Erdheim-Chester disease: Symmetric uptake in the ^{99m}Tc-MDP bone scan

Abstract

Erdheim-Chester disease (E-C D) is a rare clinicopathologic entity with nearly pathognomonic radiographic features. About half of the affected exhibit extraskeletal manifestations, including involvement of the hypothalamus-pituitary axis, lung, heart, retroperitoneum, skin, liver, kidneys, spleen and orbit. This disease usually affects individuals in their fifties to their seventies and has a male preponderance. The lesions of E-C D consist of lipid-storing CD68 (+) and CD1a (-) non-Langerhans cell histiocytes, either localized to the bone or involving multiple systems of the body as well. Skeletal involvement is characteristically bilateral and symmetric, exhibiting an osteosclerotic pattern in the metaphysis and diaphysis of the long bones, usually sparing epiphysis. We recently had a 68 years old male patient with E-C D, with a mild and persistent knee pain, who was subjected to a 3-phase technetium-99m methylene diphosphonate (^{99m}Tc-MDP) bone-scan and subsequently to gallium-67 citrate (^{67}Ga-C) whole body scan. The characteristic symmetric pattern of these scans raised the question of E-CD disease. The patient showed an excellent symptomatic response to high-dose steroids. However, the symptoms recurred after discontinuation of treatment.

Historical remarks

In 1930, W. Chester and his Viennese mentor J. Erdheim, described for the first time two patients with a granulomatous lipoidosis, which differed from other known histiocytic disorders, such as Hand-Scüller-Christian and Niemann-Pick disease [1]. H. Jaffe introduced the term Erdheim-Chester disease (E-C D) in the early 70s, when 100 cases had already been reported worldwide [2].

Definition, immunohistopathology and clinical manifestations

The E-CD is defined by a mononuclear cell infiltrate consisting of lipid-laden, foamy histiocytes, which are found mainly in the diaphysis/metaphysis of the long bones of the lower extremities [3-8]. Histiocytes are known to originate from pluripotent stem cells in the bone marrow and under the influence of various cytokines e.g., GM-CSF, TNF-a, IL–3 or IL-4, these precursor cells can differentiate into specific groups of antigen-processing cells, some of them with phagocytic capabilities. These include tissue macrophages, monocytes, dendritic cells, interdigitating reticulum cells, and Langerhans cells [3-8]. Immunohistochemical findings of the E-CD lesions reveal the presence of non-Langerhans cell histiocyte markers, namely, the absence of the CD1a antigen, the usual absence of the protein S-100 and the ubiquitous presence of the CD68 antigen (CD68: a largely lysosomal macrosialin), factor 13a (a tissue transglutaminase) and fascin (an actin-bundling protein). Fascin and factor 13a are typical of interstitial and interdigitating dendritic cells. Electron microscopy reveals the absence of Birbeck granules in the cytoplasm of non-Langerhans cell histiocytes. It is reminded that Langerhans cell histiocytes stain positive for S-100, CD1a, langerin, while Birbeck granules are always present in their cytoplasm [3-7]. Additional markers in E-C D are molecules common to macrophages: CD14, a monocyte or macrophage receptor that binds to lipopolysaccharide and CD163, a haptoglobin- and hemoglobin-scavenging receptor. Whether these histiocytic proliferations represent monoclonal neoplastic populations or are part of a polyclonal reactive process, is currently unclear, although the evidence from a limited amount of data favours the reactive nature of this disease [3, 5-7].

About 60% of the individuals affected with E-CD reveal extraosseous involvement, a pattern that is highly variable and may be life-threatening. The most common extraosseous

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manifestations are diabetes insipidus and painless bilateral exopthalmos [8-16]. These two manifestations, together with bone pain, compose the classic E-C D diagnostic triad.

