk.

CONCLUSION: The present study demonstrated that priming the tooth surface with 2% chlorhexidine gluconate may enhance antibacterial activity of the resin cement.

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Key words: Fixed prosthesis; Antibacterial activity; Chlorhexidine; Periodontitis; Resin cement

Core tip: Fixed prosthodontics is one of the most sought after services by patients in dentistry, but periodontal problems around fixed partial dentures have been the Achilles heel to date, reducing the longevity of the prosthesis. Generally, cements that are used for luting fixed partial dentures might not be as effective in controlling periodontal problems. Resin cement is the cement of choice nowadays but lacks antibacterial activity. The role of 2% chlorhexidine in reducing periodontal problems has been established in dentistry. The present study focuses on a method to increase the antibacterial activity of the cement by priming the tooth surface with chlorhexidine 2% before luting the fixed partial dentures.

Saini M, Singh Y, Garg R, Pandey A. Priming the tooth surface with chlorhexidine and antibacterial activity of resin cement. *World J Clin Cases* 2013; 1(8): 249-255 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i8/249.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i8.249>

INTRODUCTION

The establishment and maintenance of periodontal health is a prerequisite for long term success for fixed prosthesis. Periodontal diseases have been associated with bacterial origin^[1]. Retention of plaque around fixed prosthesis giving rise to periodontal problems has been Achilles heel to date^[2].

There are various reasons for the existence of periodontal diseases. Traumatic preparations, faulty impression procedures, poor provisional restorations with unsuitable laboratory support and improper crown contour^[3,4] cause insult to the gingival tissues. Subgingival margin^[5] placement is also associated with undesirable effects on the periodontium and is considered to be one of the causes for failure in fixed prosthesis. Despite advancements in materials used for castings and impression making for fixed partial dentures (FPD), we still depend on the integrity of the luting cement^[6-8] to maintain the marginal seal. Ideal luting cement should possess low viscosity, optimal film thickness, low solubility, long working time with rapid set at oral temperature, high compressive and tensile strengths, high proportional limit, adhesion to tooth structure and restorative materials, radiopacity, translucency, biocompatibility and anticariogenic activity^[9-11]. Microleakage solubility and disintegration have been common problems among a number of luting agents (water-activated polycarboxylate cement, glass ionomer, zinc oxide-eugenol, silicophosphate, zinc phosphate, *etc.*). These unwanted properties cause growth of micro-organisms in and around fixed prosthesis. Therefore, cements with antibacterial properties have been studied in the past and have been co-related with long term success of FPD^[12-15].

The antimicrobial efficacy of 2% chlorhexidine gluconate (CHX) is well established. It is bactericidal against gram positive and gram negative oral microorganisms. CHX is retained on tooth surfaces, pellicle substances, plaque and mucous membranes and is released over several hours. This phenomenon is substantial and can be accounted for the prolonged *in vivo* antiplaque effect of CHX. The effectiveness of CHX has been well documented for reduction of periodontal inflammation when used in the form of a mouth rinse^[16,17]. Chlorhexidine also promotes the formation of a hybrid layer when resin cement is^[18,19] applied to a tooth surface. CHX has been seen in the past to improve the physical properties of the resin cement. It has been found to diminish the loss of bonding effectiveness over time, associated with etch-and-rinse and self-etch cements^[20]. Chlorhexidine application in etch-rinse resin cement also reduced microleakage

at gingival margins after storage^[21]. Antibacterial activity of zinc polycarboxylate cement was increased by using CHX based cement compared to water based cement^[22]. The same effect of CHX is also expected in resin cements. The aim of this clinical study was to evaluate the effect of priming the tooth surfaces with 2% CHX on antibacterial activity of resin cement.

MATERIALS AND METHODS

Patients who required fixed prosthodontic therapy were selected from the outpatient department (OPD) of Subharti Dental College, Meerut, UP. The procedures were explained in detail to the patients and a written informed consent was taken before beginning with the treatment. Patients with any systemic disease or who were taking medications (including antibiotics, antimicrobials or fluoride rinses) affecting gingival health 2 mo before the baseline data collection were excluded from study. At the beginning of the study, all subjects demonstrated a mean Silness-Löe Plaque Index^[23] and Löe-Silness Gingival Index^[24] of less than 2 and probing sulcus depths of less than 4 mm at the abutment teeth. Clinical measurements were made at 6 points around each tooth. Ten patients in whom a single missing tooth was present on both the right and left side in the upper or lower arch were selected. Abutment teeth were evaluated for tooth preparation. Porcelain fused to metal FPD was planned for each patient and thus two FPDs in each patient on the right and left side were planned. Each FPD was assigned either to the control group or test group. In the control group, resin cement (Multilink Automix, Ivoclar Vivadent, Mumbai, India) was used as the luting agent and in test group, the abutment tooth surface was primed with 2% CHX (Hexidine, ICPA, India) before luting with resin cement.

Cementation protocol

The prepared tooth is etched with Total Etch (Ivoclar Mumbai India) for 15 s. Total Etch has 30% phosphoric acid. Cotton pellets saturated with 2% chlorhexidine are placed on the prepared tooth for 60 s and then dried for 10 s^[21]. Primer A and B are mixed in 1:1 ratio and applied to the prepared tooth surface for 30 s (as per scientific documentation provided by manufacturer). The inner surface of FPD is sandblasted and cleaned in an ultrasonic unit for 1 min. The restoration is thoroughly rinsed with water and dried. Monobond plus is applied with a brush for 60 s to the inner surface of the restoration and dispersed with a strong stream of air. Finally, Multilink Automix luting cement is applied on to the restoration's inner surface and the restoration is luted. After the cementation was done, excess cement was removed and post cementation instructions were given to the patient^[18].

Bacteriological samples were collected 3 times. One at base line level, as patient came to OPD before start of any treatment; one at 5 wk prior to cementation of FPD; and one at 13 wk (8 wk after final cementation).

After bacteriological samples were collected at the

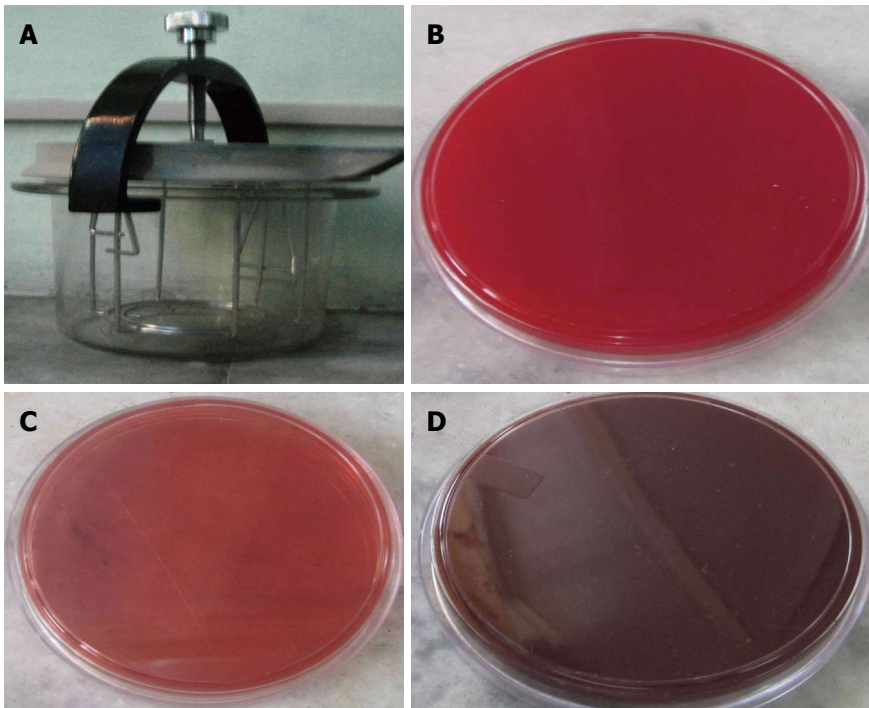


Figure 1 Jar and media used for the study. A: Anaerobic Jar; B: Blood agar; C: MacConkey agar; D: Chocolate agar.

baseline visit, all patients received oral prophylaxis treatment and were given oral hygiene instructions. Porcelain fused to metal FPDs was fabricated with minimal trauma and a chamfer finish line was given in all preparations. The margins were located at the gingival margin. Forty teeth were prepared for FPD in total. A total of 12 subgingival plaque specimens (2 tests, 2 control samples per patient at three different sample times) were collected for each patient. Thus, a total of 120 samples were collected in ten patients.

Subgingival microbiological samples were obtained by inserting sterile standardized endodontic paper points (Dia Dent, South Korea) for 30 s into the gingival sulcus subjacent to the restoration. Paper points were gently placed at 4 locations (mesiobuccal, distobuccal, midbuccal and midlingual/palatal regions) on each abutment tooth after isolating the quadrant from saliva contamination with the help of cotton wool rolls and a saliva ejector. All four samples per tooth were pooled into a single broth, providing one broth sample per tooth per patient.

Microbiological processing

The microbiological samples obtained from all subgingival sites were inserted into a Robertson's cooked medium broth and dispatched immediately to the Microbiology Department for anaerobic and aerobic culture procedures. For anaerobic bacteria, samples were cultured on (1) brucella blood agar; (2) kanamycin-vancomycin laked blood agar; and (3) Bacteroides bile esculin agar (HiMedia Laboratories Pvt. Ltd., Mumbai, India). The plates were placed into an anaerobic chamber (Figure 1) containing a gas mixture of 80% to 90% nitrogen, 5% to 10% hydrogen, and 5% to 10% carbon dioxide (CO₂), and biological

control (*Pseudomonas aeruginosa*) incubated at 37 °C for 48 to 72 h. Later, aerotolerance tests were performed for each different colony, prior to gram-staining, to determine the purity, spore formation and morphologies. Catalase and pigment activities were also evaluated. API 20A and ID32A strips (BioMerieux SA, France) were used for identification of anaerobes. Categorization of bacterial pathogenicity was done according to whether the organism was associated with progressive periodontal disease (periodontally suspected bacteria or not-periodontally suspected bacteria).

Samples were cultured for aerobic bacteria on (1) 5% blood agar (Figure 1B); (2) MacConkey agar (Figure 1C); and (3) chocolate (Figure 1D) (with vancomycin, clindamycin and bacitracin) agars in laminar air flow (Labline instruments, Kochi, India). Blood and MacConkey agars were incubated aerobically and the chocolate agar was incubated in air + 5% CO₂ at 37 °C for 24 h. Isolated bacteria were identified by using both standard microbiological methods and API automated systems.

RESULTS

Table 1 describes the overall distribution of bacteria in test and control samples at all sample times (2 test and 2 control samples per subject at baseline, 5 wk and 13 wk). Out of 338 bacterial colonies: 42.3% were facultative gram positive cocci; 13.4% were facultative gram negative bacilli; 11.8% were aerobic gram negative bacilli; 10.9% were aerobic gram positive bacilli; 9.2% were aerobic gram negative bacilli; 5 were aerobic and anaerobic gram negative cocci; and 2% anaerobic gram positive cocci. Pathogenic anaerobic gram negative bacilli were signifi-

Table 1 Overall distribution of bacteria isolated in control and test groups *n* (%)

Bacteria type	Control (<i>n</i> = 182)		Test (<i>n</i> = 156)		Total
	PSB	N-PSB	PSB	N-PSB	
Facultative GNB	2 (1.1)	17 (9.3)	5 (3.2)	21 (13.5)	45 (13.4)
Aerobic GPB	6 (3.2)	11 (6.04)	-	20 (12.8)	37 (10.9)
Aerobic GNC	-	9 (4.9)	-	8 (5.1)	17 (5.02)
Facultative GPC	3 (1.64)	62 (34.1)	6 (3.9)	72 (46.2)	143 (42.3)
Anaerobic GNB	17 (9.3)	21 (11.5)	3 (1.9)	-	40 (11.8)
Anaerobic GPB	-	16 (8.8)	-	15 (9.6)	31 (9.2)
Anaerobic GNC	11 (6.04)	-	6 (3.9)	-	17 (5)
Anaerobic GPC	-	7 (3.8)	-	-	7 (2.1)
Totals	39	143	20	136	338

PSB: Periodontally suspected bacteria; N-PSB: Not periodontally suspected bacteria; GNB: Gram-negative bacilli; GPB: Gram-positive bacilli; GNC: Gram-negative cocci; GPC: Gram-positive cocci.

Table 2 Distribution and bacteria isolated at control and test sites at baseline, 5 and 13 wk *n* (%)

	Baseline		5 wk		13 wk	
	Control	Test	Control	Test	Control	Test
<i>Actinomycesnaeslundii</i> FG+veR	3 (3.9)	-	-	-	1 (1.7)	1 (1.6)
<i>Actinomycesviscosus</i> FG+veR	2 (2.6)	-	-	-	1 (1.7)	1 (1.6)
<i>Bifidobacterium</i> spp FG+veR	4 (5.2)	3 (7.1)	2 (4)	2 (3.6)	1 (1.7)	3 (4.9)
<i>Clostridium</i> spp FG+veR	-	-	7 (14)	6 (11.3)	-	-
<i>Diphtheroid</i> bacilli AG+veR	2 (2.6)	4 (9.5)	2 (4)	2 (3.6)	3 (5.3)	1 (1.6)
<i>Escherichia coli</i> FG-veR	-	-	1 (2)	2 (3.6)	-	-
<i>Eubacterium</i> spp FG+veR ¹	1 (1.3)	-	-	2 (3.6)	-	-
<i>Fusobacteriumnucleatum</i> AnG-veR ¹	2 (2.6)	-	3 (6)	4 (7.5)	8 (14.2)	-
<i>Haemophilus</i> spp FG-veR	10 (13.1)	3 (7.1)	4 (8)	2 (3.6)	5 (8.9)	3 (4.9)
Coagulase-negative <i>Staphylococci</i> FG+veC	2 (2.6)	2 (4.7)	2 (4)	1 (1.8)	-	4 (6.5)
<i>Neisseria</i> spp AG-veC	8 (10.5)	2 (4.7)	2 (4)	2 (3.6)	1 (1.7)	-
<i>Peptostreptococcus</i> AnG+veC	5 (6.5)	-	-	-	-	-
<i>Porphyromonasgingivalis</i> AnG-veR ¹	-	-	-	-	2 (3.2)	-
<i>Prevotellaintermedia</i> AnG-veR ¹	1 (1.3)	1 (2.3)	1 (2)	1 (1.8)	8 (14.2)	-
<i>Propionibacteriumgranulosum</i> FG+veR	-	1 (2.3)	-	-	-	-
<i>Staphylococcus aureus</i> FG+veC	2 (2.6)	1 (2.3)	3 (6)	7 (13.2)	-	2 (3.2)
<i>Veillonellaparvula</i> AnG-veC ¹	1 (1.3)	1 (2.3)	3 (6)	1 (1.8)	10 (17.8)	1 (1.6)
<i>Streptococci</i> AG-veC	25 (32.8)	15 (35.7)	15 (30)	19 (35.8)	11 (19.6)	39 (63.9)
<i>Campylobacter rectus</i> FG-veR	6 (7.8)	4 (9.5)	3 (6)	-	4 (7.1)	2 (3.2)
<i>Treponemadenticola</i> AnG-veC ¹	1 (1.3)	2 (4.7)	1 (2)	1 (1.8)	-	-
<i>Gemella</i> spp FG+veC	-	-	-	-	-	2 (3.2)
<i>Filifactoralocis</i> FG+veR	1 (1.3)	3 (7.1)	1 (2)	1 (1.8)	1 (1.7)	2 (3.2)
Total (<i>n</i>)	76	42	50	53	56	61
P value	0.595		0.895		0.006 ²	

¹Periodontally suspected bacteria; ²Association is significant by χ^2 analysis ($P < 0.05$). AnG-veC: Anaerobic gram-negative cocci; AG-veC: Aerobic gram-negative cocci; AnG-veR: Anaerobic gram-negative rods; FG-veR: Facultative gram-negative rods; AnG+veC: Anaerobic gram-positive cocci; FG+veC: Facultative gram-positive cocci; FG+veR: Anaerobic gram-positive rods; FG+veR: Facultative gram-positive rods; AG+veR: Aerobic gram-positive rods.

cantly less in the test group (1.9%) than in the control group (9.3%). Pathogenic anaerobic gram negative cocci were also significantly less in the test group (3.9%) than in the control group (6.04%). The total number of pathogenic bacteria was less in the test group ($n = 20$) than in the control group ($n = 39$).

Tables 2 and 3 represent the distribution and number of bacteria isolated at all sample times. In the control group at base line level, predominantly *Streptococci* (32.8%), *Haemophilus* (13.1%) and *Campylobacter* (7.8%) were present, as well as aerobic/facultative gram positive cocci and rods atmosphere. In the test group at baseline level, predominantly *Streptococci* (35.7%), *Campylobacter* (9.5%) and *Diphtheroid* (9.5%) were present, as well as aerobic/

facultative gram positive cocci and rods atmosphere. The P value at baseline was 0.595. The application of a χ^2 test shows that the distribution of bacteria does not differ significantly at baseline at 5% level of significance.

At 5 wk, in the control samples, predominantly *Streptococci* (30%) and *Clostridium* (14%) were present, as well as aerobic/facultative gram positive cocci atmosphere. In the test group, predominantly *Streptococci* (35.8%) and *Clostridium* (11.3%) were present, as well as aerobic/facultative gram positive cocci and rods atmosphere. The P value at 5 wk was 0.895. The application of a test shows that the distribution of bacteria does not differ significantly at baseline at 5% level of significance.

At 13 wk, in control samples, predominantly *Strepto-*

Table 3 Statistical data on the distribution of bacteria isolated in control and test groups for gram stain, atmosphere of growth, morphological properties and pathogenicity at baseline, 5 and 13 wk

Type of bacteria	Control	Test	χ^2	P value
Baseline				
Aerobic/facultative	55	71	4.913	0.0839
Anaerobic	45	29		
Gram-positive	69	71	2.391	0.0052 ¹
Gram-negative	31	29		
Cocci	72	58	2.598	0.0018 ¹
Rods	28	42		
5 wk				
Aerobic/facultative	60	62	0.721	0.0251 ¹
Anaerobic	40	38		
Gram-positive	75	75	0.593	0.0134 ¹
Gram-negative	25	25		
Cocci	65	51	0.398	0.0031 ¹
Rods	35	45		
13 wk				
Aerobic/facultative	43	85	5.821	0.0051 ¹
Anaerobic	57	15		
Gram-positive	39	80	6.321	0.0032 ¹
Gram-negative	61	20		
Cocci	38	55	7.229	0.0005 ¹
Rods	72	35		

¹ Association is significant by χ^2 analysis ($P < 0.05$).

cocci (19.6%), *Veionella parvula* (*V. parvula*) (17.8%), *Prevotella intermedia* (*P. intermedia*) (14.2%) and *Fusobacterium nucleatum* (*F. nucleatum*) (14.2%) were present, as well as anaerobic gram negative rod atmosphere. In the test group, predominantly *Streptococci* (63.9%), coagulase negative *Staphylococci* (6.5%) and *Bifidobacterium* (4.9%) were present, as well as aerobic/facultative gram positive cocci and rods atmosphere. The P value at thirteen weeks was 0.006. The application of a χ^2 test shows that there is a significant association between the distributions of bacteria at 13 wk between control and test groups at 5% level of significance.

Table 4 shows the distribution of bacteria isolated in the control sample at baseline, 5 wk and 13 wk. There is an increase in anaerobic bacteria from 45% at baseline level to 57% at 13 wk. There is an increase in gram negative bacteria from 31% at baseline level to 61% at 13 wk. There is also an increase in rod shape bacteria from 28% at base line level to 72% at 13 wk. Table 4 shows the distribution of bacteria isolated in the test sample at baseline, 5 wk and 13 wk. There is a decrease in anaerobic bacteria from 29% at baseline level to 15% at 13 wk. There is a decrease in gram negative bacteria from 29% at baseline level to 20% at 13 wk. There is also a decrease in rod shape bacteria from 42% at base line level to 35% at 13 wk.

DISCUSSION

Cardinal signs of gingival inflammation are redness, edema and bleeding. Primary etiology of gingival inflammation is the presence of local irritants initiated by the

presence of plaque. If plaque accumulation and growth can be limited, gingival inflammation can be controlled. Chlorhexidine is bactericidal and its role as an antibacterial agent is well established. Orug *et al.*^[22] reported an increase in antibacterial activity of CHX based Zn polycarboxylate cement.

Chlorhexidine also promotes the formation of a hybrid layer^[18,19] and improves the physical properties of the resin cement. It has been found to diminish the loss of bonding effectiveness over time associated with etch-and-rinse and self-etch cements^[20]. Chlorhexidine application in etch-rinse resin cement also reduced microleakage at gingival margins after storage^[21].

In the present study, changes in subgingival microflora were detected following the cementation of FPDs with or without priming the tooth surface with 2% CHX. It was seen that the priming of a tooth surface with CHX significantly affected the distribution of bacteria compared with that of the control group of patients.

The bacteria cultivated from periodontally healthy sites consist predominantly of gram-positive facultative rods and cocci (approximately 75%). Small proportions of gram-negative species are also found. The most frequently found bacteria are *P. intermedia*, *F. nucleatum*, *Capnocytophaga*, *Neisseria* spp and *Veillonella* spp^[25]. The bacteria found in chronic gingivitis comprise of roughly equal proportions of gram-positive species (56%) (predominantly *Streptococcus sanguis*, *Streptococcus mitis*, *Actinomyces viscosus*, *Actinomyces naeslundii* and *Peptostreptococcus micros*) and gram-negative species (44%) (predominantly *F. nucleatum*, *P. intermedia*, *V. parvula*, *Haemophilus* and *Campylobacter* spp), as well as facultative (59%) and anaerobic (41%) microorganisms^[26].