Imaging modalities

Conventional radiography of the E-C D typically shows a bilateral symmetric pattern of medullary sclerosis involving the diaphysis in 100% of the lesions and the metaphysis in 83% of the lesions of the lower extremities, with partial epiphyseal involvement in 45 % of the lesions. The bilateral, symmetric and osteosclerotic pattern of the long bones on conventional radiography is a virtually pathognomonic sign for the presence of E-C D [17-21]. Magnetic resonance (MR) imaging of the lesions indicates replacement of the normal fatty bone marrow, by exhibiting heterogeneous signal intensity on T_1 and T_2-weighted spin-echo images. Lesion extent, epiphyseal involvement and periostitis can be clearly depicted in MR imaging. Periostitis is seen in 66% and endosteitis in 94% of the long bone lesions [20].

Technetium-99m methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy in E-C D reveals a symmetrically increased uptake of the distal ends of the long bones of the lower limbs and sometimes of the upper limbs. Besides, in E-CD, symmetric ^{99m}Tc-MDP uptake is observed in progressive diaphyseal dysplasia (Engelmann-Camurati disease) [22] and in systemic mastocytosis [23] (Fig.1). The 3-phase ^{99m}Tc-MDP bone scan images in E-C D show markedly increased radiotracer uptake on all 3 phases [24-27]. In early cases, detection may rely solely on ^{99m}Tc-MDP bone scintigraphy, which may also reveal radiographically silent bone involvement, with the characteristic bilateral and symmetric metaphyseal and diaphyseal involvement of the long bones [20]. Gallium-67 citrate (^{67}Ga-C) scintigraphy also exhibits the same accumulation pattern seen in the ^{99m}Tc-MDP bone scintigrams, but it is additionally capable of revealing any soft tissue involvement, a very important prognostic sign for the patient. Thus, both ^{99m}Tc-MDP bone and ^{67}Ga-C scintigraphy are useful tools for the diagnosis and for determining the extent of the E-CD [28]. The role of ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) PET/CT imaging has not been well established in E-C D, but it appears that it can be used for accurate assessment of the extent of the disease and also for the assessment of response after treatment [29-31].

There is no standard treatment of E-CD and its prognosis is related to the extent of multisystem involvement. Most patients die within 2 to 3 years after diagnosis, as a result of congestive heart failure, respiratory failure from lung fibrosis, or renal insufficiency [8]. Numerous treatments have been used for this disease, but with minimal success. The first-line treatment of controlling symptoms is corticosteroids [32, 33]. Treatment options also include bisphosphonates, in treating bone involvement [34], radiotherapy [35], chemotherapy [36] and alpha interferon therapy [37, 38]. None of these treatments has been highly effective and their efficacy is difficult to evaluate, due to the rarity of the disease.

Usual imaging findings

As an example of a case of E-C D in everyday medical practice, we have recently examined with a 3-phase ^{99m}Tc-MDP bonescan a 68 years old male. He had a persistent knee pain for 6 months. His cell blood count was normal, with no eosinophilia or thrombocytopenia and he had no evidence of an infectious process, with normal erythrocyte sedimentation rate and C-reactive protein. Blood chemistries showed normal calcium, phosphorus and alkaline phosphatase levels. A conventional knee radiograph showed the presence of an osteosclerotic bilateral and symmetric pattern in the tibial diaphysis and metaphysis, while the computerized tomography (CT) knee examination showed inhomogeneities, compatible with the presence of medullary infarcts (Fig.2). Thoracic and abdominal CT showed no evidence of parenchymal abnormalities or hepatosplenomegaly. The 3-phase ^{99m}Tc-MDP knee bone-scan (Fig. 3) was performed using 740 MBq of ^{99m}Tc-MDP (Amerscan™ Medronate II, GE Healthcare, Buckinghamshire UK) in a dual-head γ-camera (Siemens e-cam, Erlangen Germany). The ^{67}Ga-C (Mallinckrodt Medical B.V., Petten, The Netherlands) whole-body scan (Fig. 4) was obtained 48 h after the radiopharmaceutical administration (185 MBq).