In the present study, at 13 wk, the subgingival microflora of control sites had a significant shift towards a gram negative anaerobic rod atmosphere. It is evident as the % of *Fusobacterium nucleatum* increased from 2.6% at baseline to 14.2% at 13 wk. Similarly, *Porphyromonas gingivalis* was missing at the baseline level in the control group and was 3.2% at 13 wk in the control group. *Prevotella intermedia* increased from 1.3% at baseline level to 14.2% at 13 wk in the control group. *Veionella parvula* increased from 1.3% to 17.8% from baseline to 13 wk in the control group. In contrast to this, subgingival microflora in the test group at 13 wk had a composition that was similar to the microflora at baseline. The difference which was present at these two sample times in the test group at 13 wk was an increased percent of Coagulase negative *Staphylococci* from 4.7% to 6.5%, an increase in *Streptococci* from 35.7% to 63.9%. *Neisseria* was 4.7% at baseline in test group and was found to be missing at 13 wk. *Gemella* was missing at baseline level and was 3.2% at 13 wk. The percent of anaerobic and gram negative bacteria decreased from 29% to 15% and 29% to 20% consecutively. Thus, it was found that in the test group, the atmosphere of aerobic/facultative gram positive cocci rod was present which indicates a healthy periodontal site, whereas in the control group, an anaerobic gram negative

Table 4 Distribution of bacteria isolated in the control group at baseline, 5 and 13 wk

Time	Bacteria (control group)			Bacteria (test group)		
	Anaerobic	Gram-negative	Rod-shaped	Anaerobic	Gram-negative	Rod-shaped
Baseline	45%	31%	28%	29%	29%	42%
5 wk	40%	25%	35%	38%	25%	45%
13 wk	57%	61%	72%	15%	20%	35%
2	6.022	2.091	5.412	10.171	5.021	6.118
P value	0.089	0.021 ¹	0.098	0.081	0.285	0.192

¹Association is significant by χ^2 analysis ($P < 0.05$).

rod atmosphere was present which indicates an unhealthy periodontal condition. To evaluate only the effects of CHX treatment, no professional scaling, root planing or oral prophylaxis was performed after cementation of the crowns in this study.

In the present study, the tooth preparation margins were completed with a chamfer finish line and crown margins placed at the gingival margin. Many luting agents show bacteriostatic/bactericidal properties but polycarboxylate cement and resin cement does not show such properties. This study shows a favorable shift in distribution of bacteria towards gram positive facultative aerobes in the test group compared to the control group in which a shift in distribution of bacteria towards gram negative facultative anaerobes was observed.

In conclusion, this study has shown that priming the tooth surfaces with 2% CHX before luting FPDs with resin cement significantly increased inhibition of periodontally suspected bacteria. This is evident from the finding that the number of aerobic/facultative gram positive cocci rod which enhances the periodontal health increased in the test group from 1.6% at baseline to almost 4% at 13 wk. At the same time, the number of anaerobic gram negative rods which decrease periodontal health was significantly found in the control group. Thus, we can conclude that priming tooth surfaces with 2% CHX may enhance antibacterial activity of the cement and create favorable distribution of bacteria towards aerobic/facultative gram positive cocci rods atmosphere at least 13 wk post-cementation of the prostheses.

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Cortical laminar necrosis related to migrainous cerebral infarction

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done to rule out other known causes of cerebral infarct with CLN was unrevealing. Only ten of 3.808 consecutive stroke patients included in our stroke registry over a 19-year period fulfilled the strictly defined International Headache Society criteria for migrainous stroke. The present case is the unique one in our stroke registry that presents CLN related to migrainous cerebral infarction. Migrainous infarction can result in CLN.

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Key words: Cortical laminar necrosis; Migrainous stroke; Migraine; Cerebrovascular diseases; Stroke

Core tip: A 29-year-old migrainous woman developed dysarthria and focal sensorimotor neurological deficit during a typical migraine attack with aura. Brain magnetic resonance imaging showed a right temporo-parietal ischemic lesion compatible with cortical laminar necrosis (CLN). The present case is the unique one in our stroke registry over a 19-year period that presents CLN related to migrainous cerebral infarction. Our case shows that CLN can be associated with cerebral ischemia due to migrainous infarction, an infrequent ischemic cerebral infarct of unusual etiology.

Abstract

We present a 29-year-old woman with a long history of attacks of migraine with and without visual aura. She was a heavy smoker (20 cigarettes/d) and was currently taking oral contraceptives. During a typical migraine attack with aura, she developed dysarthria, left brachial hemiparesis and hemihypoesthesia and brief and autolimited left clonic facial movements. Four hours after onset, vascular headache and focal sensorimotor neurological deficit were the only persisting symptoms and, on seventh day, she was completely recovered. Brain magnetic resonance imaging on day 20 after onset showed a subacute ischemic lesion in the right temporo-parietal cortex compatible with cortical laminar necrosis (CLN). Extensive neurological work-up

Arboix A, González-Peris S, Grivé E, Sánchez MJ, Comes E. Cortical laminar necrosis related to migrainous cerebral infarction. *World J Clin Cases* 2013; 1(8): 256-259 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i8/256.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i8.256>

INTRODUCTION

Cortical laminar necrosis (CLN) is an infrequent type of cortical infarction which causes a selective pannecrosis of the cerebral cortex (involving neurons, glia and blood vessels) while underlying white matter is completely or

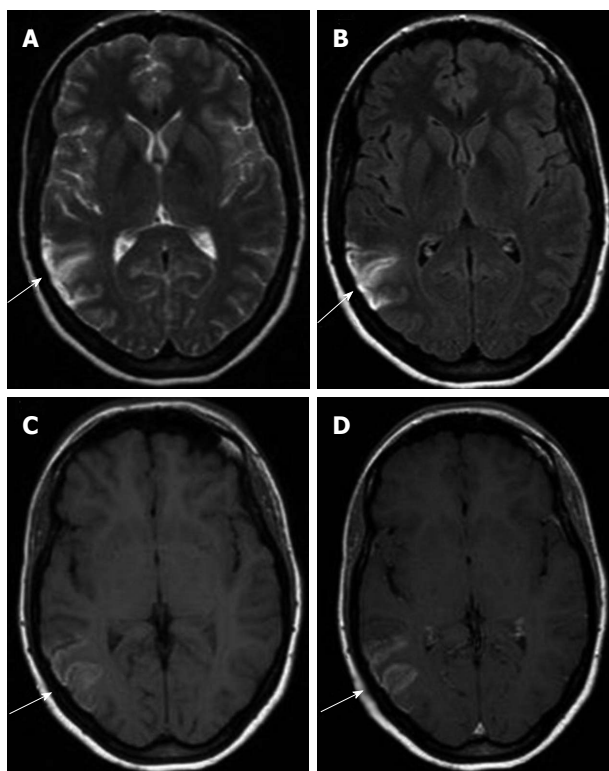


Figure 1 Magnetic resonance imaging at day 20 after ictus: Axial T2-weighted (A), fluid-attenuated inversion-recovery (B) and T1-weighted (C) sequences show high hyperintense cortical lesion (arrows). Minimum enhancement on Axial T1 post-contrast (D).

relatively spared^[1,2]. It has been reported to be associated with hypoxic encephalopathy^[3,4], hypoglycemic encephalopathy^[5], status epilepticus^[6], cerebral infarction^[7] and rarely cerebral infarction due to migraine^[8,9].

On magnetic resonance imaging (MRI) CLN is characterized by a high intensity cortical signal on T1-weighted and fluid-attenuated inversion-recovery (FLAIR) images, without signs of hemorrhage, which shows a typical curvilinear gyriform distribution, following the cerebral convolutions affected^[1-3].

We report the case of a young female patient who suffered an unusual case of cerebral infarction secondary to a migrainous cerebral infarction manifested as CLN on brain MRI.

CASE REPORT

We present a 29-year-old woman with a long history of attacks of migraine (8 years) with and without visual aura. She was a heavy smoker (20 cigarettes/d for the last 4 years) and was currently taking oral contraceptives. At the age of 18 years, she had an ectopic pregnancy and a unilateral salpingo-oophorectomy was done. At the age of 20 years she had a voluntary abortion. She was diagnosed with anxiety disorder and was taken alprazolam (0.50 mg/d for 3 years) under the periodic supervision of his psychiatrist. During a typical migraine attack with visual aura symptomatology, she developed dysarthria, left

brachial hemiparesis, left hemihypoesthesia and autolimited left clonic facial movements (< 1 min lasting). Four hours after onset, severe holocranial vascular headache persisted along with nausea and vomiting and mild left brachial sensorimotor deficit [magnetic resonance spectroscopy (mRS) = 2, National Institute of Health stroke scale (NIHSS) = 2]. She had neither nuchal rigidity nor semiology of meningeal syndrome. The patient was not treated with triptans or any other drugs which might have led to vasoconstriction.

The following investigations were normal or unremarkable: chest roentgenography, 12-lead electrocardiography, brain computed tomography scan, two-dimensional echocardiography, and Doppler ultrasonography of the supra-aortic trunks, complete hematological screening, routine biochemical profile, urinalysis, serology for syphilis, immunologic blood test (including antinuclear antibodies, extractable nuclear antigens, lupus anticoagulant, Immunoglobulin G and Immunoglobulin M anticardiolipin antibodies, rheumatoid factor), basic hemostasis study and hypercoagulable panel (including protein C and S, antithrombin III, factor V Leiden mutation and homocysteine). The use of cocaine or other substances with vasoconstrictive properties as amphetamines was ruled out.

The clinical course was favorable. A gradual regression of symptomatology was observed and, seven days after onset, focal neurological deficit was completely recovered (mRS = 0, NIHSS = 0).

Brain MRI on day 20 after the migraine attack showed increased signal on FLAIR, T-1 and T2-weighted sequences and diffusion images involving the right temporo-parietal cortex compatible with subacute infarct with CLN, showing a minimum enhancement post-contrast (Figure 1). Intracranial MR angiography was normal and negative for dural sinus thrombosis. Electroencephalography was non-epileptiform, showing only right hemisphere slowing.

At the 9th and 18th month follow-up control, brain MRI revealed that the characteristic cortical high signal intensity on T1 and FLAIR images progressively faded (Figure 2). Hemosiderin due to chronic hemorrhage was never demonstrated. The patient remained entirely asymptomatic.

DISCUSSION

CLN as a presenting neuroimaging sign of migrainous stroke has been infrequently reported^[8,9]. CLN has been associated with cerebral hypoxia, metabolic disturbances, drugs and infections^[1-7]. CLN usually shows characteristic cortical high intensity on T1-weighted images from 2 wk to 2 years after ischemia and on FLAIR sequences, hypersignal appears a little later but remains longer^[1,2,10].

Furthermore, the blood-brain barrier breakdown due to the necrosis of the blood vessels results in the curvilinear “gyriform” enhancement on gadolinium-enhanced scans typically seen in these cortical infarcts.

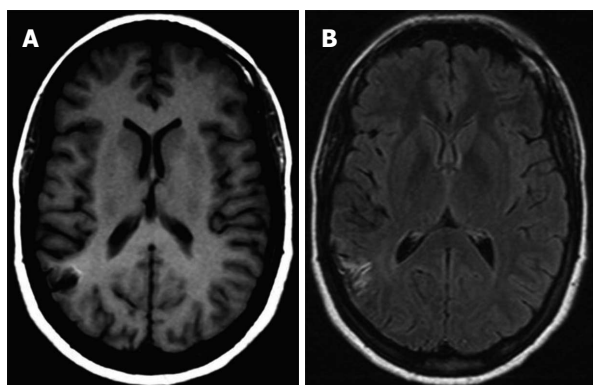


Figure 2 Magnetic resonance imaging at 18-mo follow-up. Axial T1-weighted (A) and fluid-attenuated inversion-recovery sequences (B). Faint hyperintense cortical laminar lesion is still present.

tions^[6-8]. Hyperintense signal on T1-weighted images can reflect the presence of any of the following substances: hemoglobin, fat, melanin, paramagnetic substances or protein-rich fluid^[5-7]. The T1 hyperintensity observed in CLN is not secondary to hemorrhagic transformation of cerebral ischemia and is thought to be due to the selective neuronal damage followed by higher concentration of proteins (and other macromolecules), glial cell proliferation and deposition of fat laden macrophages in the cortical area affected, that enhance relaxivity by restricting the motion of water molecules, thus causing T1 shortening^[4-7,10].

Little is known about the frequency of association of CLN and migrainous stroke, but the present case report is compatible with CLN related to migrainous cerebral infarction. Only 10 of 3,808 consecutive stroke patients included in our stroke data bank over a 19-year period fulfilled the criteria defined by the International Headache Society for migrainous stroke and in whom other causes of stroke were ruled out^[11]. Migrainous stroke is a known etiology of cerebral infarction of unusual case^[12]. The present case is the unique one in our stroke registry that presents CLN related to migrainous cerebral infarction.

To the best of our knowledge we have only found two similar case-reports of migrainous infarction involving CLN: the study of Liang *et al*^[11] including a case report of a 57-year-old white female with migrainous infarct with appearance of CLN on MRI^[8] and also, a report by Black *et al*^[12] involving possible CLN in the setting of familial hemiplegic migraine in a patient with Erdheim-Chester disease (a rare non-Langerhans cell histiocytosis).

The patient present initial autolimited left clonic facial seizures which can be explained by the involvement of the cerebral cortex related to CLN. Seizures in acute ischemic stroke occur in approximately 5% of patients and are related to involvement of the cerebral cortex or to very large strokes^[13].

Our patient fulfilled the strict diagnostic criteria for migraine-induced stroke of the International Headache Society^[14,15], which include: (1) the patient has previously fulfilled criteria for migraine with aura; (2) the neurologi-

cal deficit is manifested in the exactly vascular distribution as the aura, persisting for more than 60 min, and is associated with an ischemic brain lesion in a suitable territory demonstrated by neuroimaging; and (3) all other potential causes of ischemic stroke with CLN have to be ruled out by appropriate investigations. Migrainous stroke occurs more frequently in women and in patients ≤ 45 years of age^[11]. The heavy smoking history and the use of oral contraceptives are risk factors for migrainous cerebral infarction.

The physiopathology of migrainous stroke remains controversial. Potential mechanisms of migrainous infarction include vasospasm, hypercoagulability and vascular changes related to cortical spreading depression^[16,17]. Endothelial dysfunction, a process mediated by oxidative stress, may be a cause or a consequence of migraine, thus explaining the relationship of migraine to vascular factors and stroke^[16-18]. Therefore, all this processes may be considered in the genesis of CLN.

The present case shows that CLN can be considered a rare potential cause of migrainous infarction, an ischemic cerebral infarct of unusual etiology.

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Heat stroke induced cerebellar dysfunction: A “forgotten syndrome”

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Abstract

We report a case of heat stroke induced acute cerebellar dysfunction, a rare neurological disease characterized by gross cerebellar dysfunction with no acute radiographic changes, in a 61 years old ship captain presenting with slurred speech and gait ataxia. A systematic review of the literature on heat stroke induced cerebellar dysfunction was performed, with a focus on investigations, treatment and outcomes. After review of the literature and detailed patient investigation it was concluded that this patient suffered heat stroke at a temperature less than that quoted in the literature.

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Key words: Heat stroke; Cerebellar syndrome; Ataxic hemiparesis; Hyperthermia; Cerebellar atrophy

Core tip: Heat stroke induced cerebellar damage is a

rare and challenging neurological problem. The cerebellum is vulnerable to high temperature which may cause irreversible cell damage with permanent disability. Thorough evaluation with neuroimaging and laboratory investigations are required to exclude alternative diagnosis.

Kosgallana AD, Mallik S, Patel V, Beran RG. Heat stroke induced cerebellar dysfunction: A “forgotten syndrome”. *World J Clin Cases* 2013; 1(8): 260-261 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i8/260.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i8.260>

INTRODUCTION

Heat stroke induced cerebellar damage is a rare and challenging neurological problem. The cerebellum is vulnerable to high temperature which may cause irreversible cell damage with permanent disability. Thorough evaluation with neuroimaging and laboratory investigations are required to exclude alternative diagnosis.

CASE REPORT

A previously well 61 years old man presented to Bahrain hospital with acute cerebellar dysfunction and was subsequently transferred to Australia. He was the captain of an oil tanker, sailing from Mozambique to Bahrain, when found by his crew, lying on his bed, awake but unresponsive, except blinking his eyes and moving his head, having failed to respond to several calls. The ship's log recorded the cabin's air conditioner non-functioning for several days, with temperature reaching 38 °C. He reported feeling unwell with reduced oral intake in the preceding days with bridge officers questioning dehydration. On presentation, he was semiconscious, (Glasgow Coma scale: 11/15), febrile (38 °C), stable vital signs and severe dehydration. Pupils were equal and reacting to light. Doll's eye

manoeuvre was normal. He had slurred dysarthria, bilaterally flaccid limbs, up-going toes and a maculopapular truncal rash. Provisional diagnosis favoured heat stroke, rather than vascular stroke or viral/post viral illness. He was transferred from Bahrain to Sydney, after initial resuscitation. Arriving to Liverpool, he was alert and oriented, responsive to commands but cerebellar dysarthria made speech unintelligible. Cranial nerve examination was normal with no nystagmus and motor function revealed normal tone, 5/5 power, brisk, symmetrical reflexes but positive Babinski sign bilaterally. Sensation was unimpaired. Cerebellar examination was grossly abnormal, with severe dysarthria, dysmetria, disdiadochokinesis, heel to shin ataxia and ataxic gait, requiring two people to assist ambulation. Routine biochemistry and haematology were normal. Lumbar puncture revealed marginally raised protein (0.64 g/L, normal range 0.15-0.45 g/L) with normal cells and negative viral polymerase chain reaction.

Vasculitic screen, paraneoplastic antibodies and heavy metal screen were normal. Infectious aetiologies were excluded, with negative serology for HIV, *tropheryma whipplei*, hepatitis and other viral pathogens. Imaging, including computed tomography (CT) brain, CT Circle of Willis, magnetic resonance imaging (MRI) and MRI spectroscopy were normal. The patient made very slow progress and was transferred for rehabilitation.

DISCUSSION

Heat adversely affects almost all organ systems, with the central nervous system (CNS) particularly vulnerable and, within the CNS, the cerebellum is most susceptible^[1]. Hyperthermia may cause organ failure, unless managed aggressively in the acute setting, especially if the core body temperature exceeds 40 °C^[1,2]. Such elevated temperature was not reported in this case but that does not exclude it. Although the mechanism is not fully understood, several theoretical and experimental models have been described. A recent report claims that hyperthermia increases heat shock protein synthesis and cytokine activation, with a sepsis like reaction disrupting the blood brain barrier, causing vasogenic oedema and cell death^[2]. This theory is supported by animal models where inhibition of the cytokine pathways inhibits cell damage from heat stroke^[2,3]. Heat is directly toxic to cerebellar purkinje cells, which have the highest concentration of heat shock protein in order to counteract increased sensitivity^[3]. A post mortem series in the early 1950's showed that the cerebellum is particularly vulnerable to heat damage. This was confirmed by recent radiological studies^[4,5]. The presentation

is variable, ranging from coma to tetraparesis. Post mortem studies have shown swelling of purkinje cells and cell death^[3], with the duration of hyperthermia correlating with the extent of cell death^[6]. A case report identified a diffuse pattern of heat related brain injury, involving the subcortical white matter and hippocampus in addition to the cerebellum^[7].

Despite the air conditioner malfunctioning for some days, in the present case, the duration of exposure to hyperthermia was not defined. Heat stroke induced cerebellar atrophy, as per CT and MRI, generally involves both the vermis and cerebellar hemispheres, with cerebral hemispheres being spared in almost all reported cases.

Similar changes are seen in other degenerative, drug induced and paraneoplastic diseases^[5,6]. Patients with marked cerebellar dysfunction, may be radiologically normal with cerebellar atrophy appearing months or years later on CT or MRI scans^[5]. This patient had normal investigations and has been clinically stable over the last month, suggestive of non-progressive cerebellar damage. He was transferred for rehabilitation and will be followed with imaging to determine future cerebellar atrophy. While the literature describes hyperthermia involving temperatures in excess of 40 °C^[1,2] such elevated temperatures were not recorded in this patient, yet other alternative diagnoses were excluded with detailed investigations, thereby suggesting cerebellar damage may occur with lower temperatures than previously described.

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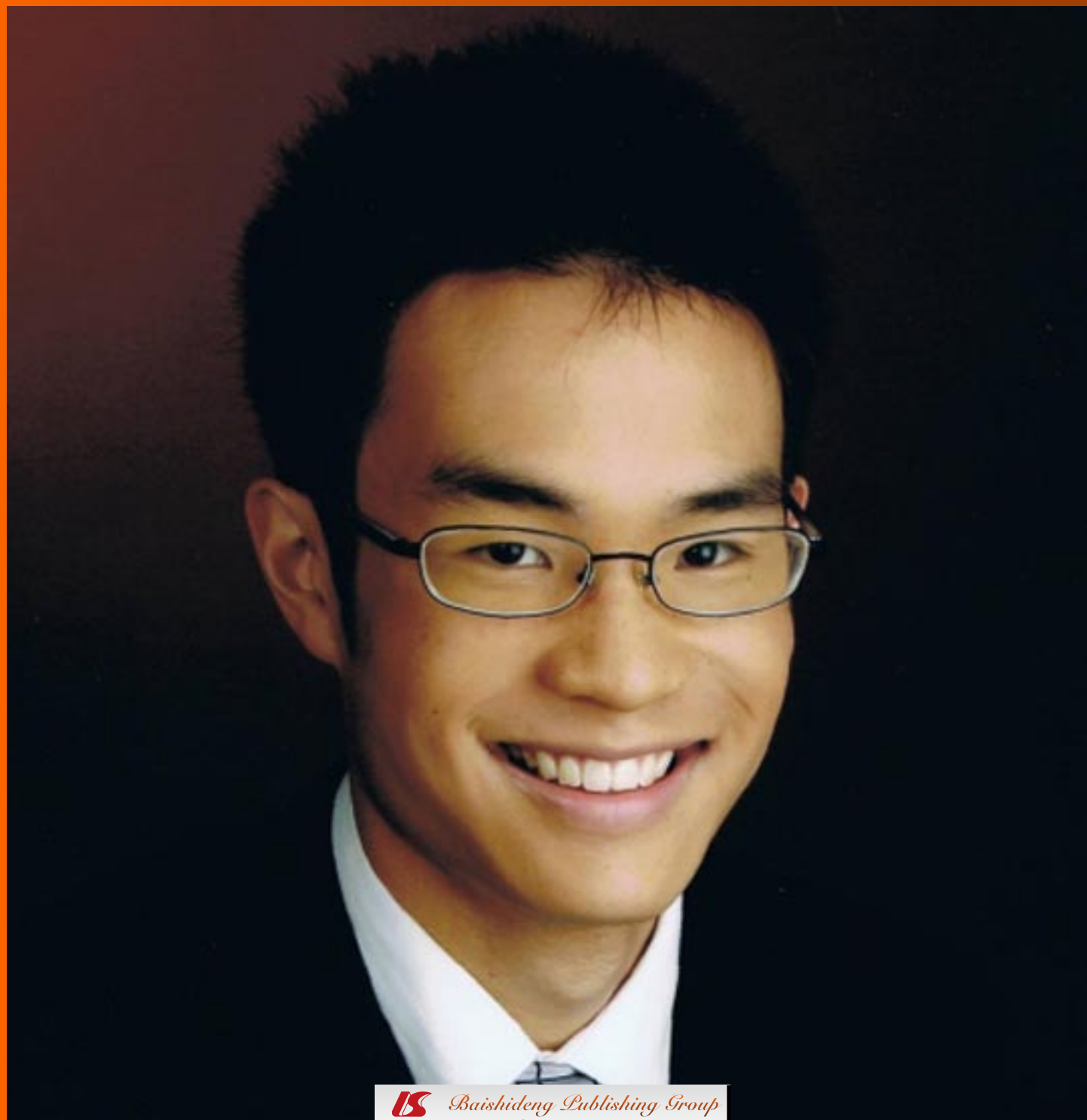
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Renal cell carcinoma: Evolving and emerging subtypes

Suzanne M Crumley, Mukul Divatia, Luan Truong, Steven Shen, Alberto G Ayala, Jae Y Ro

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Key words: Renal cell carcinoma; Subtypes; Xp11 translocation; Mucinous tubular and spindle cell; Multilocular cystic clear cell; Carcinoma associated with neuroblastoma recently described entities; Clear cell papillary renal cell carcinoma; Acquired cystic kidney disease; Hereditary leiomyomatosis; Candidate entities; Renal cell carcinoma with t(6;11) translocation

Core tip: New concepts in selected renal cell carcinoma (RCC) subtypes are reviewed. We describe evolving concepts in Xp11 translocation carcinoma, mucinous tubular and spindle cell carcinoma, multilocular cystic clear cell RCC, and carcinoma associated with neuroblastoma. Additionally, tubulocystic carcinoma, thyroid-like follicular carcinoma of kidney, acquired cystic disease-associated RCC, and clear cell papillary RCC are described. Finally, candidate entities, including RCC with t(6;11) translocation, hybrid oncocytoma/chromophobe RCC, hereditary leiomyomatosis and RCC syndrome, and renal angiomyoadenomatous tumor are discussed. This review provides a targeted summary of recent updates for those who diagnose and treat renal cancer.

Abstract

Our knowledge of renal cell carcinoma (RCC) is rapidly expanding. For those who diagnose and treat RCC, it is important to understand the new developments. In recent years, many new renal tumors have been described and defined, and our understanding of the biology and clinical correlates of these tumors is changing. Evolving concepts in Xp11 translocation carcinoma, mucinous tubular and spindle cell carcinoma, multilocular cystic clear cell RCC, and carcinoma associated with neuroblastoma are addressed within this review. Tubulocystic carcinoma, thyroid-like follicular carcinoma of kidney, acquired cystic disease-associated RCC, and clear cell papillary RCC are also described. Finally, candidate entities, including RCC with t(6;11) translocation, hybrid oncocytoma/chromophobe RCC, hereditary leiomyomatosis and RCC syndrome, and renal angiomyoadenomatous tumor are reviewed. Knowledge of these new entities is important for diagnosis, treatment and subsequent prognosis. This review provides a targeted summary of new developments in RCC.

Crumley SM, Divatia M, Truong L, Shen S, Ayala AG, Ro JY. Renal cell carcinoma: Evolving and emerging subtypes. *World J Clin Cases* 2013; 1(9): 262-275 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i9/262.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i9.262>

INTRODUCTION

Many new discoveries have been made with regards to renal cell carcinoma (RCC) in recent years. At the recent meeting of the International Society of Urologic Pathology, the newly defined, recently described, and candidate entities within RCC were discussed. An understanding of these new subtypes is essential for the surgical

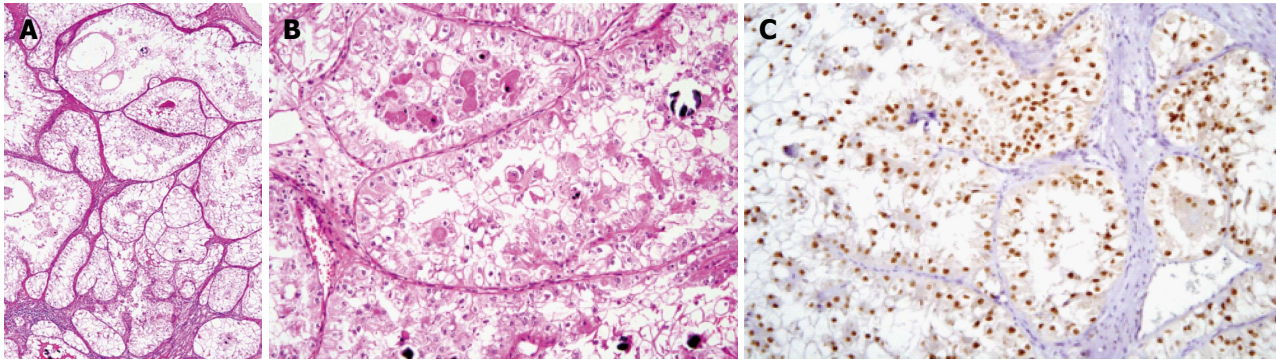


Figure 1 Xp11 translocation carcinoma (hematoxylin and eosin). A: The tumor is composed of cells with clear to eosinophilic, abundant voluminous cytoplasm ($\times 40$); B: Psammoma bodies in stromal hyaline nodules are frequently seen, but are not required for diagnosis ($\times 100$); C: TFE3 nuclear immunohistochemical stain can assist with confirmation of the diagnosis ($\times 100$), but can also be positive in tumors without the molecular translocation.

pathologist and urologist. An awareness of the current knowledge among these physicians will enable effective communication for proper diagnosis, prognosis, and treatment.

The five traditional and well-defined subtypes of RCC (conventional clear cell, papillary, chromophobe, collecting duct, and unclassified) comprise the overwhelming majority of RCC, but will not be discussed in detail here. In this review, we discuss three categories of evolving and emerging entities of renal tumors. The first category includes the newly defined RCC subtypes, the second includes recently described entities and the final category includes candidate entities for RCC subtypes (Table 1). The category of recently described tumors includes neoplasms with accruing evidence that they should be considered independent subtypes. The category of candidate entities includes both renal carcinomas seen in familial cancer syndromes and neoplasms on which there is still speculation to whether they deserve designation as distinct entities. The tumors within all three categories have received much scrutiny in recent years with important updates.

NEWLY DEFINED RCC SUBTYPES

Xp11 translocation carcinoma

Xp11 translocation RCC was first established by the World Health Organization (WHO) as an independent subtype in 2004^[1]. This tumor is defined by a translocation involving the *TFE3* gene with various gene partners, the most common of which are *ASPL* and *PRCC*. The name Xp11 translocation RCC comes from the chromosomal location of the *TFE3* gene (specifically Xp11.2). The tumor is defined by both papillary and clear cell morphology. These tumors can also have a nested architecture, and the type (location) of gene translocation may be reflected in the tumor morphology. *ASPL-TFE3* translocation carcinomas have more abundant cytoplasm and frequent psammoma bodies, while *PRCC-TFE3* translocations have less cytoplasm, less frequent psammoma bodies, and closely nested tumor cells^[2]. In general, these tumors have voluminous, clear to eosinophilic cytoplasm, and well-defined cell borders^[2-4] (Figure 1). Cystic

Table 1 Renal cell carcinoma subtypes

Renal cell carcinoma	
Newly defined subtypes	Xp11 Translocation RCC Mucinous tubular and spindle cell carcinoma Multilocular cystic clear cell RCC Carcinoma associated with Neuroblastoma
Recently described entities	Tubulocystic carcinoma Thyroid-like follicular carcinoma of kidney Acquired cystic kidney disease-associated RCC Clear cell papillary RCC
Candidate entities	RCC with t(6;11) translocation Hybrid oncocytoma/chromophobe RCC Hereditary leiomyomatosis and RCC syndrome Renal angiomyoadenomatous tumor

RCC: Renal cell carcinoma.

change, psammoma bodies, spindle cells, giant cells, and biphasic appearance have been described^[5,6]. Grossly, they appear similar to clear cell RCC. Xp11 translocation RCC has traditionally been described as occurring more frequently in young adults and children. Recent reports speculate whether these carcinomas may be associated with chemotherapy^[7].

These tumors are typically negative for cytokeratin and positive for CD10, RCC marker, vimentin, PAX2, and PAX8^[3-5]. A strongly positive nuclear stain for the C-terminal of the *TFE3* gene product is indicative of Xp11 translocation RCC. However, recently, some have questioned the specificity of the TFE3 staining. A recent series by Klatte *et al*^[8] examined 848 patients over a 20-year period and found 75 RCCs with features morphologically consistent with Xp11 translocation RCC or occurring in patients 40 years or younger. Of these 75 tumors, 17 (23%) tumors had strong nuclear TFE3 expression. However, only two of these cases had a translocation detected by FISH, yielding a dismal positive predictive value of 12%. This study suggests that the TFE3 immunohistochemical stain can also stain non-translocated *TFE3* product. The average age of patients with RCC positive for TFE3 immunohistochemical staining in this study was 33.4 years. Interestingly, this study also found that strong TFE3 expression in both non-translocated and translocated tu-

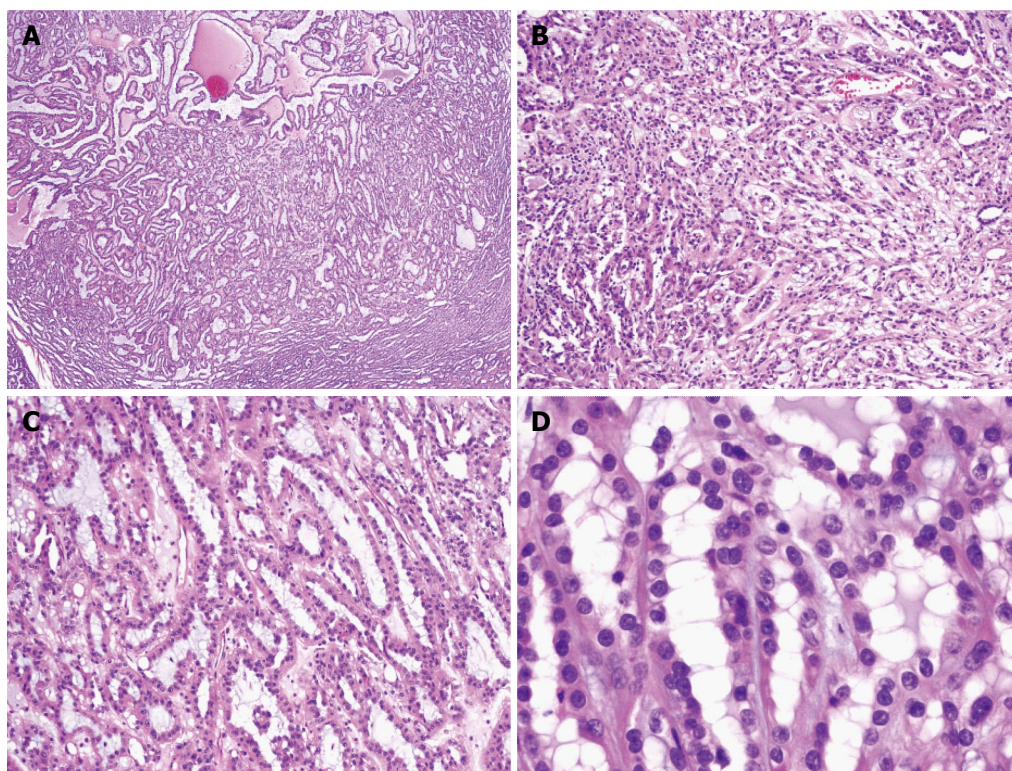


Figure 2 Mucinous and tubular spindle cell carcinoma (hematoxylin and eosin). A: The tumor has a tubular pattern on low power with mucin present between glands ($\times 20$); B: In some areas, a spindle cell pattern is also seen ($\times 40$); C: The tubular pattern with intervening mucin is prominent in some tumors ($\times 100$); D: Round nuclei with prominent nucleoli are evident on higher power ($\times 400$).

mors was associated with larger tumor size, lymph node involvement, and metastasis^[8]. Positive TFE3 staining was also associated with worse survival in univariate analysis ($P = 0.032$), albeit this was not significant in multivariate analysis ($P = 0.404$). This evidence suggests that strong TFE3 immunohistochemical staining in adults may be informative for prognosis as well as diagnosis.

Traditionally, Xp11 translocation carcinoma is described primarily in children and young adults. However, recent studies have suggested the presence of these tumors in adults may go unrecognized. A recent study by Zhong *et al*^[9] of 121 consecutive RCCs from 2001-2009 in adults at one institution found 6 tumors with Xp11 translocation for a frequency of 5%^[9]. While in pediatric RCC, Xp11 translocation RCC has been found in up to one third of all tumors^[3], RCC, in general, is much more frequent in adults than in children. Therefore, the majority of Xp11 translocation RCC may occur in the adult population. Additionally, in adults, these tumors may behave more aggressively and have an association with the female gender. Xp11 translocation RCC in adults has been found to present with advanced stage, lymph node metastases, and have a poor survival rate^[5]. A recent commentary by Klaassen *et al*^[10] in the *Journal of Urology* suggests that adult patients with Xp11 translocation RCC should be classified as high risk for metastasis. They suggest these patients should follow a vigilant surveillance protocol, which includes lifelong follow-up after diagnosis^[10].

The differential diagnosis for Xp11 translocation RCC includes clear cell RCC, clear cell papillary RCC,

papillary RCC (especially type 2), and the closely related translocation 6;11 carcinoma (discussed below). The *TFE3* translocation is diagnostic for tumors with overlapping morphology. The diagnosis of Xp11 translocation RCC should be investigated in children and young-to-middle-aged adults with characteristic histology that is negative for cytokeratins^[9]. New evidence suggests that if the classic morphology is present, the diagnosis should also be considered in adults. Based on these clinicopathologic features, we recommend a cytokeratin stain using a broad spectrum antibody in all RCCs diagnosed before the age of 30. If the cytokeratin is negative or weakly and focally positive, then proceed with a TFE3 stain and/or translocation study to confirm the diagnosis. A translocation carcinoma should be suspected in adults when papillary or nested pattern carcinoma, containing very voluminous clear to eosinophilic tumor cells (with or without psammoma bodies), are present, usually within hyaline stromal nodules. We recommend doing a similar battery of immunostains for RCCs of young adults and children.

Mucinous tubular and spindle cell carcinoma

Mucinous tubular and spindle cell carcinoma (MTSCC) is a fairly newly described tumor which is included in the 2004 WHO classification^[11]. This is a tumor defined by the presence of three histologic components: mucin, tumor cells forming tubules, and spindle cells, herein earning its appropriately descriptive name (Figure 2). This tumor occurs throughout life (age range 17-82 years) and is more

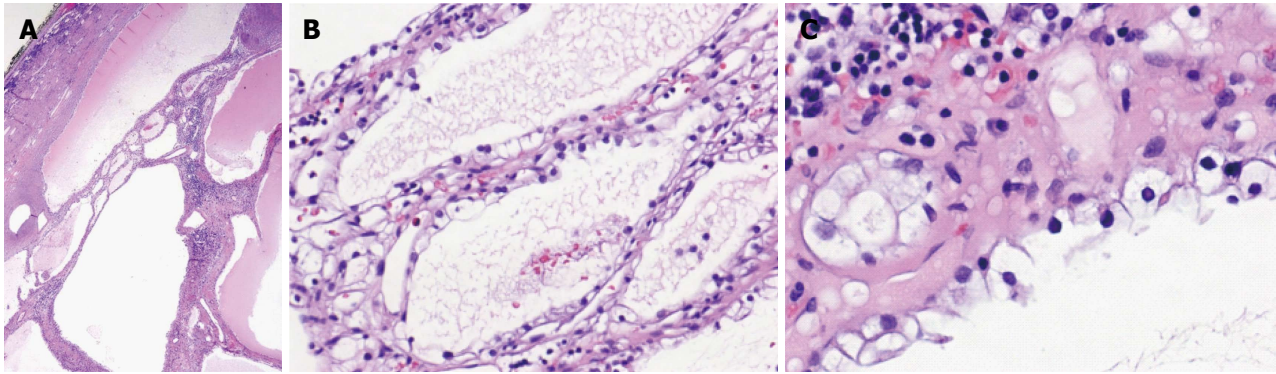


Figure 3 Multilocular cystic clear cell renal cell carcinoma (hematoxylin and eosin). A: The tumor is composed of multiple cysts with intervening thin, fibrous septa and scattered chronic inflammatory cells ($\times 40$); B: On higher power, the cysts are lined by a single layer of cells with clear cytoplasm ($\times 200$); C: Low-grade nuclear features (Fuhrman nuclear grade 1) are seen and clear cells are present within the cyst wall and on the surface lining ($\times 400$).

frequent in females^[11]. MTSCC has a similar gross appearance to papillary RCC. Similarly, the immunohistochemical staining pattern of MTSCC is nearly identical to papillary RCC (positive for CK7 and AMCAR, and negative for CD10 and RCC-marker)^[12], leading some to speculate that they may be a variant of papillary RCC^[13]. However, genetic studies have shown that MTSCC does not show the characteristic molecular aberrations as seen in papillary RCC^[14]. The characteristic gains of chromosome 7 and 17 and loss of chromosome Y typically seen in papillary RCC are not seen in MTSCC^[14], which instead displays frequent losses and gains of other chromosomes^[15].

MTSCC is a rare neoplasm, and can be a difficult diagnosis due to its morphologic heterogeneity. A study by Fine *et al.*^[16] describes the histologic variations of MTSCC and, in particular, what they described as the “mucin-poor variants”. These variants show a predominance of tubular or spindle cell components and only minimal pale mucinous background. In addition, focal papillations or papillary cores and foamy histiocytes can be seen, creating confusion with papillary RCC. They note that helpful features in recognizing these variants are bland cytologic features and adjacent tubular and spindle cell components. It is important to be aware that focal areas of clear cells and oncocyctic change can also be present^[16].

MTSCC is considered a low-grade entity, with only rarely described cases of lymph node metastasis and recurrence. However, two cases of MTSCC with sarcomatoid change have been described, one with widespread metastasis to distant organs, including lung and bone^[17]. A spindled component is characteristic of MTSCC, but the presence of significant pleomorphism with prominent nucleoli and mitotic activity, and necrosis should raise concern for a sarcomatoid change^[17]. Microscopic necrosis alone can be seen focally in MTSCC, but its significance is unknown. The presence of any necrosis should be mentioned in the final diagnosis^[16].

Multilocular cystic clear cell RCC

Multilocular cystic clear cell RCC is defined as a distinct entity in the 2004 WHO classification. It is defined by the presence of low-grade clear cells lining cystic spaces and

by the lack of a solid or expansive nodular component (Figure 3)^[18]. Clear cells are commonly seen within the cyst wall (Figure 3), and can sometimes be difficult to distinguish from histiocytes. However, the neoplastic clear cells will be positive for cytokeratin and carbonic anhydrase IX (CA-IX), distinguishing them from histiocytes^[19].

Multilocular cystic RCC shares similar genetic abnormalities with clear cell RCC, *i.e.*, the characteristic 3p deletions^[20]. However, there have been no reported cases of progression or metastasis of this tumor, with a 5-year survival of 100%. In fact, the prognosis of this tumor is so favorable that, in the largest review utilizing the strict 2004 WHO criteria (45 cases), they suggested renaming this entity “multilocular cystic renal cell neoplasm of low malignant potential” and conservative management was suggested^[21].

The distinction between a low grade (Fuhrman nuclear grade 1-2) clear cell RCC or clear cell papillary RCC can be difficult. A recent paper by Williamson *et al.*^[19] examined the immunohistochemical characteristics of multilocular cystic RCC. In contrast to conventional clear cell RCC, they found that CK7 was frequently diffusely positive and CD10 was less frequently positive in multilocular cystic RCC. This is similar to clear cell papillary RCC, which is also typically cystic. However, the absence of true papillae and the lack of CA-IX apical staining should distinguish these two entities^[19]. Clear cell RCC with extensive cystic or necrotic change is important to include in the differential. Clear cell RCC will typically have large solid areas of neoplastic cells, which are not present in multilocular cystic RCC.