The bone-scan showed the typical symmetric pattern of involvement of the distal ends of the long bones (tibiae, femora, radii), with the unusual involvement of the metacarpals (Fig. 3). The positivity of the 1st and 2nd phases of the bone scan is compatible with the inflammatory component of this disorder, in agreement with the reported periostitis and endosteitis findings of the magnetic resonance imaging (MRI) [16] studies. Involvement of the mandible, seen in the late phase of the ^{99m}Tc-MDP scan, could not be excluded, since only the lesion in the tibia was biopsied. ^{67}Ga-C scintigraphy showed the same symmetric uptake in the long bones observed in the
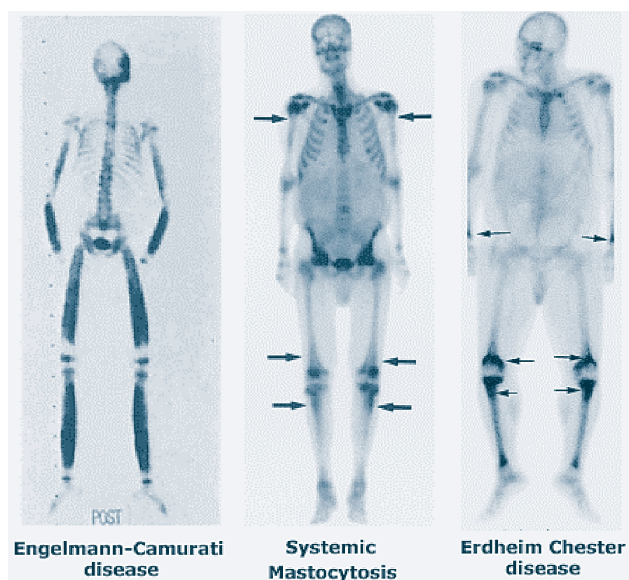

Figure 1. Symmetric uptake in ^{99m}Tc-MDP bone scintigrams is encountered in progressive diaphyseal dysplasia (Engelmann-Camuratti disease), in systemic mastocytosis and in Erdheim-Chester disease [22-26].
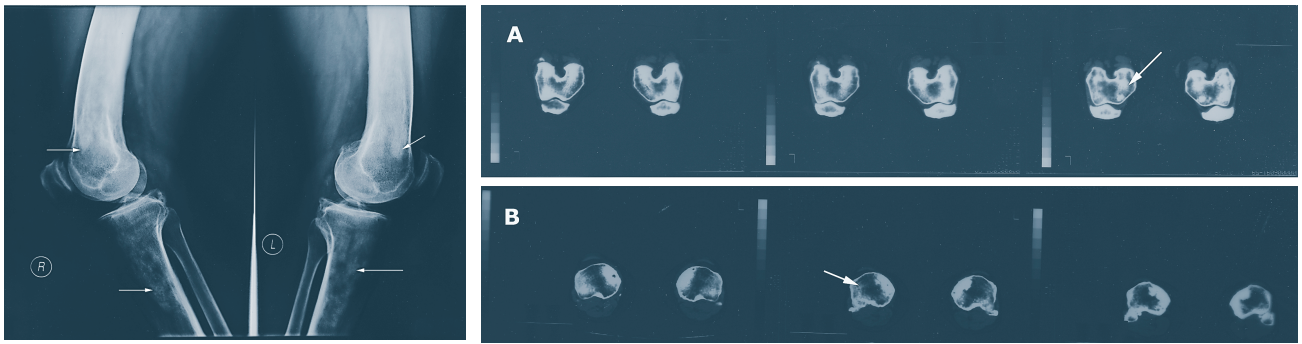
Figure 2. Knee radiologic examination results of the patient in the described case. Left: X-rays of the knees revealed the symmetric pattern of osteosclerotic changes in the metaphysis and diaphysis of tibiae and femora (white arrows). Right: CT of femora and tibiae showed inhomogeneities (white arrows) described as infarcts in the CT report.
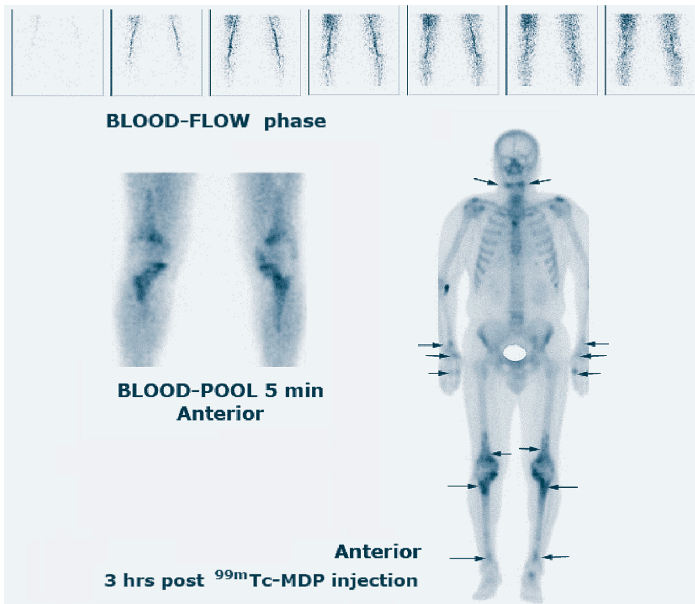