Carcinoma associated with neuroblastoma

Carcinoma associated with neuroblastoma is a distinct entity included in the 2004 WHO classification. It is defined as RCC which occurs in survivors of neuroblastoma^[22]. A series of four cases from 1999 described RCC with papillary and solid patterns, abundant cytoplasm, and occasional oncocyctic morphology, which occurred in patients with a previous diagnosis of neuroblastoma^[23]. The tumors initially described were considered a distinct subset, morphologically and genetically distinct from other RCC subtypes. In recent years, Xp11 translocation

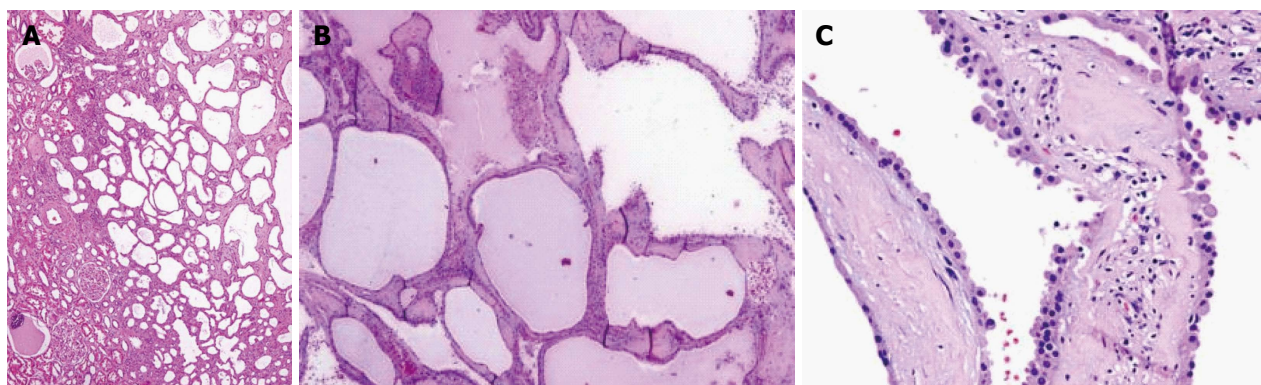


Figure 4 Tubulocystic carcinoma (hematoxylin and eosin). A: Tubulocystic carcinoma, on low power, is composed of many small cystic spaces with intervening fibrous septae ($\times 20$); B: The cysts vary in size and shape ($\times 40$); C: On higher power, bland cuboidal and hobnail-shaped cells are identified lining the cystic spaces ($\times 200$).

RCC and papillary RCCs have also been described in neuroblastoma survivors^[7,24,25].

The risk of developing another malignancy after neuroblastoma is well known^[26]. RCC is the second most common type of such tumor, following thyroid carcinoma^[26]. A survey of survivors of childhood cancer found a 329-fold risk of RCC in children with neuroblastoma^[27]. The health risk after neuroblastoma is not limited to malignancy. A survey of 954 neuroblastoma survivors found an 8-fold likelihood of chronic health conditions, compared to their matched siblings, including musculoskeletal complications, endocrine abnormalities, and sensory abnormalities such as deafness and blindness. Many of these long-term effects are associated with treatment, which could also be associated with development of RCC^[7]. However, there is evidence that the carcinoma associated with neuroblastoma is not related to therapy, but instead to an underlying genetic defect that predisposes individuals to development of cancer^[23,27]. Regardless of the pathogenetic mechanism, knowledge of this entity in neuroblastoma survivors is essential for monitoring and early diagnosis.

RECENTLY DESCRIBED TUMORS

Tubulocystic carcinoma

Tubulocystic RCC is a recently described tumor composed of variably sized cystic tubules lined by a single epithelial layer with intervening fibrotic stroma (Figure 4). The neoplastic cells lining the cystic spaces have eosinophilic cytoplasm, hobnail nuclear morphology, and prominent nucleoli^[28]. Tubulocystic RCC is not currently recognized by the WHO. However, accruing evidence suggests tubulocystic RCC merits consideration as a distinct entity.

Tubulocystic RCC was initially believed to derive from the collecting duct; in fact, it was originally considered a well-differentiated variant of collecting duct carcinoma. However, recent gene expression profiling evidence tends to refute this possibility^[29]. The immunohistochemical staining pattern, ultrastructural features, and gene expression profiling favor a proximal convoluted tubule or intercalated cell origin^[28,29]. In fact, some suggest that tubu-

locystic RCC may be closely related to papillary RCC^[30,31]. One study of tubulocystic RCC found that 5 of their 13 cases of TCRCC had coexistent papillary renal cell neoplasms. In addition, a similar immunohistochemical staining pattern and gene expression profile between papillary RCC and TCRCC was identified^[30]. This finding was supported by another study, which had 10 of 12 TCRCC cases with associated papillary neoplasms, including admixed TCRCC and papillary RCC in 4 cases^[31]. This study also found gains of chromosome 17 in 8 of 12 cases of TCRCC^[31]. Synchronous TCRCC with clear cell RCC has also been reported^[32].

The largest clinicopathologic study to date on TCRCC was compiled by Amin *et al.*^[28] in 2009. They found TCRCC is more common in males and is a low-grade entity, with the majority of tumors presenting as stage pT1. Often, the tumor is an incidental finding. Tumors were both subcapsular (61.5%) and cortico-medullary or medullary (38.5%) in location. Only one case had local recurrence (3%) and two cases (6%) developed metastases. All cases had a Fuhrman nuclear grade of 3 despite an indolent behavior in the majority of cases, suggesting little value of Fuhrman grading in these neoplasms^[28].

The differential diagnosis includes other cystic renal neoplasms, including multilocular cystic RCC. Focal cytoplasmic clearing has been noted in TCRCC^[28]. Multilocular cystic clear cell RCC typically has lower Fuhrman grade nuclei, and scattered clear cells will be seen within the intervening fibrous stroma. Cystic nephroma could also be considered, but typically has larger cystic spaces and inconspicuous nucleoli. Mixed epithelial and stroma tumor also has cystic spaces, but will display an ovarian-type stroma. Oncocytoma with prominent tubules and cysts could also be considered, but typically will have nests of oncocytic cells, which are not present in TCRCC^[28].

Thyroid-like follicular carcinoma of kidney

Thyroid-like follicular RCC was first described by Jung *et al.*^[33] in 2006. They described a case of primary renal carcinoma with morphology similar to a thyroid follicular carcinoma^[33]. To date, only about 10 cases of this entity

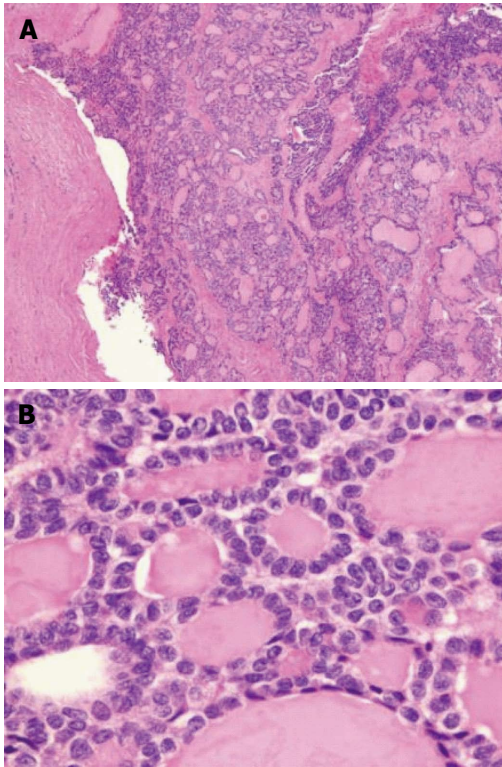


Figure 5 Thyroid-like follicular carcinoma of kidney (hematoxylin and eosin). A: The tumor has thyroid-like follicles filled with colloid-like material on low power ($\times 40$); B: On high power, cells with enlarged, irregular nuclei and follicular architecture, similar to the follicular neoplasms of the thyroid, are seen; Nuclear grooves are also evident ($\times 400$). Courtesy of Dr. Pheroze Tamboli, MD Anderson Cancer Center.

have been described in the literature^[33-37].

The largest case series to date was compiled by Amin *et al*^[34] in 2009 and includes 6 cases. They describe well-circumscribed tumors which grossly resemble thyroid parenchyma. The microscopic morphology mimics follicular carcinoma of the thyroid and contains colloid-like material (Figure 5). They are predominantly of low grade, but metastases to lymph nodes and to the lungs have been reported^[34,35]. Six of the 10 reported cases in the literature occurred in patients in the 2nd and 3rd decades of life. However, the age range is wide, with cases reported from 29-83 years. Equal gender distribution is seen, and most of the cases are incidental findings (7 of 10 cases). No deaths from disease have been reported^[37].

Distinction from a metastatic thyroid carcinoma is essential. The characteristic morphology and negative staining for thyroglobulin and thyroid transcription factor 1 confirms the diagnosis. The differential diagnosis also includes metastases from a teratoma (struma ovarii). Thyroidization of the kidney is also common in end-stage renal disease, but the cells lining the tubules are bland. Also, end-stage renal disease, in general, does not form a distinct tumor mass.

Acquired cystic kidney disease-associated RCC

Renal tubular cystic changes may develop in end-stage renal disease (ESRD), and this condition is termed ac-

quired cystic kidney disease (ACKD). Renal tumors often occur in kidneys with ESRD with or, less frequently, without ACKD. The risk of RCC in patients with ACKD is greater than 100 times that of the general population, although the incidence is less than 10%^[38-41]. A prior history of dialysis is often associated with the development of ACKD and RCC, with direct correlation to duration of dialysis^[42]. The various tumor types encountered in cases with ESRD include the three common subtypes of RCC, *i.e.*, clear cell (conventional) RCC, papillary RCC, and chromophobe RCC, with papillary RCC as the most common. However, there are at least two other subtypes of RCC that are more frequently associated with ESRD: ACKD-associated RCC and clear cell papillary RCC. ACKD-associated RCC is reported only in patients with ESRD and ACKD, thus the name; whereas clear cell papillary RCC can be seen in patients with both cystic and non-cystic ESRD, as well as in those without ESRD^[42-44].

The ACD-associated RCC is usually multifocal and bilateral. These tumors may be incidentally discovered on imaging studies or in nephrectomy specimens performed for renal cysts with complications or renal parenchymal bleeding, which not infrequently masks the underlying tumor. Most tumors are well circumscribed, and often appear to arise within cysts. Tumors which are larger in size are grossly solid with a thick, fibrous capsule and may be accompanied by foci of necrosis and hemorrhage.

Microscopically, the tumors demonstrate a growth pattern comprised of various proportions of acinar, alveolar, solid, cystic, and papillary architectural patterns. Tumor cells display characteristic features, including abundant granular, eosinophilic cytoplasm and large nuclei with prominent nucleoli (Figure 6). A cribriform or sieve-like appearance is characteristic and present in most cases. Most, but not all, cases also show intratumoral oxalate crystals, a relatively specific feature quite consistently observed in ACD-associated RCC and not in other tumor types^[42,45]. Immunohistochemical stains aid in distinguishing these tumors as ACD-associated RCC stains diffusely positive for α -methylacyl-coenzyme A racemase (AMACR), but is negative or only focally positive for CK7. Stains for CD10, RCC antigen, and glutathione S-transferase A are also reported to be positive^[46]. On a molecular level, these tumors do not show trisomy of chromosomes 7/17 or loss of 3p, characteristic of papillary and clear cell RCC, respectively. A recent study by Pan *et al*^[46] on 9 cases of ACD-associated RCC showed variable combined gains of chromosomes 3, 7, 16, 17, and Y using fluorescence *in situ* hybridization and comparative genomic hybridization. It is also important to note that the nonneoplastic renal parenchyma often contains cysts lined by large eosinophilic cells that show an immunophenotype similar to that of ACD-associated RCC.

The biologic behavior of RCCs in ESRD in general is reported to be less aggressive than that of the RCCs in non-ESRD settings. These tumors often present at a lower stage and are smaller in size^[47]. However, there are

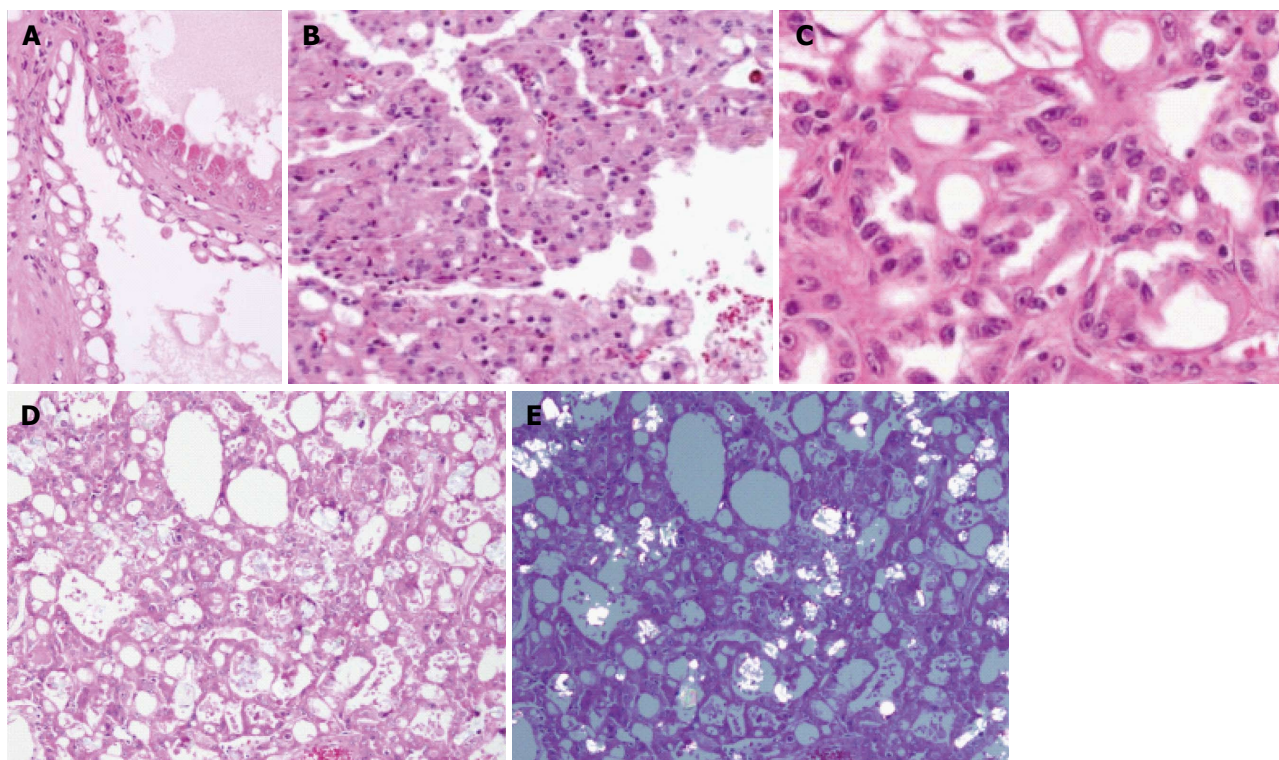


Figure 6 Acquired cystic disease-associated renal cell carcinoma. A, B: The tumor cells in acquired cystic disease-associated renal cell carcinoma typically have abundant eosinophilic cytoplasm and are seen lining the cystic spaces (A, $\times 400$), and sometimes also show a solid growth pattern (B, $\times 200$); The tumor characteristically arranges in a sieve-like cribriform pattern; C: The nuclear features are consistent with a Fuhrman nuclear grade 3, with prominent nucleoli ($\times 600$); D, E: Calcium oxalate crystals are often associated with these tumors, and can be seen on hematoxylin and eosin staining (D, $\times 600$) and with polarization (E, $\times 100$).

a few case reports with metastasis or aggressive behavior. ACD-associated RCC may have a greater potential for aggressive behavior than other tumor types in ESRD. Rare cases with sarcomatoid features and unfavorable clinical outcomes have been reported^[43,48].

The exact mechanisms underlying the increased incidence of RCC in ESRD, especially in those with superimposed ACKD are not completely understood. Multiple molecular alterations in diverse types of renal tumors indicate an acquired mechanism for renal tumorigenesis. Possible precursor lesions in ESRD include papillary adenomas and dilated tubules or clustered microcystic lesions lined by the eosinophilic cells^[49]. Further research is necessary in order to delineate an etiologic relationship for these tumors.

Clear cell papillary renal cell carcinoma

Clear cell papillary RCC is a recently recognized renal tumor. This tumor was originally described in a background of ESRD and ACKD, although it has subsequently been reported in normal kidneys^[42,43,50]. Metastasis from a clear cell papillary RCC has not been reported, highlighting the likelihood that these tumors are less aggressive than other RCC subtypes^[42-44,50-53].

Clear cell papillary RCC is usually small and grossly encapsulated. The tumors may be solid, white tan, pale yellow or reddish brown in external appearance; however, the typical bright or golden-yellow heterogeneous cut surface of clear cell RCC is not identified. The cystic

component is usually located at the periphery of the tumor, near its junction with renal parenchyma, and may be angulated, flattened, or irregular. Bilaterality and multifocality have been documented, especially in tumors arising in a background of ACKD^[42-44,50-53].

On microscopic examination, clear cell papillary RCC is composed of a varying admixture of cystic, glandular, solid, and papillary components. The tumor cells have clear cytoplasm and are usually of low nuclear grade (Figure 7). One of the most distinctive features of clear cell papillary RCC is the linear positioning of the nuclei away from the basement membrane (inverted polarity). It is the presence of this feature within these tumors that aids in identification, irrespective of the architectural growth pattern, which can be markedly variable^[43,44]. Papillary architecture is almost always present, but may be focal, and is commonly branched. Stellate tubular structures may also be seen. Some cases may have a prominent tubular pattern, as supported by previous reports describing this entity as tubulopapillary carcinoma. Other growth patterns include cystic, alveolar/nested, and retiform^[43,50]. These tumors often have a fibrous capsule of varying thickness and often have variable amounts of eosinophilic hyalinized or sclerotic stroma^[42-44,50-53]. Clear cell papillary RCCs sometimes contain foci of calcification or ossification, often within the tumor pseudocapsule^[53].

In most cases, the morphologic features of clear cell papillary RCC are unique enough to allow for distinction from clear cell RCC based on HE-stained slides. In some

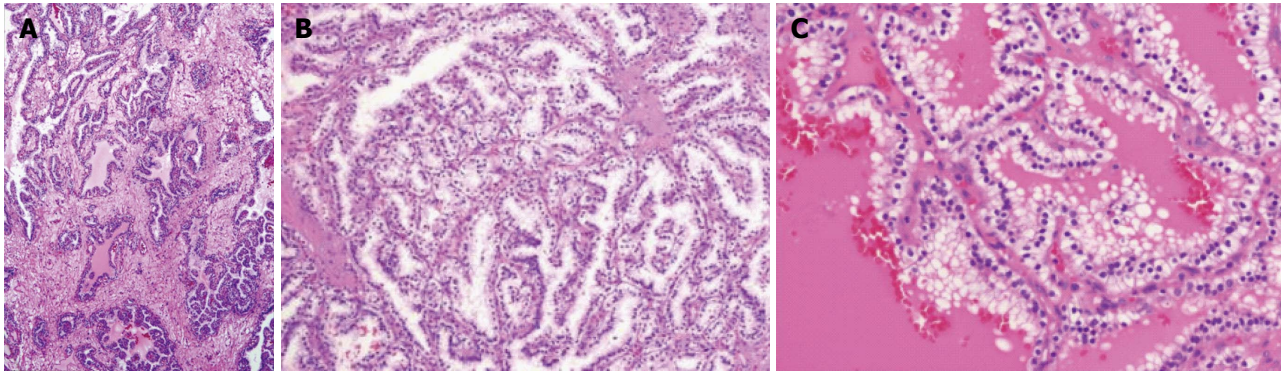


Figure 7 Clear cell papillary renal cell carcinoma (hematoxylin and eosin). A: The tumor has both a tubular and papillary architecture within a dense fibrous stroma ($\times 40$); B: Other areas show a tubulopapillary growth pattern with delicate fibrovascular cores and conspicuous cytoplasmic clearing ($\times 100$); C: The characteristic clear cells with low Fuhrman nuclear grade are seen with inverted linear positioning of the nuclei away from the basement membrane ($\times 200$).

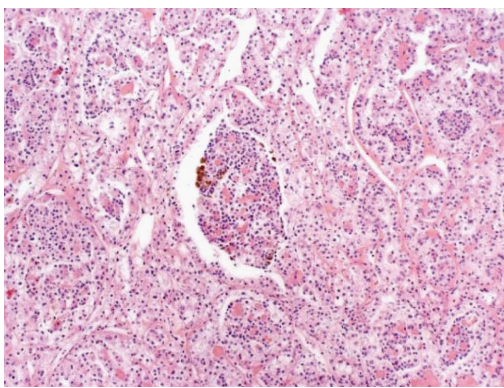


Figure 8 Renal cell carcinoma with t(6;11) translocation (hematoxylin and eosin). The tumor is composed of large epithelioid cells with abundant clear to eosinophilic cytoplasm; the distinctive feature of hyaline material with surrounding cells "rosette forming" is seen ($\times 100$). Courtesy of Dr. Liang Cheng, Indiana University.

cases, immunohistochemical stains can be helpful, as clear cell papillary RCC and clear cell RCC have different immunoprofiles. Both clear cell papillary RCC and clear cell RCC typically express CA-IX, but the former usually exhibits weak expression, which is localized to the basal and lateral aspects of the tumor cells, so-called cup-shaped expression^[44]. CD10 and 34 β E12 show variable expression in these 2 tumor types, with the former more frequently positively expressed in clear cell papillary RCC. CK7 appears to be the most reliable marker for differentiating these 2 entities, as it is nearly always diffusely, strongly positive in clear cell papillary RCC, while only infrequently positive in clear cell RCC^[43,44]. In general, when CK7 labeling is present in a clear cell RCC, it is focal or, at most, patchy and centered around cystic spaces^[44]. Expression of AMACR is usually negative in both of these tumor types; thus, it is not of any use in this differential, but it can be extremely useful in cases of clear cell papillary RCC if the differential diagnosis includes papillary RCC^[42-44,50-53].

Molecular changes in clear cell papillary RCC are distinctly different from those identified in clear cell and papillary RCCs. Sporadic clear cell papillary RCCs lack

VHL mutations, 3p25 deletions, hypermethylation of the *VHL* promoter, and other recurrent copy number changes which are characteristically seen in clear cell RCCs. Of the cases reported to date, there has been only 1 *VHL* mutation occurring in a clear cell papillary RCC in a patient with known *VHL* disease, and 1 case of loss of heterozygosity of the *VHL* locus has been described^[43]. Although low copy number gains of chromosomes 7 or 17 have been documented in a small subset of cases, the vast majority of clear cell papillary RCCs do not exhibit these findings^[43,44,54,55]. No pathognomonic genetic alteration has been identified. However, a recent gene expression profile meta-analysis of clear cell RCC by Brannon *et al*^[56] identified 3 distinct molecular subgroups within clear cell RCC. One of these groups corresponded to a *VHL* wild-type pattern of gene expression and, from the images provided in the article, morphologically appears to represent clear cell papillary RCC. This study highlights the fact that many clear cell papillary RCCs were incorrectly diagnosed as clear cell RCC in the past, while also emphasizing that clear cell papillary RCC and clear cell RCC are distinct entities.

CANDIDATE ENTITIES

RCC with t(6;11) translocation

An extremely rare subset of renal translocation tumors is associated with t(6;11) (p21;q12)/Alpha-TFEB gene fusion. This distinctive tumor was first described by Argani *et al*^[57] in 2001. Since then, a handful of cases of this rare entity have been documented in the literature. TFEB RCCs are predominantly seen in younger patients and are generally indolent, with rare reported cases of metastatic disease^[58-66]. The most common histologic pattern is large epithelioid cells with voluminous clear to slightly eosinophilic cytoplasm, and clusters of small cells, usually clustered around hyaline material (rosette-forming) (Figure 8). However, TFEB RCCs may demonstrate unusual morphologic features, such as papillary, tubular, chromophobe RCC, clear cell RCC, and epithelioid angiomyolipoma-like structures^[58-66].

A recently developed antibody to TFEB and cathep-

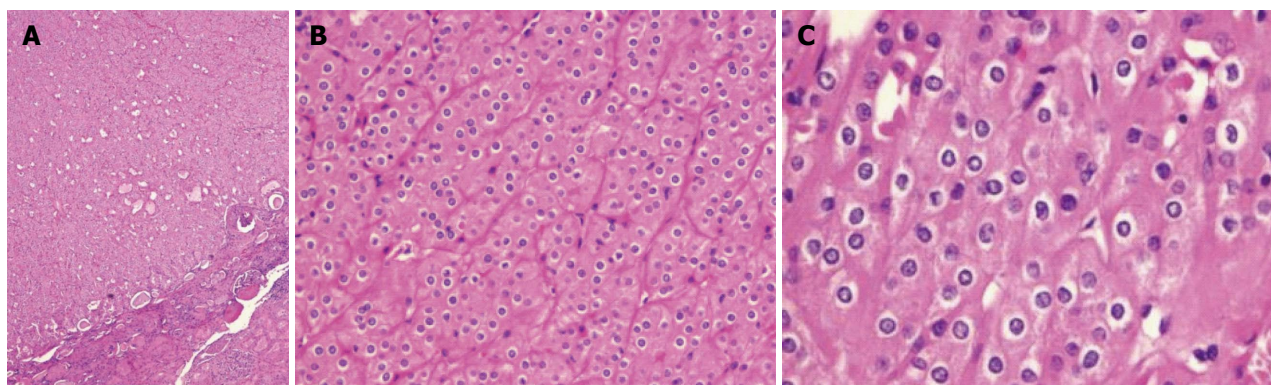


Figure 9 Hybrid oncocytoma/chromophobe renal cell carcinoma (hematoxylin and eosin). A: Low power assessment of the tumors shows a well-circumscribed tumor with a solid growth pattern ($\times 40$); B: The tumor cells have abundant eosinophilic cytoplasm and round, monotonous nuclei ($\times 200$); C: Perinuclear halos are prominent throughout, with some areas showing mild nuclear irregularity ($\times 400$). The overlapping features of oncocytoma (round nuclei with abundant eosinophilic cytoplasm) and chromophobe (perinuclear halos) are noted.

sin K proteins is highly sensitive and specific for TFEB RCCs^[58,67]. It is important to recognize there must be nuclear positivity for TFEB, as the fusion product will be present in the nucleus. Non-translocated TFEB can cause falsely positive cytoplasmic staining^[58]. Both *TFEB* and *TFE3* (described above in Xp11 translocation RCC) are part of the microphthalmia transcription factor/transcription factor family translocation RCCs. Overexpression of *TFE3* and *TFEB* in these neoplasms is known to increase the expression of cathepsin K proteins^[67]. A study by Martignoni *et al*^[67] showed that 7 of 7 TFEB RCC and 6 of 10 Xp11 translocation RCC had strong expression of cathepsin K, which was not seen in any other renal neoplasms^[67]. In the study by Rao *et al*^[66], all of the tumors showed moderate to strong immunoreactivity for TFEB, Ksp-cadherin, and vimentin, but were negative for TFE3, CD10, and CK7. Cathepsin K, HMB45, and melan A are moderately or strongly expressed in TFEB RCCs^[58-67].

TFEB RCCs are often diagnosed based upon their distinctive morphology and immunophenotype. However, molecular methods such as PCR, RT-PCR, and FISH are extremely helpful and sometimes mandated for an accurate diagnosis. An interphase FISH assay is useful in the definitive identification of TFEB RCCs, and plays an essential role in identifying previously undiagnosed cases^[66,68].

As these are rare tumors, there is still a degree of uncertainty regarding the final clinical outcome of patients. In the study by Rao *et al*^[66], all 6 patients with follow-up available were alive with no recurrent disease. Their follow-up ranged from 6 to 55 mo, with a mean follow-up time of 31 mo. Other studies have shown a similar good prognosis^[59,61], and TFEB RCC appears to be a relatively indolent tumor. However, further studies are warranted to determine long-term clinical outcomes.

To detect this tumor, we recommend the same approach of immunostains as for Xp11 translocation carcinoma in young patients under 30. If the initial cytokeratin stain is negative or weakly to focally positive, a TFE3 stain is recommended. If the TFE3 stain is negative, TFEB and HMB45 immunostains are recommended to

diagnose a RCC with t(6;11) translocation tumor (both TFEB and HMB45 positive), and exclude the possibility of epithelioid angiomyolipoma (TFEB negative and HMB45 positive).

Hybrid oncocytoma/chromophobe RCC

Hybrid oncocytoma/chromophobe RCC was first recognized in patients with Birt-Hogg-Dubé (BHD) syndrome, a rare autosomal dominant condition characterized by fibrofolliculomas, renal tumors, pulmonary cysts, and spontaneous pneumothorax^[69]. Mutation of the *BHD* gene on chromosome 17, a tumor suppressor gene, is attributed to this syndrome^[70]. The renal tumors in these patients are characterized by the morphologic features of both oncocytoma and chromophobe RCC within the same tumor, known as hybrid oncocytoma/chromophobe RCC^[69]. BHD patients also have an increased incidence of other RCCs, including chromophobe and clear cell RCC. The renal tumors in BHD patients are frequently bilateral and multifocal, and background renal oncocytosis within the kidney may be seen^[69]. Renal oncocytosis is characterized by oncocytic change in the renal tubules and multiple oncocytomas.

Hybrid oncocytoma/chromophobe has been described as occurring in patients with renal oncocytosis; however, there has been an increased recognition of this entity in sporadic tumors without a background of renal oncocytosis or BHD syndrome^[71-73]. These tumors are composed of cells with abundant granular eosinophilic cytoplasm, round nuclei, perinuclear halos, and CK7 positivity (Figure 9). Some of these sporadic hybrid tumors have distinctly different morphology in separate areas, while others have mixed features throughout^[71].

The heightened awareness of hybrid tumors leads to questions of the utility of core needle biopsy in oncocytic neoplasms, which may miss a chromophobe component in a hybrid tumor due to sampling error. The distinction between oncocytoma and chromophobe RCC is clinically important, and the behavior of these hybrid entities is yet unknown. However, small, retrospective studies have

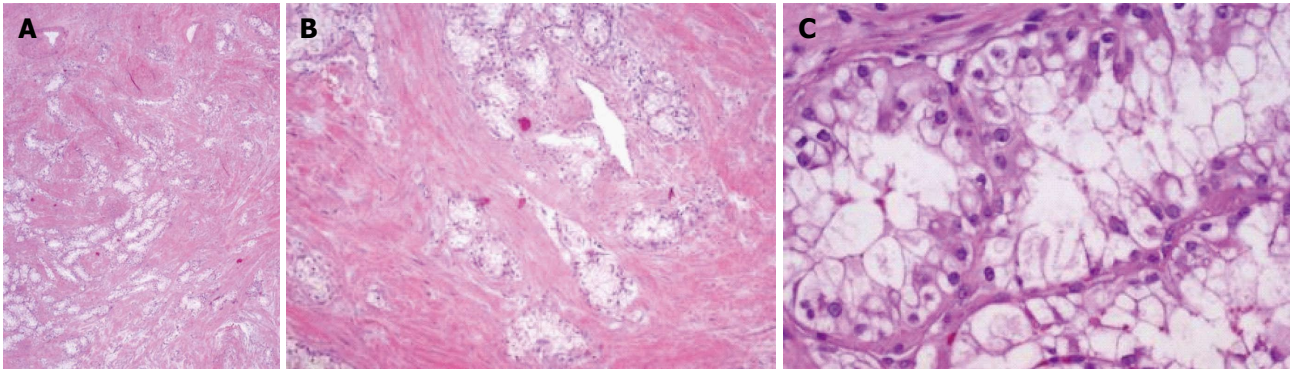


Figure 10 Renal angiomyoadenomatous tumor (hematoxylin and eosin). A, B: The tumor is composed of epithelioid cells in a background of dense, leiomyomatous stroma (A, $\times 40$ and B, $\times 100$); C: The tumor cells have oval nuclei of low Fuhrman nuclear grade with clear to eosinophilic cytoplasm and protrude into the lumen, resembling a so-called “shark’s smile” ($\times 400$). Courtesy of Dr. Melissa Stanton, Mayo Clinic, Arizona.

shown that these hybrid oncocytoma/chromophobe tumors have a clinically indolent course^[73]. Further studies are needed to determine the behavior and pathogenesis of these neoplasms.

Hereditary leiomyomatosis and RCC syndrome

Hereditary leiomyomatosis and RCC (HLRCC) is an autosomal dominant familial syndrome characterized by the development of cutaneous and uterine leiomyomata, as well as renal tumors^[74]. The hallmark mutation in this syndrome is the fumarate hydratase (*FH*, 1q42.3-q43) gene, but the exact prevalence of HLRCC is unknown. Kidney cancers are less penetrant than the leiomyomatous manifestations in HLRCC-affected families^[75-77]. The association between cutaneous and uterine leiomyomata has been known for many years as Reed syndrome^[78].

The renal tumors in this syndrome are aggressive, as demonstrated by the fact that 9 out of 13 patients in the first reported cohort of North American families died of metastatic disease within 5 years of initial diagnosis^[75]. Other studies have shown lymph node metastasis is common, and there is a poor prognosis^[79]. In the largest series published by Merino *et al*^[79], 40 renal tumors resected from 38 HLRCC patients with proven fumarate hydratase germline mutations were studied. The patient age ranged from 17 to 75 years and tumors ranged in size from 2.3 to 20 cm. A papillary architecture was most common (25 of 40 cases), but tubulopapillary, tubular, solid, and mixed patterns were also seen. Immunohistochemical stains were nonspecific. The defining characteristic of HLRCC, as described by Merino *et al*^[79], is the presence of a large nucleus with a prominent inclusion-like eosinophilic nucleolus, surrounded by a perinucleolar clearing. This distinctive morphology is also seen in the leiomyomata of these patients (described below).

Leiomyomatosis is a condition defined by the occurrence of multiple leiomyomas throughout the body, with often poorly defined nodules involving areas of the skin on the arms, chest, legs, and, in extremely rare cases, the uterus. In a study by Sanz-Ortega *et al*^[80], uterine leiomyomata were identified in HLRCC patients at a young age (median age of 32 years). They were often multiple

and ranged from 1 to 8.5 cm in size. Histopathologically, HLRCC leiomyomata frequently had increased cellularity, multinucleated cells, and atypia. All cases showed tumor nuclei with large orangeophilic nucleoli surrounded by a perinucleolar halo similar to the changes found in HLRCC^[79]. This study also showed that loss of heterozygosity (LOH) at 1q43 was frequent in HLRCC leiomyomas (8/10 cases), similar to the molecular alterations in renal tumors. LOH is considered to be the second hit that inactivates the *FH* gene, and *FH* mutations and LOH at 1q43 are unusual in sporadic leiomyomas.

Uterine leiomyomas and renal tumors in HLRCC share similar morphologic changes and genotypic features. It is important to recognize these features in leiomyomata so patients undergo early genetic testing for germline *FH* mutations and screening for renal cell cancer.

Renal angiomyoadenomatous tumor

Michal *et al*^[81] reported a series of 5 cases which they designated as renal angiomyoadenomatous tumor, wherein the tumors were composed of clear cells, leiomyomatous stroma, and adenomatous structures with apical snouting (described as resembling a “shark’s smile”) (Figure 10). The epithelial tumor cells were positive for EMA, CK7, CK20, AE1-AE3, CAM5.2, and vimentin. In this series of cases, no *VHL* mutation was identified.

Cases of clear cell papillary RCC with smooth muscle metaplasia of intratumoral stroma, also recently described as “RCC with angioleiomyoma-like proliferation” or “clear cell RCC with smooth muscle stroma”, share a significant degree of morphologic overlap with this entity^[82,83]. It is currently debated whether these two tumors are related, or perhaps even variants of the same tumor^[84-88]. Losses of chromosome 3 and 3p have been demonstrated in at least a subset of these tumors^[83]. Some studies report that these lesions have demonstrated abnormalities of chromosomes 3 and the *VHL* gene, in addition to abnormalities of chromosomes 1, 11, and 16^[83,85,86,88].

CONCLUSION

Our understanding of RCC continues to evolve. The

review of recent updates in selected tumors herein will hopefully serve as a useful prognostic and treatment guide for both the urologist and surgical pathologist, particularly in the era of personalized medicine.

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Etiology of non-traumatic acute abdomen in pediatric emergency departments

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Abstract

Acute abdominal pain is a common complaint in pediatric emergency departments. A complete evaluation is the key factor approaching the disease and should include the patient's age, any trauma history, the onset and chronicity of the pain, the related symptoms and a detailed physical examination. The aim of this review article is to provide some information for physicians in pediatric emergency departments, with the age factors and several causes of non-traumatic acute abdominal pain. The leading causes of acute abdominal pain are divided into four age groups: infants younger than 2 years old, children 2 to 5, children 5 to 12, and children older than 12 years old. We review the information about acute appendicitis, intussusception, Henoch-Schönlein purpura, infection, Meckel's diverticulum and mesenteric adenitis. In conclusion, the etiologies of acute abdomen in children admitted to the emer-

gency department vary depending on age. A complete history and detailed physical examination, as well as abdominal imaging examinations, could provide useful information for physicians in the emergency department to narrow the differential diagnosis of abdominal emergencies and give a timely treatment.

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Key words: Abdominal pain; Non-traumatic acute abdominal pain

Core tip: The mini review provides the essential information for physicians in pediatric emergency departments, mainly focused on the clinical diagnosis in different age groups and on several major causes of acute abdominal pain in children.

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INTRODUCTION

A common complaint in pediatric emergency departments (ED), abdominal pain is sometimes hard to assess in ill children due to the variation of pain degree, the difficulty in describing it, and being localized to the abdomen. Although most children with abdominal pain have a self-limiting course, some critical medical and surgical emergencies may occur in the ED. The diverse etiologies include acute surgical disease, intra-abdominal medical disorders, extra-abdominal conditions, systemic illness and, commonly, functional abdominal pain. A timely diagnosis is necessary for preventing further complications

Table 1 Differential diagnosis of acute abdominal pain by predominant age

Younger than 2 yr	2 to 5 yr	5 to 12 yr	Older than 12 yr
Infantile colic	Gastroenteritis	Gastroenteritis	Appendicitis
Gastroenteritis	Appendicitis	Appendicitis	Gastroenteritis
Constipation	Constipation	Constipation	Constipation
UTI	UTI	Functional pain	Dysmenorrhea
Intussusception	Intussusception	UTI	Mittelschmerz
Volvulus	Volvulus	Trauma	PID
Incarcerated hernia	Trauma	Pharyngitis	Threatened abortion
Hirschsprung's disease	Pharyngitis	Pneumonia	Ectopic pregnancy
	Sickle cell crisis	Sickle cell crisis	Ovarian/Testicular torsion
	HSP	HSP	
	Mesenteric adenitis	Mesenteric adenitis	

UTI: Urinary tract infection; PID: Pelvic inflammatory disease; HSP: Henoch-Schonlein purpura.

and, of course, the possible legal problems. This article reviews the non-traumatic causes of acute abdominal pain in pediatric EDs.

Theoretically, abdominal pain results from visceral, somatic and referred pain. Visceral pain results from the distension of a viscus stimulating nerves and generally presents with a dull, poorly localized pain over the epigastric, periumbilical or suprapubic midline area. The somatic pain comes from the stimulation on somatic nerves in the parietal peritoneum, muscle or skin unilateral to the spinal cord level from T6 to L1, presenting as well localized, intense and sharp. Referred pain is felt distant from the diseased organs, characterized by either a sharp, localized sensation or a vague ache. However, all the pains above can present clinically with agonizing pains, making it hard for the pediatrician to take a history and accurate physical examination.

EVALUATION

The evaluation should begin with a competent clinical evaluation, including the patient's age, any trauma history, the onset and chronicity of the pain, the related symptoms and a detailed physical examination. Abdominal imaging is not always required but is sometimes invaluable for narrowing the differential diagnosis or confirming a diagnosis. When assessing the child who develops abdominal pain without a history of trauma in the pediatric ED, the first priority is stabilization if the child is seriously ill. It should be emphasized that abdominal emergency may progress to a shock status and cardiorespiratory shock can present with acute abdominal pain. The second priority is to identify the child who requires immediate or potential surgical intervention, such as acute appendicitis or bowel perforation. The third priority is to diagnose any medical illness from among a large group of acute and chronic abdominal and extra-abdominal inflammatory disorders that require emergency nonoperative management.

During diagnosis, the factors of age, chronicity and any presence of obstruction, peritonitis or a mass should be carefully considered.

AGE

Age is a very important factor when assessing abdominal pain in children and the prevalence of each etiology varies greatly in children of different age groups (Table 1).

Infants younger than 2 years old

The infant with acute abdominal pain in this age group is very difficult for primary clinicians to evaluate because the only symptom may be inconsolable crying and finally lethargy. Bilious emesis is key information and must be taken seriously as a possibility of malrotation with volvulus. A contrast study of the upper gastrointestinal tract is necessary if no other cause is evident. The history taken should include the bowel movement pattern, presence of fever or diarrhea or even currant jelly stool, amount of vomiting and the timing, the sequence of pain and vomiting, and the presence of a productive cough.

Paralytic ileus, manifesting clinically with distension and absent bowel sounds, often accompanies surgical conditions, sepsis and infectious enterocolitis and should be closely followed up. An incarcerated hernia and intussusception are the two most common causes of bowel obstruction in this age range. Abdominal imaging could provide useful evidence of obstruction or perforation signs and any signs of partial or complete obstruction with peritonitis may indicate a perforated viscus from intussusceptions, volvulus or occasionally appendicitis or Hirschsprung's disease.

Infants with recurrent or chronic abdominal pain in this age group may not have any symptoms. The differential diagnosis includes recurrent intussusceptions, malrotation with intermittent volvulus, milk allergy syndrome and various malabsorptive diseases, such as lactase deficiency. Abdominal sonography should be arranged for any irritably crying infants or infants with lethargy for any evidence of intussusception. Reduction with air or barium is also indicated in cases of suspected intussusceptions which cannot be clearly and directly revealed by ultrasound. Abdominal computed tomography (CT) with contrast is indicated during the process of evaluation when clinicians are suspicious of serious

morbidity, such as complex abdominal masses and fluid accumulation.

Children 2 to 5 years old

Common causes of acute abdominal pain in this age group include inflammatory processes such as gastroenteritis and urinary tract infection (UTI). Preschool children may be able to verbally describe the types of abdominal pain and localize the site of pain. Related histories should be taken seriously. Some associated symptoms are helpful in the differential diagnosis, such as that lower gastrointestinal (LGI) bleeding may indicate infectious enterocolitis, intussusceptions, Meckel's diverticulum or inflammatory bowel disease *etc.* and extra-abdominal symptoms such as productive cough and pyrexia may be attributed to lobar pneumonia. A diabetic child with acute abdominal pain may be considered as having diabetes ketoacidosis. The important surgical causes of children with abdominal pain in this age group include acute appendicitis, intussusception and malrotation. Clinically ill children with abdominal pain may suffer from life-threatening diseases or some uncommon etiologies. Physical examinations of such patients may appear as jaundice (hepatitis, hemolytic anemia), rash or arthritis (anaphylactoid purpura), or cardiac murmurs (myocarditis). Moreover, chronic constipation starts to increase in frequency in this age group.

Right lower quadrant (RLQ) tenderness, especially persistent pain over here, should be always considered for the probability of acute appendicitis. The most specific finding of an abdominal plain film is the presence of a calcified appendicolith; however, this is only present in a minority of patients ($< 10\%$)^[1,2]. Besides, localized bowel obstruction and obliteration of the psoas shadow may be found in cases of acute appendicitis. Abdominal sonography should also be performed over the entire abdomen, including the pelvis area, to exclude any probability of ovarian torsion which is rarely noted but actually presents in female patients of this age group.

Children 5 to 12 years old

In this age group, nonorganic or psychogenic illness, or functional abdominal pain start to increase as causes of acute abdominal pain. The leading organic causes are still inflammatory processes, including gastroenteritis, appendicitis and UTI. If intussusception presents in this age group, a leading point, such as mesenteric adenitis, lymphoma, polyp and anaphylactoid purpura, should be sought for and abdominal ultrasound and CT may be helpful for clinicians to identify the leading points.

The description of abdominal pain is generally reliable in children in this age range. In clinical presentations, the presence of fever may come from infectious causes; diarrhea may be caused by infectious colitis, IBD from an appendiceal abscess irritating the bowel, urinary frequency and dysuria may increase the possibility of UTI. The clinical history of abdominal pain, beginning from the periumbilical area first and migrating to the

RLQ of the abdomen after several to 24 h, may commonly present in older children suspected of having acute appendicitis.

Clinical presentations of functional abdominal disorders are generally episodic periumbilical, rarely occur during sleep, have no particular associations with eating and activity and are not of organic causes. Although a worrisome patient and parents may search for definite causes of recurrent abdominal pain, abdominal CT rarely helps. However, the premise is that the diagnosis of functional abdominal pain should be made through complete history, physical examination and even whole abdominal and pelvis ultrasound scan. Of course, if the abdominal pain still presents without improving after a period of light diet or no oral intake, further survey should be carried out, *e.g.* abdominal CT.

Children older than 12 years old

The history and physical examination of acute abdominal pain should be taken carefully, especially for female patients. Complete history taking should involve menstrual history and sexual activity, although it is often hard to ascertain.

Acute pain with peritonitis in adolescents usually results from acute appendicitis. In addition, the differential diagnosis should include testicular or ovary torsion and for females PID and ectopic pregnancy should be considered. Acute abdominal pain without peritoneal signs in males often results from gastroenteritis or a viral syndrome, whereas in females it may often be attributed to UTI or pyelonephritis.

In the ED, postmenarchal girls with abdominal pain should have a pregnancy test when pregnancy cannot be excluded. Ultrasound is often helpful to check the gestational sac and evaluate the condition of adnexa. Especially for the female patient with RLQ pain, sonography with color Doppler is helpful for differentiating acute ovarian torsion from appendicitis and may also be helpful for assessing ovary viability. Besides, some experts have suggested that ovarian cysts greater than 5 centimeters rarely cause ovarian torsion and most cases of ovarian torsion are secondary to adnexal pathology, such as ovarian tumors or cysts, and torsion of normal adnexa is less common.

ETIOLOGIES

The diverse etiologies include acute surgical disease, intra-abdominal medical ailments, extra-abdominal conditions, systemic illness and, commonly, functional abdominal pain. We review five non-traumatic causes of acute abdominal pain in the pediatric ED, including acute appendicitis, intussusception, Henoch-Schönlein purpura (HSP), infection, Meckel's diverticulum and mesenteric adenitis.

Acute appendicitis

Acute appendicitis is the most common condition re-



Figure 1 A nodular calcified appendicolith (arrow) in the right lower abdominal quadrant.

quiring emergency abdominal surgery in children and is ultimately diagnosed in 1% to 8% of children presenting to the pediatric ED with acute abdominal pain^[2,3]. Clinically, the diagnosis of acute appendicitis is often based on a brief history, physical examination and laboratory findings. Common clinical appearances of acute appendicitis in children include migration of abdominal pain, RLQ tenderness, rebound pain, muscle guarding and vomiting. Very young children may reveal diarrhea as a presenting symptom. The classic constellation of symptoms in acute appendicitis is periumbilical pain followed by nausea, right lower quadrant pain, vomiting and fever. Unfortunately, this sequence is present in only less than one-third of all pediatric patients and is less common in children younger than 5 years of age^[4]. Appendicitis may be missed at initial clinical examination in 28% to 57% of children aged 12 years or younger and in nearly 100% of children under 2 years old. Because of the difficulty in evaluating young children with abdominal pain, perforation rates for appendicitis are higher than in the general adult population (30% to 65%)^[3,5].

No laboratory test is both 100% sensitive and 100% specific for diagnosing appendicitis. White blood cell count may be helpful in the diagnosis of appendicitis and the presence of elevated serum C-reactive protein (CRP) also has been studied as a biomarker for appendicitis. Moreover, the changes after short-term observation in percentage neutrophil counts on the first day of the onset of patients' symptoms (day 1) and CRP on day 2 and day 3 are relatively specific for diagnosing acute appendicitis and may be used to exclude other inflammatory conditions in the abdomen^[6].

Plain film abdominal series are often obtained in children suspected of having acute appendicitis and the most specific finding is calcified appendicolith. Appendicoliths are present only in approximately 10% of true cases with appendicitis (Figure 1)^[1,2,4].

Diagnostic imaging, including graded-compression US and helical CT, play an increasing role in the prompt and accurate diagnosis of acute appendicitis in children. The principal advantages of graded-compression US are its lower cost, lack of ionizing radiation and ability to

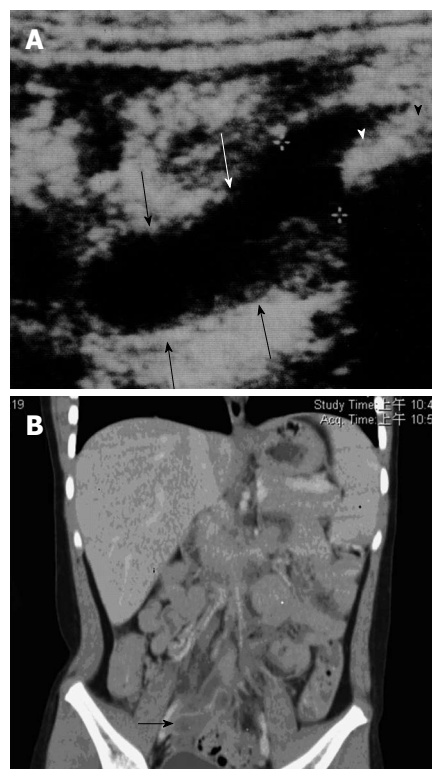


Figure 2 Acute appendicitis. A: A blind-ending, non-compressible tubular structure (arrows); an echogenic appendicolith with an acoustic shadow over tip (arrowheads); B: An enlargement of whole diameter of the appendix (arrows) with enhancement and thickening of the appendiceal wall associated with intraluminal fluid collections.

delineate gynecological disease. However, an important limitation of graded-compression US for the diagnosis of acute appendicitis is that the diagnostic accuracy is highly dependent on the skill of operators, as evidenced by the great variability in its reported diagnostic sensitivity and specificity for this condition. The reported sensitivity of US in children has ranged from 44% to 94% and the specificity has ranged from 47% to 95%^[3]. An inflamed appendix is usually aperistaltic, difficult to compress and measures ≥ 6 mm in diameter (Figure 2A). It is important for US performers to visualize the entire appendix to avoid a false-negative reading because sometimes only the distal tip of the appendix is inflamed. A periappendiceal fluid accumulation may indicate an early perforation but may simply result from inflammation.

CT has become the test of choice for surgeons when ultrasonography fails to give a definitive diagnosis. The reported sensitivity of CT for the diagnosis of acute appendicitis in children has ranged from 87% to 100% and the specificity has ranged from 89% to 98%^[4,5]. Direct signs of CT for acute appendicitis include an enlarged appendix (> 7 -mm transverse diameter), a nonopacified appendiceal lumen and significant wall enhancement with intravenous contrast material administration (Figure 2B). Secondary signs of acute appendicitis include periappendiceal fat stranding or free fluid in the RLQ of the abdomen or pelvis. Focal cecal wall thickening adjacent to an inflamed appendix has been given specific names:

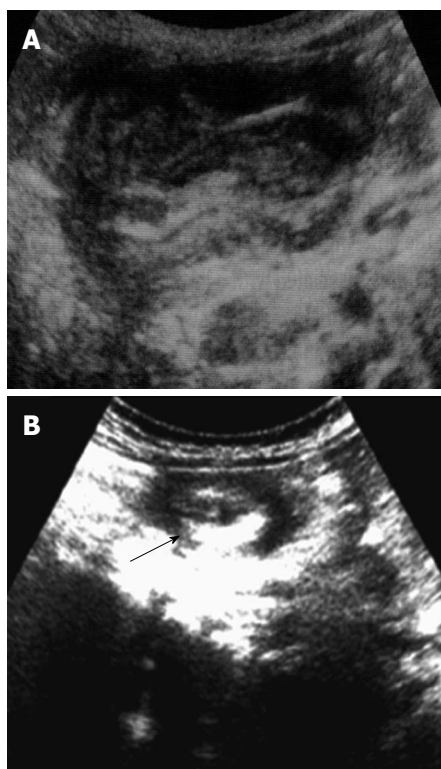


Figure 3 “Pseudokidney” sign (A) and “target sign (arrow)” (B) on ultrasonography.

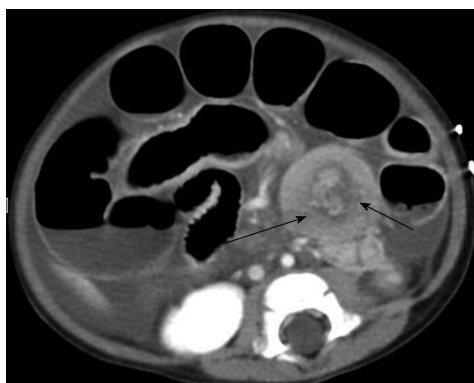


Figure 4 A concentric ring of the ileum (arrows) from ileo-colic intussusception.

focal cecal apical thickening, the so-called arrowhead sign which involves focal thickening of the cecum pointing toward an inflamed appendix, or the so called cecal bar in which an appendicolith is separated from a contrast material-filled cecum by an inflammatory process at the base of the appendix.

CT has dramatically improved our ability to detect appendicitis and its complications. It has led to improved patient outcomes and lessened the number of unnecessary surgeries. Magnetic resonance imaging (MRI) is also superior in its ability to diagnose appendicitis in children but it may not be available or practical.

When the diagnosis of appendicitis is made, preparing the child for the operating room is essential. If there

are clinical or radiological signs of perforation, antibiotics with gram negative and anaerobic coverage should be started in the ED.

Intussusception

Intussusception, defined as an invagination of the proximal portion of the bowel into an adjacent distal bowel segment, is the second most common cause of intestinal obstruction in infants. It appears predominantly in males and the most common type is ileocolic invagination. Intussusception is seen most frequently between the ages of 3 mo and 5 years, with 60% of cases occurring in the first year and a peak incidence at 6 to 11 mo of age. In children younger than 2 years of age, a pathological lead point is found in less than 5% to 10% of cases^[7,8]. However, pathological lead points are more common in older children, with Meckel’s diverticulum being the most common. Other causes of lead points are submucosal hemorrhage from Henoch-Scholein purpura, lymphomas and intestinal polyp. The classic triad of intussusception, including intermittent colicky abdominal pain, vomiting and bloody mucus stools (currant jelly stools) is encountered in only 20% to 40% of cases^[7]. At least two of these findings present in approximately 60% of patients.

A palpable sausage-like abdominal mass in the right upper or lower quadrant may be found but it is difficult to perform in crying infants.

Plain abdominal radiographs are usually the initial studies in children with possible intussusception. Moreover, they are neither sensitive nor specific for intussusception. Plain films may show a variety of abnormalities, including a visible abdominal mass, abnormal distribution of gas and fecal contents, air fluid levels and dilated loops of the small intestine. A “target sign” on plain film consists of concentric circles of fat density similar in appearance to a doughnut visualized to the right of the spine. Ultrasonography is useful for diagnosing intussusception and the classic findings, including the “target sign”, a single hypoechoic ring with a hyperechoic center and the “pseudokidney” sign, superimposed hypo and hyperechoic areas representing the edematous walls of the intussusceptum and layers of compressed mucosa (Figure 3)^[7].

CT may be considered in highly suspected bowel obstruction or surgical emergencies when US cannot determine a definite cause in children. However, CT would not be performed routinely in patients with suspected intussusception. The findings of intussusception on CT reveal bowel loops containing alternating high and low rings of attenuation and a dilated proximal small bowel with air-fluid levels (Figure 4).

Barium enema is the gold standard study for the diagnosis of intussusception and is also a therapy. However, air-contrast enema has been used for many years in some countries and has been shown to be as effective as barium enema for intussusception. Air contrast decreases the risks of chemical peritonitis caused by

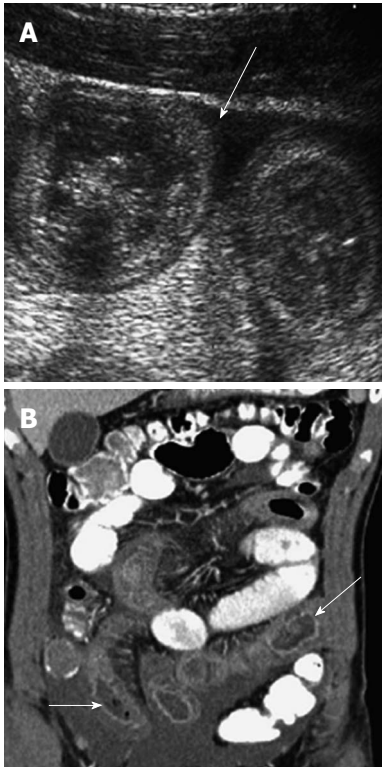


Figure 5 Henoch-Schonlein purpura. A: Sagittal ultrasound image shows more moderate wall thickening of small bowel with ascites; B: Coronal computed tomography shows long segments of thickened, enhancing, fluid filled small bowel (arrows).

perforation with barium enema in this disease. An ileo-ileac type of intussusception can be much harder to diagnose and is much harder to be released by air or barium reduction. Not every child with intussusception should undergo bowel reduction by enema. Clinical signs of peritonitis, bowel perforation and hypovolemic shock are clear contraindications to enemas. Relative contraindications to enemas include prolonged symptoms (≥ 24 h), evidence of obstruction, such as air fluid levels on plain abdominal films, and ultrasonography findings of intestinal ischemia or trapped fluid. Even in well-selected patients, enemas may cause the reduction of necrotic bowel, perforation and sepsis. After a successful reduction, the child should be admitted for observation. A small percentage of patients (0.5% to 15%) may have a recurrence of intussusception, usually within 24 h but sometimes after days or weeks. Even after reduction by laparotomy, the recurrence rate is approximately 2% to 5%^[8,9].

HSP

HSP is the most common vasculitis of childhood and is an acute, systemic, self-limited, small-vessel vasculitis usually seen in otherwise healthy children. The incidence of HSP is reported as ranging from 6 to 22 cases per 100000 children in different populations. Although it most often affects young children, it may develop at any age. Most HSP occurs between 3 and 5 years of age and

ninety percent of HSP patients are under 10 years of age. It is thought to occur more often in female children, although some have found a male predominance or both genders to be equally affected^[5]. The etiology of HSP remains unknown, although many antigens, such as infective agents, vaccinations, drugs and insect bites are suspected. In 1990, the American College of Rheumatology published diagnostic criteria for HSP, including: (1) palpable purpura, that is slightly raised hemorrhagic skin lesions not related to thrombocytopenia; (2) age, 20 years or younger at onset of first symptoms of the disease; (3) bowel angina, that is diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea; and (4) wall granulocytes on biopsy, that is histological changes showing granulocytes in the walls of arterioles or venules. A patient is diagnosed with HSP if at least two of the four criteria are present; this yields a sensitivity of 87.1% and a specificity of 87.7%^[10].

The disease usually lasts for 1 to 4 wk. The predominant cutaneous finding of HSP is painless, palpable purpura. In more than 70% of patients, palpable purpura alone or purpura associated with abdominal and/or joint pain is the first sign. Abdominal pain is the most common gastrointestinal symptom, affecting two-thirds of children. The pain is usually localized to the periumbilical or epigastric region and described as blunt in nature. Bowel wall thickening caused by vasculitis-associated ischemia has a mean thickness of 9 mm and involves longer segments than bowel thickening associated with hematoma (Figure 5)^[11].

Treatment for children with HSP is mostly supportive, relieving associated arthralgia and abdominal pain. In patients with normal renal function, therapy should focus on the maintenance of hydration, nutrition and electrolyte balance. Most agree that analgesics and/or nonsteroidal anti-inflammatory agents should be used for the control of arthralgia and inflammation in children. Gastrointestinal involvement has been reported to occur in approximately 50% to 75% of patients with HSP^[10,11]. Severe abdominal pain that is unresponsive to conventional treatments may respond dramatically to a trial of intravenous corticosteroids. Systemic steroids, such as oral prednisolone or pulsed intravenous methylprednisolone, may be effective in children with massive gastrointestinal hemorrhage and ischemic bowel.

Infections

AGE is the most common gastrointestinal inflammatory process in children. The cause is usually viral and rotavirus is the most common in children. Vomiting usually precedes the diarrhea by as much as 12 to 24 h. A low grade fever may or may not be associated with AGE. Examination of the abdomen usually reveals a nondistended soft abdomen with no localized tenderness (may be diffusely, mildly tender) and usually there is minimal to no guarding. AGE may cause an ileus in severe cases^[12]. Viral diarrhea will target the small bowel, resulting

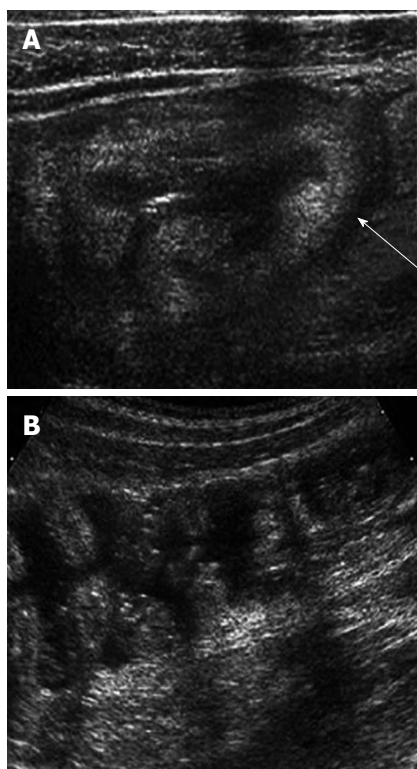


Figure 6 Bacterial enteritis. A: Ultrasound showing marked wall thickening of the cecum (arrow) in a child with right lower quadrant pain, which returned to normal; B: 4 d later. Stool cultures were positive for enterohemorrhagic *Escherichia coli*.

in mid-abdominal cramping and large volumes of watery diarrhea. Bacterial diarrhea will target the large bowel, resulting in lower abdominal pain and smaller volumes of bloody mucoid diarrhea. Other diagnoses need to be considered when a child presents with vomiting, such as urinary tract infection, appendicitis, inborn errors of metabolism or volvulus, especially in very young infants, diabetic ketoacidosis and hemolytic uremic syndrome (the appearance of illness in children usually is preceded by diarrhea).

Plain radiographs are often normal but may show mild dilatation of small and large bowel. US is helpful in gastroenteritis to exclude other emergencies such as acute appendicitis or intussusception. US may show fluid-filled hyperperistaltic loops of bowel with little or no wall thickening in patients with gastroenteritis (Figure 6). However, abdominal CT scan is seldom used in patients with AGE except for cases with acute abdomen caused by AGE, such as septic peritonitis caused by bowel perforation.

Meckel's diverticulum

Meckel's diverticulum is defined as incomplete closure of the intestinal end of the omphalomesenteric duct that disappears normally by the seventh week of gestation. It is a true diverticulum, containing all layers of the bowel wall, and up to 60% of these diverticula contain heterotopic gastric tissue and heterotopic pancreatic, en-



Figure 7 Meckel's diverticulum. A: Small-bowel obstruction shown on computed tomography (CT) in an 18-year-old boy with pathologically proven Meckel's diverticulum; B: CT image in an 11-year-old girl shows intussusception (arrows) as a bowel loop containing alternating rings of attenuation. Note dilated proximal small bowel (D) and collapsed terminal ileum (arrowheads).

dometrial and duodenal mucosa^[13,14]. It is the most common congenital gastrointestinal tract anomaly and affects 2% of the population. In addition, it is more common in males than females, with a male-to-female ratio of two to four and with the lifetime complication rate of about 4%^[14]. The features of Meckel's diverticulum are commonly described by "the rule of 2s": it is present in approximately 2% of the population, with only 2% of affected patients becoming symptomatic. Forty-five percent of symptomatic patients are under 2 years of age. The most common location is 40 to 100 centimeters from the ileocecal valve and the diverticulum typically is about 5 cm long^[15].

The classical presentation of Meckel's diverticulum is painless or minimally painful rectal bleeding. Such painless bleeding is a result of heterotopic gastric tissue in the diverticulum or the adjacent ileum. Abdominal pain, distension and vomiting may occur if obstruction has occurred and the clinical presentations may mimic appendicitis or diverticulitis. Meckel's diverticulum may also ulcerate and perforate, presenting as a bowel perforation, or act as a lead point, resulting in intussusception.

Abdominal films may show signs of obstruction, such as dilated loops of bowel or a paucity of bowel gas. A scan of Meckel's diverticulum can detect the presence of gastric mucosa within the diverticulum with up to 85% accuracy. Meckel's diverticulum may show one

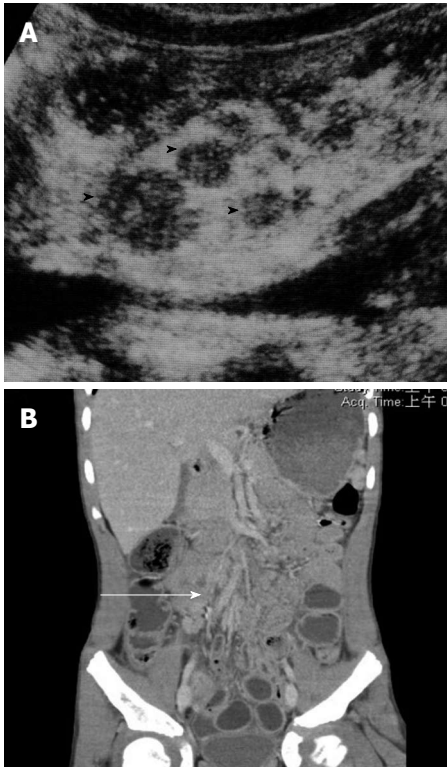


Figure 8 Mesenteric adenitis. A: Ultrasound shows multiple enlarged lymph nodes (arrowheads) at the base of mesentery, anterior to the inferior vena cava; B: Computed tomography of the abdomen showing clustering of mesenteric lymph nodes with largest diameter of about 11.2 mm (black arrow) and thickening of the bowel wall of terminal ileum.

of following patterns of presentations on CT: isolated small-bowel obstruction; intussusception with small-bowel obstruction; or a cystic mass with surrounding inflammatory changes (Figure 7)^[15]. However, calcifications are not a common feature of CT for the diagnosis of Meckel's diverticulum.

A Tc-99m scan is the gold standard but is a less-sensitive tool for making a diagnosis preoperatively. Repeated Tc-99m scans in highly suspected cases and RBC scans in continuous bleeding patients improves the detection rate.

Mesenteric adenitis

In 1926, Wilensky and Hahn classified mesenteric lymphadenitis into four groups: Group I: Simple mesenteric lymphadenitis; Group II: Suppurative mesenteric lymphadenitis; Group III: Tuberculous mesenteric lymphadenitis; and Group IV: Terminal stage of mesenteric lymphadenitis (calcification). It can, however, cause severe consequences and may at times be fatal. The severe form of this disease with suppuration, abscess formation and peritonitis is rare. Mesenteric adenitis is usually a self-limiting clinical condition characterized by fever, nausea, vomiting, diarrhea, diffuse or right lower quadrant abdominal pain and tenderness, and frequent leukocytosis. The causes of mesenteric adenitis have been reported to be viral, bacterial and mycobacterial infections. Numerous bacteria have been demonstrated to be involved in mesenteric nodes: *B. coli*, *staphylococci*, *streptococci*, *pneumo-*

cocci, *typhoid*, *paratyphoid* and *tubercle bacilli*.

Due to the clinical presentation of the abdomen, it could be difficult to discriminate this condition from other acute abdominal diseases such as acute appendicitis. Imaging examinations, such as an abdominal CT scan, can be a valuable tool in accurately diagnosing mesenteric adenitis and can help to avoid normal appendectomy due to the clinical misdiagnosis of appendicitis. Findings of mesenteric adenitis on CT include: (1) cluster of > 3 lymph nodes in RLQ mesentery with > 5 mm in short axis diameter; (2) normal appendix; (3) ileal wall thickening; and (4) colonic wall thickening (Figure 8)^[16,17].

CONCLUSION

The etiologies of acute abdomen in children admitted to the emergency department vary depending on the age. A complete history and detailed physical examination, as well as abdominal imaging examinations, could provide useful information for physicians in the emergency department in order to narrow the differential diagnosis of abdominal emergencies and give a timely treatment.

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Midline synovial and ganglion cysts causing neurogenic claudication

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Abstract

Typically situated posterolateral in the spinal canal, intraspinal facet cysts often cause radicular symptoms. Rarely, the midline location of these synovial or ganglion cysts may cause thecal sac compression leading to neurogenic claudication or cauda equina syndrome. This article summarizes the clinical presentation, radiographic appearance, and management of three intraspinal, midline facet cysts. Three patients with symptomatic midline intraspinal facet cysts were retrospectively reviewed. Documented clinical visits, operative notes, histopathology reports, and imaging findings were investigated for each patient. One patient presented with neurogenic claudication while two patients developed partial, subacute cauda equina syndrome. All 3 patients initially responded favorably to lumbar decompression and midline cyst resection; however, one patient required surgical stabilization 8 mo later. Following the three case presentations, we performed a thorough literature search in order to identify articles describing

intraspinal cystic lesions in lateral or midline locations. Midline intraspinal facet cysts represent an uncommon cause of lumbar stenosis and thecal sac compression. Such entities should enter the differential diagnosis of midline posterior cystic lesions. Midline cysts causing thecal sac compression respond favorably to lumbar surgical decompression and cyst resection. Though laminectomy is a commonly performed operation, stabilization may be required in cases of spondylolisthesis or instability.

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Key words: Midline; Synovial; Ganglion; Intraspinal; Cyst; Neurogenic; Claudication; Laminectomy; Facet

Core tip: Midline, intraspinal cysts arise from facet joint degeneration. The lesions represent an important and often over-looked cause of back pain and other neurological symptoms. Radiographic identification of the fluid-filled sacs is particularly important in the setting of cauda equina syndrome, in which immediate surgical intervention is required in order to address the compressive lesion. Although the treatment of choice is a spinal decompression and resection, posterior fusions may prevent cyst recurrence.

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INTRODUCTION

Intraspinal facet cysts, also known as synovial and/or ganglion cysts, typically reside adjacent to the facet joints

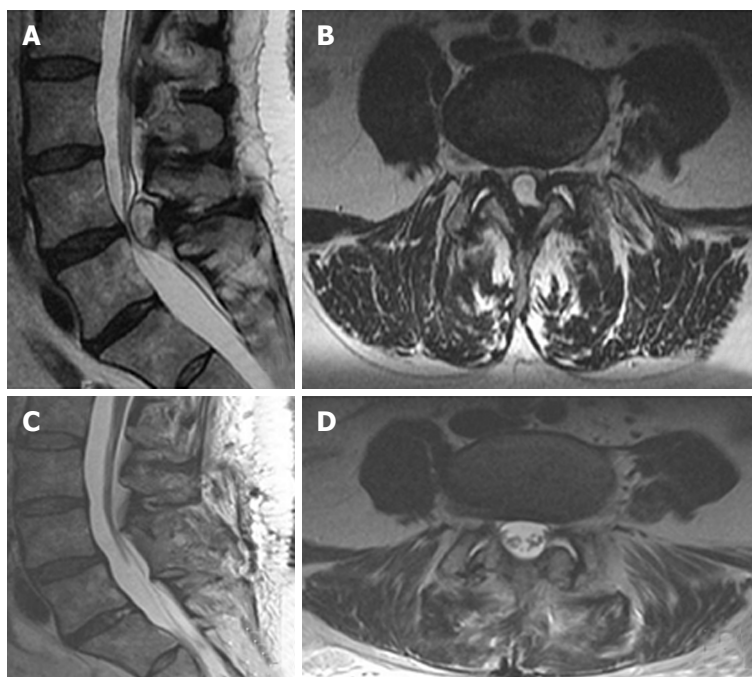


Figure 1 T2-weighted imaging of case 2. A, B: In the preoperative images, sagittal (A) and axial (B) T2 weighted magnetic resonance imaging displays a large intraspinal cystic lesion at the L4-5 level causing stenosis and thecal sac compression. The cystic lesion appears to have an eccentric component extending towards the left facet joint; C, D: Post-operative imaging following decompressive laminectomy and cyst excision. Bilateral laminectomies at L4-5 and cyst resection provide adequate decompression of the dorsal thecal sac and cauda equina, as shown in sagittal (C) and axial (D) images.

and may cause radicular symptoms due to nerve root compression and foraminal compromise. Representing a zygapophyseal joint, facet joints lie enclosed within a capsule lined by synovial epithelium^[1]. Breakdown of this articular lining or encapsulated accumulation of fluid outside of the facet joint may lead to pathologic cyst formation. Synovial and ganglion cysts typically occur in the lower lumbar region, frequently the site of degenerative changes and dynamic instability^[1-5]. They are found in the postero-lateral region of the canal, consistent with their source of pathology. Lined with cuboidal epithelium and filled with synovial fluid, synovial cysts frequently retain communication with their facet joint of origin^[4,6]. In contrast, ganglion cysts lack synovial lining and structural communication to facet joints^[3,6]. Ganglion cysts contain a collagenous or fibrous wall encircling gelatinous or myxoid substance^[4,7-9]. Clinically, however, both terms are used interchangeably to describe intraspinal facet cysts or juxtafacet cysts^[2-4,7,9]. This article presents 3 unique cases of midline intraspinal facet cysts causing significant lumbar stenosis and symptomatic thecal sac compression.

Three patients with symptomatic midline intraspinal facet cysts were reviewed. Clinical visits, operative notes, histopathology reports, and imaging findings were investigated for each patient. A thorough literature search was used to identify case reports or series describing intraspinal cystic lesions.

CASE REPORTS

Case 1

A 65-year-old woman presented with a 1-mo history of bilateral buttock pain and lower extremity weakness. The patient had full strength in her upper extremities and 4/5 strength in her proximal lower extremities. Magnetic resonance imaging (MRI) showed a grade 1 anterior listhesis

of L4 on L5 as well as a well-circumscribed midline synovial cyst posterior to the thecal sac at the L4-L5 level; the hyperintense lesion on T2 weighted sequences measured approximately 8 mm × 8 mm × 10 mm. Differential diagnosis includes perineural (Tarlov) cysts, arachnoid cysts, and migrated disc fragment. The patient underwent bilateral laminectomies at L4-L5, bilateral foraminotomies, medial facetectomies, and cyst resection. Smaller cysts were encountered at the bilateral L4-L5 and the right L5-S1 facet joints. Histologic sections of the excised midline cyst revealed fragments of dense connective tissue with overlying synovium. The patient had an uncomplicated post-operative course and remained asymptomatic at 15-mo follow up.

Case 2

A 57-year-old woman presented with a 3-mo history of lower back, left lower extremity radiculopathy in the L5 and S1 distributions, and urinary incontinence. She exhibited full strength in the bilateral upper and lower extremities, with an unremarkable sensory exam. MRI revealed a large midline, well-circumscribed cystic lesion at the L4-L5 level, causing significant compression of the thecal sac and cauda equine; however, the images were unremarkable for spinal instability (Figure 1A and B). The patient underwent L4-L5 bilateral decompressive laminectomies with bilateral foraminotomies and cyst resection. Intraoperatively, a large intraspinal extradural cystic lesion appeared centrally, exerting significant compression on the thecal sac. While gross inspection revealed a cystic lesion containing clear viscous fluid, absence of epithelium lining the cystic cavity microscopic examination confirmed the final diagnosis of a ganglion cyst (Figure 2). The patient did well post-operatively. Imaging confirmed total cyst resection and adequate decompression of the thecal sac (Figure 1C and D). The patient

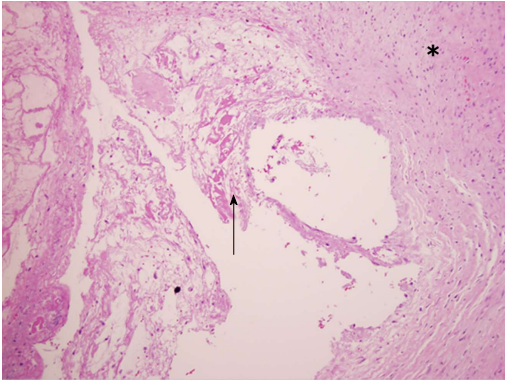


Figure 2 Case 2, pathological findings of midline ganglion cyst (hematoxylin eosin staining, $\times 400$). Photomicrograph (original magnification $\times 400$) reveals proteinaceous material (arrow) surrounded by dense fibro-connective tissue (asterisk), without the presence of synovial epithelium. These findings confirm the diagnosis of a ganglion cyst.

reported improvement in all symptoms, including urinary incontinence, at her latest follow-up 17-mo post-operatively.

Case 3

A 70-year-old woman presented with a 1-mo history of bilateral buttock and lower extremity pain. The patient denied bowel or bladder incontinence. On examination, she was neurologically stable. MRI revealed multilevel lumbar spondylosis as well as a large multiseptated cystic lesion appearing centrally and dorsolaterally in the L4-L5 extra-dural space with subsequent severe canal stenosis, without foraminal compromise. The patient underwent with bilateral L3-L5 laminectomies, medial facetectomies, and cyst resection. Gross inspection of the excised midline lesion revealed a cystic structure. Histologic examination of specimen permanent sections was consistent with a ganglion cyst. The patient had an uncomplicated post-operative course. A post-operative MRI demonstrated complete removal of the ganglion cyst with posterior decompression from L3-L5. The patient remained well until 3 mo after surgery when she developed low back, right buttock, and right anterior thigh pain. Epidural and facet injections were tried without symptomatic relief. Given the findings of junctional stenosis at L2 and mechanical instability suggested by imaging and clinical evaluation, the patient underwent L2-L5 bilateral, instrumented fusion eight months later. At last follow-up, the patient was completely asymptomatic (total follow-up period: 15 mo).

DISCUSSION

Juxtafacet cysts may reside deep or superficial to the posterior elements of the vertebral canal, or have a bi-lobed architecture existing in both compartments^[7]. Intraspinous facet cysts usually neighbor degenerated facet joints in the postero-lateral epidural space^[1-3,5,7,10]. The cysts most frequently occur at L4-L5, the lumbar level characterized by greatest mobility and prevalence of degenerative disease^[4,7,9,11-13].

Imaging characteristics of intraspinal facet cysts vary

depending on cyst content. Computed tomography (CT) typically portrays a well circumscribed hypodense lesion with hyperdense rim due to calcification^[9,10]. MRI typically shows hyperintense cystic extradural lesions. The cysts appear centrally iso- to hyperintense compared to cerebrospinal fluid (CSF) and iso- to hypointense compared to soft tissue on T1 weighted sequences^[1,4,6,7,10,14]. Facet arthropathy and degenerative spondylosis frequently accompany juxtafacet cysts on CT or MRI^[2,3,7,9,10].

Clinically indistinguishable, histopathologic analysis distinguishes synovial from ganglion cysts. The presence of cuboidal synovial epithelium encircling synovial fluid corroborates the diagnosis of a synovial cyst. In contrast, the absence of synovial epithelial lining or the presence of chronic fibrotic tissue along the cavity wall supports the diagnosis of a ganglion cyst^[4,7,8,11].

Several mechanisms have been described to explain the development of juxtafacet cysts. Ganglion cysts most likely result from cystic or myxoid degeneration of connective tissue. The most likely mechanism of synovial cyst formation involves degenerative articular changes due to abnormal and increased motion at the facet joint^[4,6,9,11]. Several studies have described associations between spinal instability or degenerative changes, reflected by lumbar spondylosis or spondylolisthesis, and intraspinal facet cysts^[11,12]. Acquired defects in the joint capsule allow protrusion of synovial epithelium and cyst formation adjacent to the joint; hence, the communication between degenerated facet joints and synovial cysts found in many cases^[4,9]. Furthermore, juxtafacet cysts occur most frequently at the level of greatest motion and prevalence of degenerative changes, L4-5, followed by L5-S1 and L3-4^[4,9,11-13].

In the absence of neurologic deficits, symptomatic patients with intraspinal facet cysts may benefit from conservative management. Non-surgical treatments include activity restrictions, supportive bracing, oral analgesics or anti-inflammatories, physical therapy, and epidural or facet steroid injections^[7,11,12]. Minimally invasive procedures include percutaneous injection or cyst aspiration^[4,11,12]. However, failure of conservative measures has been widely documented by several clinical series^[6,10-12]. Standard surgical techniques include hemilaminotomy or laminectomy, foraminotomy, medial facetectomy, and cyst excision^[2,4,6,10-12].

Most clinical series demonstrate moderate to high rates of successful outcomes in patients undergoing decompressive surgery with juxtafacet cyst resection^[6,10,12]. Epstein reported good to excellent results in 58%-63% of patients undergoing decompressive surgery for synovial cysts and accompanying stenosis, with or without spondylolisthesis^[10]. Most other clinical series report similar or even higher rates of favorable outcomes^[10]. In their meta-analysis, Bydon *et al.*^[12] reported short-term post-operative resolution of back and lower extremity pain in above 90% of patients compiled. In prolonged follow-up, nearly 22% and 13% of patients reported recurrent back pain and radiculopathy, respectively. Delayed surgical complications include intraspinal facet cyst recurrence

and the development or progression of spinal mechanical instability^[11,12]. Static or dynamic imaging may reveal low grade spondylolisthesis or minimal instability in a minority of asymptomatic patients^[6].

In the present case series, one patient demonstrated clinical and radiographic evidence of post-operative spinal instability and required an instrumented fusion at 8 mo follow-up. Such outcomes speak to the role of spinal fusion as an adjunct to decompression and cyst excision given the likely role of facet joint hypermobility and degeneration in the pathophysiology of synovial cyst formation^[10-13]. While potentially improving mechanical back pain, concomitant spinal fusion may limit further destabilization and prevent cyst recurrence^[6,11-13]. Although current studies reflect the predominance of decompression and cyst excision without fusion in the majority (> 80%) of surgical cases for synovial cysts^[12], patients with clinical and radiographic evidence of post-operative spinal instability may benefit from concomitant surgical fixation and/or fusion^[6,10-12]. Some authors suggest that radiographic indications for pre-operative spinal instability, such as spondylolisthesis, are the strongest predictor for post-operative instability, especially after spinal decompression^[15-19]. However, patients without pre-operative spondylolisthesis may still develop post-operative spinal instability requiring a fusion, as demonstrated in case number three. Furthermore, same level cyst recurrence occurred in nearly 2% of patients, all following decompression and cyst resection alone. In contrast, cyst reformation did not occur in any patients following concomitant spinal fusion^[12]. These findings stress the importance of considering concomitant spinal fusion with decompression and synovial cyst excision.

Lessons learned from this case series is that despite their rare occurrence, midline synovial and ganglion cysts should be considered in the differential diagnosis of centrally located posterior extradural cysts. When causing symptomatic lumbar stenosis and thecal sac compression, midline synovial and ganglion cysts may require decompressive laminectomy and resection to relieve patients' symptoms and restore neurologic function. In the setting of baseline back pain or radiographically proven mechanical instability, concomitant spinal fusion may be considered. Following decompression and cyst excision alone, patients should be monitored closely for the progression or development of mechanical instability.

In this manuscript, we present a unique presentation of symptomatic, intraspinal cysts. Following the cyst recurrence, lumbar fusion may prevent long-term spinal instability or cyst recurrence. However, we do recognize that our manuscript is a limited case series of three patients. Larger cohorts are required to delineate the clinical outcomes in patients with midline synovial and ganglion cysts.

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preparing, and reviewing specimens sent from the operating room.

COMMENTS

Case characteristics

Three patients with symptomatic midline intraspinal facet cysts were retrospectively reviewed. Documented clinical visits, operative notes, histopathology reports, and imaging findings were investigated for each patient.

Clinical diagnosis

One patient presented with neurogenic claudication while two patients developed partial, subacute cauda equina syndrome.

Differential diagnosis

All 3 patients initially responded favorably to lumbar decompression and midline cyst resection; however, one patient required surgical stabilization 8 mo later.

Imaging diagnosis

Radiographic identification of the fluid-filled sacs is particularly important in the setting of cauda equina syndrome, in which immediate surgical intervention is required in order to address the compressive lesion.

Treatment

All 3 patients initially responded favorably to lumbar decompression and midline cyst resection; however, one patient required surgical stabilization 8 mo later.

Related reports

Some authors suggest that radiographic indications for pre-operative spinal instability, such as spondylolisthesis, are the strongest predictor for post-operative instability, especially after spinal decompression.

Experiences and lessons

The authors present a unique presentation of symptomatic, intraspinal cysts. Following the cyst recurrence, lumbar fusion may prevent long-term spinal instability or cyst recurrence.

Peer review

This manuscript illustrates a unique presentation, location, and management of intraspinal cysts. The article is well-written and does not require modifications.

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Tissue plasminogen activator *via* cross-collateralization for tandem internal carotid and middle cerebral artery occlusion

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cerebral artery occlusion; Intra-arterial tissue plasminogen activator; Carotid artery dissection

Core tip: Tandem internal carotid artery and middle cerebral artery occlusions secondary to carotid artery dissections are refractory to stand alone medical management and often result in poor outcomes in patients receiving systemic tissue plasminogen activator (tPA). Cervical carotid stent assisted endovascular thrombolysis is effective, but carries the risk of worsening the dissection and propagating further thromboembolic events. Avoidance of carotid occlusions and recanalization with intra-arterial tPA using cross-collateralization, may be an effective, alternative treatment for patients with tandem internal carotid artery and middle cerebral artery occlusions.

Bulsara KR, Ediriwickrema A, Pepper J, Robertson F, Aruny J, Schindler J. Tissue plasminogen activator *via* cross-collateralization for tandem internal carotid and middle cerebral artery occlusion. *World J Clin Cases* 2013; 1(9): 290-294 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i9/290.htm>
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Abstract

Tandem internal carotid and middle cerebral artery occlusion after carotid dissection predicts poor outcome after systemic thrombolysis. Current treatments include the use of endovascular carotid stenting, which carries with it a high risk of propagating further embolic events and worsening the dissection. New strategies for avoiding the aforementioned side-effects include recanalization using cross-collaterals for delivery of intra-lesional tissue plasminogen activator (tPA). We present two cases that provide further support for this novel approach. Both patients presented with a National Institute of Health Stroke Scale of 20, received intra-arterial tPA *via* cross-collateralization, and made full recoveries without the need for stenting.

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Key words: Tandem internal carotid artery and middle

INTRODUCTION

Dissection of the internal carotid artery (ICA) accounts for a significant proportion of ischemic stroke in young patients, representing up to a quarter of such cases^[1,2]. Lucas and colleagues illustrated that the underlying pathophysiology of carotid artery dissection ischemia is most often due to thrombus formation and secondary embolization^[3]. In many cases, this embolization can result in a tandem ICA and middle cerebral artery occlusion (TIM)^[4]. At presentation, patients with TIM occlusions usually have a similar clinical severity to those with isolated middle cerebral artery (MCA) obstruction. However, they have a lower chance of MCA recanalization

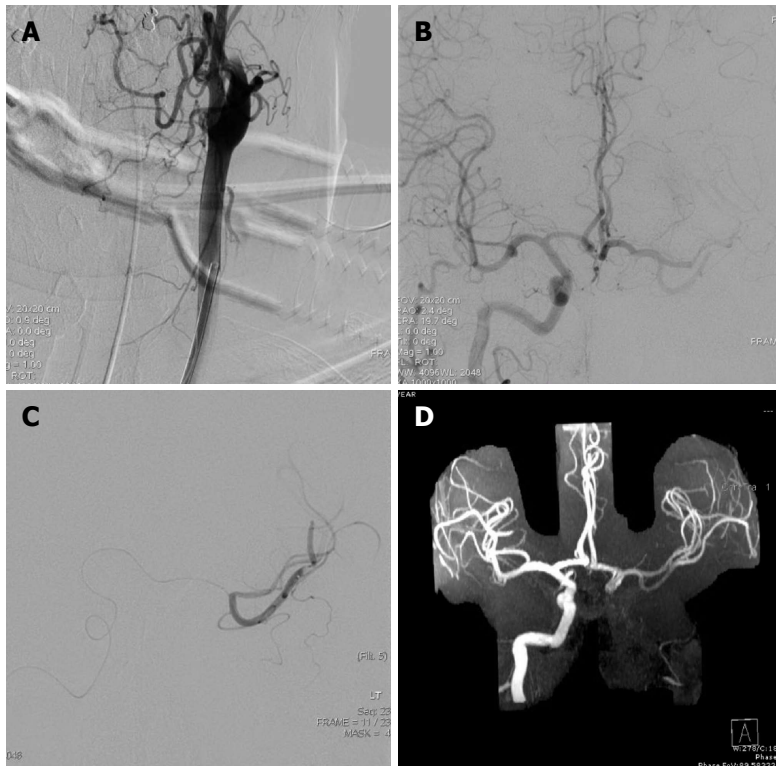


Figure 1 Pre and post intervention cerebral angiography. A: Left carotid occlusion from likely dissection; B: Cross filling of the left internal carotid artery distribution via right internal carotid artery injection. The left middle cerebral artery (MCA) distribution does not completely opacify due to thrombus; C: Microcatheter crossing into the left MCA via the anterior communicating artery. Intra-arterial tissue plasminogen activator was delivered; D: Magnetic resonance angiography performed 10 h later confirms patency of the left MCA branches correlating with the patient's resolution of clinical symptoms.

after systemic tissue plasminogen activator (tPA) therapy and often result in worse clinical outcomes^[4-6]. A review of 221 stroke patients identified TIM occlusions as an independent predictor of poor outcomes after systemic thrombolysis^[6].

The current treatment regime involves systemic tPA within 3 h of presentation. However, as previously noted, this may not allow adequate cerebral reperfusion in a TIM occlusion and may, unfortunately, predispose the development of a malignant brain infarct^[7]. In order to improve clinical outcomes, this group of patients may need more aggressive intervention to restore cerebral perfusion. However, the ideal treatment for such cases remains elusive^[8,9].

Recently, treatment of patients with ICA dissections refractory to medical management has focused on endovascular stenting and angioplasty^[10]. A small patient series described stent-assisted thrombolysis in TIM occlusions. Specifically, the proximal ICA was recanalized with stent implantation followed by MCA recanalization *via* subsequent intra-arterial thrombolysis or thrombectomy^[11]. In theory, endovascular therapies in the treatment of carotid dissection occlusions may lead to significant procedural complications, as the lesion pathology requires the interventionist to navigate the true lumen. Failure to do so may result in extending the dissection or vessel perforation, which in turn may lead to worse outcomes.

In certain cases, avoidance of the ICA may be preferred. Treatment of the MCA occlusion in a TIM by bypassing the ICA has only been described in three previous reports^[12-14]. We provide two additional cases demonstrating the successful recanalization of an MCA occlusion by administering intra-arterial tPA through a

microcatheter guidewire *via* cross-collateralization.

CASE REPORT

A 52-year-old male arrived at an outside hospital with global aphasia, right hemiplegia and a National Institute of Health Stroke Scale (NIHSS) of 20. He was found to have a left MCA stroke on head computed tomography (CT). Tele Stroke was activated and he was given intravenous (*iv*) tPA at 1.5 h after symptom onset and transferred to a tertiary hospital. The patient's exam remained unchanged on arrival, head CT showed no evidence of stroke, and he was subsequently taken to the angiography suite.

Under general anesthesia, the left common carotid artery was catheterized and images of the cervical carotid arteries were obtained (Figure 1A). He was found to have a left carotid artery dissection (CAD). At this point, the proximal left ICA was partially opened. The true lumen, however, was difficult to identify and further attempts risked propagating the dissection intracranially.

Subsequently, the right ICA was catheterized through the right common carotid artery for angiography. A thrombus was located in the middle Sylvian (M2) position; imaging was obtained during the arterial phase so opacification was not seen. The anterior communicating artery (ACOMM) was slightly greater than 1 mm. At this point, a microcatheter was advanced from the right internal carotid system *via* the ACOMM into the left MCA. Both the superior and inferior trunks were catheterized and a total of 2 mg of tPA was delivered in each trunk providing an additional 4 mg to the systemic tPA dose (Figure 1B and C).

Post-procedure Thrombolysis in Cerebral Infarc-

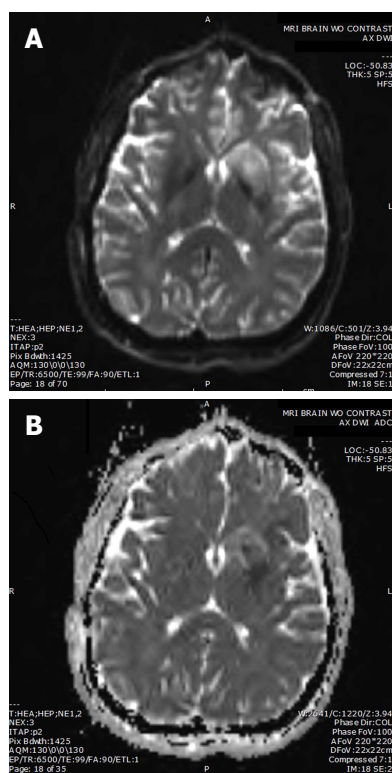


Figure 2 Ten hours post procedure imaging demonstrating small left subcortical infarct. A: Post procedure diffusion weighted magnetic resonance imaging; B: Post procedure apparent diffusion coefficient.

tion (TICI) score and immediate arteriogram were unchanged. The intervention was performed three hours post symptom onset and the procedure duration was two hours. Ten hour magnetic resonance angiography (MRA) confirmed recanalization of the MCA (Figure 1D), and magnetic resonance imaging (MRI) revealed a small stroke (Figure 2). Pre-procedure MRI was not performed. Heparin (*iv*) was given on the following day. Of note, anticoagulation was not started earlier since the patient received a full dose of *iv* tPA prior to the intervention. After twenty-four hours, the patient had full strength and minimal word finding with an NIHSS of two. After 3 mo, his NIHSS was zero. Three years later, he has returned to work and continues without neurological deficits.

Our second patient was a 40-year-old male who presented with left hemiplegia, and was diagnosed with CAD after obtaining a cerebral angiogram. He was treated with intra-lesional tPA *via* cross-collateralization, and recanalization of the right MCA was obtained eight hours post presentation. His pre and post-procedure NIHSS, as well as his NIHSS 3 mo later, were by coincidence the same as the first patient. He continues to have a non-focal neurologic exam three years post treatment.

DISCUSSION

Ischemic stroke associated with CAD is primarily due to embolic phenomena, which can affect many vessels and commonly targets the ICA, MCA or both in tandem. The

latter independently predicts poor clinical outcome and so efficacious and consistent treatments are highly desired^[6]. Thrombolysis has typically been the management of choice for CAD, and is thought to prevent subsequent embolic events^[15]. However, a definitive treatment of choice for CAD does not exist. Evidence for tPA use in CAD is lacking, and may be associated with certain risks including hematoma extension and subarachnoid hemorrhage. Thrombolytics (*iv*) have been shown to cause recanalization in approximately 30%-40% of patients. This treatment has not been efficacious in the case of TIM^[6]. Of interest, endovascular stenting has successfully been employed to treat medical refractory CAD that resulted in thromboembolic events^[11,16].

Lavallée *et al*^[11] analyzed the benefits of stent assisted endovascular thrombolysis with *iv* tPA involving a small series of ICA dissections. In this study, 10 patients who met the selection criteria were given either systemic tPA ($n = 4$) or endovascular stenting and intra-lesional tPA ($n = 6$). Those in the endovascular group had significantly better prognosis, which was linked to recanalization of the occluded vessels, particularly the MCA. The MCA was patent in all endovascular cases and occluded in three of the four cases in the systemic tPA group. Both embolization and in stent thrombosis were side effects of endovascular treatment.

Opening the ICA is the ideal option, however, given the difficulty of observing the true carotid lumen and associated risk of extending the dissection intracranially, bypassing the dissection was considered the optimal strategy. Rahme *et al*^[13] describes 15 cases in the literature of treating MCA thrombosis in TIM occlusions *via* cross-collateralization, and recanalization was achieved in 54.5%-75.0% of cases. Our report provides further support for the strategy of treating TIM occlusion *via* delivery of intra-lesional tPA using collateral vessels. In both cases presented, intra-lesional tPA was administered through a microcatheter passed through the ACOMM, and recanalization was observed *via* angiographic improvement on MRA. At 3 mo, both patients had fully recovered and returned to their daily activities. They continued to have a non-focal neurologic exam three years later.

Our presented cases did not have any complications, however, the risk of the described intervention includes endangering the contralateral carotid circulation, damaging smaller collateral arteries, and compromising collateral flow. Specifically, instrumenting small caliber arteries may result in dissection, occlusion, or distal thrombosis. This approach is ideal for patients in whom it is felt that the cervical carotid artery cannot be safely recanalized or in whom recanalization of the cervical carotid artery may lead to significant reperfusion hemorrhage. The ideal patient for this procedure is directly dependent on the presence of a collateral vessel, like the ACOMM, having an adequate diameter for passage of a microcatheter. Radiographic studies have demonstrated that an intact anterior circulation is present in 74%-90% of the population and

an intact posterior circulation is present in 48.5%-63% of the population^[17-20]. Of note, a review of anatomic variants in healthy Chinese individuals demonstrated that a complete anterior circulation with incomplete posterior circulation is present in 47.7% of individuals; a complete posterior circulation with an incomplete anterior circulation is only present in 5.2% of individuals^[17]. Another risk includes receiving an additional 4 mg of tPA to the systemic dose which increases risk for hemorrhage. It is important to analyze the risks and benefits of any procedure. The presented patients were highly functional with a devastating stroke, and, therefore, the intervention was considered worthwhile.

TIM secondary to CAD are refractory to pure medical management and strongly predict poor outcomes in patients. Stent assisted endovascular thrombolysis is effective when compared against traditional management but carries an additional risk of worsening the dissection and propagating further thromboembolic events. Therefore, avoidance of the occluded carotid artery may be preferred in certain scenarios. In these cases, delivery of intra-lesional tPA using collateral vessels resulted in complete clinical recovery and recanalization of the occluded MCA. Our experience provides further support for utilization of this novel method of treatment when other modalities may not be feasible.

COMMENTS

Case characteristics

Tandem internal carotid artery and middle cerebral artery occlusions secondary to carotid artery dissections are refractory to stand alone medical management, and recanalization with intra-arterial tissue plasminogen activator (tPA) using cross-collateralization may be an effective alternative for treating these patients.

Clinical diagnosis

The patient presented with global aphasia and right hemiplegia suggestive of a left middle cerebral artery stroke.

Differential diagnosis

The differential diagnosis includes left middle cerebral artery thrombosis or dissection.

Imaging diagnosis

Cerebral angiography revealed left internal carotid artery dissection and left middle cerebral artery occlusion.

Treatment

tPA (iv) was first used for recanalization but failed, therefore, catheter guided intra-arterial delivery of tPA was then implemented towards successfully recanalizing the middle cerebral artery occlusion.

Related reports

There have only been three reports describing the use of intra-arterial tPA delivery via cross-collaterals in the literature, and we provide two more cases supporting its use in treating tandem internal carotid artery and middle cerebral artery occlusions.

Term explanation

Cross-collateralization: Using collateral vessels to navigate endovascular instruments around abnormal or damaged vessels.

Experience and lessons

Stent assisted endovascular thrombolysis of tandem internal carotid artery and middle cerebral artery occlusions (TIM) is effective but carries the risk of worsening the dissection and propagating further thromboembolic events, and, therefore, avoidance of carotid occlusions and recanalization with intra-arterial tissue plasminogen activator, using collateral vessels may be an effective alternative for treating patients with TIM.

Peer review

The strengths of this article is that it provides additional cases where utilizing collateral vessels was an effective strategy for treating tandem internal carotid artery and middle cerebral artery occlusions. The report also summarizes important factors to consider when determining whether a patient is a good candidate for this intervention. The study is well-written and interesting.

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Intracranial hypotension syndrome in a patient due to suboccipital craniectomy secondary to Chiari type malformation

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Author contributions: Stylianos G participated in data acquisition, analyzed and interpreted the patient data regarding the clinical picture and treatment options and corrected the final version of this manuscript; Nikolaos B participated in data acquisition, analyzed and interpreted the patient data regarding the radiological imaging and corrected the final version of this manuscript; Dora B participated in data acquisition, analysis and interpretation of data and was a major contributor in writing the manuscript; Damianos S conceived and coordinated this study and participated in the interpretation of data; all authors contributed in conception, design and drafting the article, read and approved the final manuscript.

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Abstract

Intracranial hypotension syndrome (IHS) is a rare disorder characterized by a decrease in cerebrospinal fluid pressure to less than 60 mm H₂O. The syndrome is associated with occipital headache radiating to the frontal and temporal zones. The current clinical case describes the manifestation of IHS in a twenty-five year old female with a history of suboccipital craniectomy due to Chiari I malformation nine years earlier. The patient was admitted to the hospital complain-

ing about postural, mainly occipital, headache during the last three months, aggravated by being in an upright position. The magnetic resonance imaging (MRI) revealed engorgement of the dural venous sinuses, significant enlargement of the pituitary gland and downward displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern, while the spinal T2W MRI revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine. The previous imaging did not reveal subdural effusions.

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Key words: Headache; Craniectomy; Cerebrospinal fluid; Intracranial hypotension syndrome; Effusion; Chiari

Core tip: A 25-year-old female presented with a history of suboccipital craniectomy due to Chiari I malformation nine years earlier. The patient was admitted to the hospital with symptoms of postural, mainly occipital, headache during the last three months, aggravated by being in an upright position. The spinal T2W magnetic resonance imaging revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine. The current clinical case indicates that a longer follow-up and increased alertness are required in a patient with a history of craniectomy due to Chiari I malformation.

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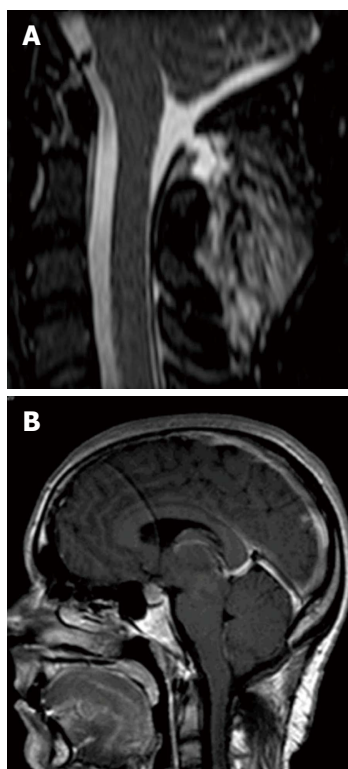


Figure 1 Magnetic resonance imaging signs of intracranial hypotension syndrome nine years after the craniectomy. A: 7 mm × 2.5 mm dural defect with an extradural collection at the dorsal soft tissues of the cervical spine; B: Less prominent engorgement of the dural venous sinuses, further enlargement of the pituitary gland and download displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern.

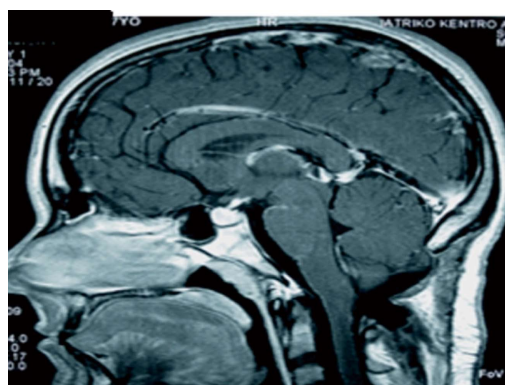


Figure 2 Magnetic resonance imaging signs of intracranial hypotension syndrome postoperatively. There is significant engorgement of the dural venous sinuses and mild enlargement of the pituitary gland without signs of download displacement or sagging of the brain.

terns and the prepontine cistern (Figure 1B), while the spinal T2W MRI revealed a 7 mm × 2.5 mm dural defect with an extradural CSF collection at the dorsal soft tissues of the cervical spine (Figure 1A). The postoperative MRI nine years earlier revealed significant engorgement of the dural venous sinuses and mild enlargement of the pituitary gland without signs of download displacement or sagging of the brain (Figure 2). Even although the previous imaging did not reveal subdural effusions, the postoperative MRI revealed signs of intracranial hypotension syndrome soon after the suboccipital craniectomy. Nevertheless, the typical clinical symptoms of IHS only manifested three months before the admission of the patient. During the postoperative follow-up, the patient complained of intermittent occipital headaches, mostly explained by the Chiari malformation.

INTRODUCTION

Intracranial hypotension syndrome (IHS) is a rare disorder characterized by a decrease in cerebrospinal fluid pressure. IHS is associated with occipital headache similar to the orthostatic headache after lumbar puncture. They both radiate to the frontal and temporal zones and are aggravated in an upright position. IHS is also characterized by dural thickening and pachymeningeal contrast enhancement as a consequence of decreased cerebrospinal fluid (CSF) volume. Although spinal cerebrospinal fluid leaks may be the cause of this syndrome, only a few clinical or radiological cases have been reported.

CASE REPORT

A 25-year-old female presented with a history of suboccipital craniectomy due to Chiari I malformation 9 years earlier. The patient was admitted to the hospital complaining about postural, mainly occipital, headache during the last three months. The headache was aggravated by being in an upright position. The magnetic resonance imaging (MRI) revealed mild engorgement of the dural venous sinuses, significant enlargement of the pituitary gland and download displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern.

DISCUSSION

IHS is a rare disorder with a prevalence of about 1 per 50000 population^[1]. The latest studies indicate that the estimated incidence is higher because the disorder remains under recognized^[2]. This rare syndrome is characterized by a decrease in cerebrospinal fluid pressure to less than 60 mm H₂O. IHS is associated with occipital headache radiating to the frontal and temporal zones, dural thickening and pachymeningeal contrast enhancement as a consequence of decreased CSF volume. The 5 characteristic imaging features of spontaneous intracranial hypotension visible on MRI are: (1) subdural fluid collections; (2) enhancement of the pachymeninges; (3) engorgement of venous structures; (4) pituitary hyperemia; and (5) sagging of the brain (mnemonic: SEEPS)^[3]. Headache due to IHS is similar to the orthostatic headache after lumbar puncture. They both are aggravated in an upright position. IHS is highly related to a spontaneous CSF leak. In most cases, spinal cerebrospinal fluid leaks are related to the pathogenic mechanism of the syndrome. Nevertheless, they have rarely been demonstrated radiographically or surgically^[1]. Some of the spontaneous CSF leaks are related to weakness of the meningeal sac, likely

in connection with a connective tissue abnormality^[4]. In clinical practice, the 2004 International Classification of Headache Disorders criteria cannot satisfy 100% of patients with IHS because of the variability of clinical and radiological manifestations^[5]. Furthermore, although both intracranial hypotension syndrome and Chiari I malformation have been well described, their simultaneous presence has rarely been reported^[6]. The current case indicates that even although the patient's postoperative MRI revealed signs of IHS, the clinical features were intermittent and did not meet the IHS criteria. Therefore, a patient with a history of Chiari I malformation and intermittent occipital headache after craniectomy requires increased alertness and a longer follow-up.

COMMENTS

Case characteristics

A 25-year-old female presented with a history of suboccipital craniectomy due to Chiari I malformation nine years earlier.

Clinical diagnosis

The patient was admitted to the hospital complaining of postural, mainly occipital, headache during the last three months. The headache was aggravated in an upright position.

Imaging diagnosis

The magnetic resonance imaging (MRI) revealed engorgement of the dural venous sinuses, significant enlargement of the pituitary gland and downward displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern, while the spinal T2W MRI revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine.

Treatment

The spinal T2W magnetic resonance imaging revealed a 7 mm × 2.5 mm dural

defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine.

Related reports

Latest studies indicate that the estimated incidence is higher because the disorder remains under recognized.

Experiences and lessons

A patient with a history of Chiari I malformation and intermittent occipital headache after craniectomy requires increased alertness and a longer follow-up.

Peer review

This clinical association is very rare and a larger number of patients are needed in order to have a wide clinical picture.

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