Figure 3. The 3-phase ^{99m}Tc-MDP bone-scan of the patient in the described case. The positive 1st and 2nd phase (knees) indicates the inflammatory component of the disease (periostitis and/or endosteitis), but the characteristic symmetry of the increased osteoblastic activity in the metabolic phase in the long bones (see arrows), suggested the presence of Erdheim-Chester disease.
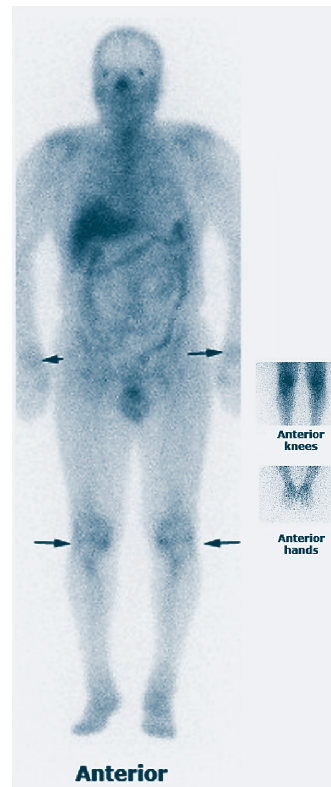

Figure 4. ^{67}Ga- citrate whole body scan of the patient in the described case, 48 hrs post-injection. The symmetric pattern of the radiopharmaceutical uptake is apparent, without evidence of other organ involvement. The spot images of hands and knees are also shown, exhibiting a relatively faint but discernible uptake.

^{99m}Tc-MDP scintigraphy, without evidence of soft tissue infiltration. However, it seems that the ^{67}Ga-C scintigraphy (Fig. 4) underestimates the extent of the bone involvement, although it is of unquestionable value in detecting extraosseous disease and therefore it offers additional important prognostic information.

The Engelmann-Camuratti disease was easily excluded, since this is a rare autosomal dominant disease, accompanied by splenomegaly and it is discovered early in life [22]. The possibility of systemic mastocytosis was also ruled out, based on the clinical presentation, laboratory findings, i.e. absence of eosinopohilia/thrombocytopenia and no alkaline phosphatase elevation and also because of the abdominal CT findings that showed no hepatosplenomegaly [23]. The patient refused biopsy-verification of our presumptive diagnosis, which was based on the typical ^{99m}Tc-MDP and the ^{67}Ga-C scans

findings and was treated with high-dose steroids, with an initial improvement of his symptoms. However, the patient discontinued the medication on his own initiative and his symptoms recurred. The course of his disease is to be monitored with serial 3-phase ^{99m}Tc-MDP bone scans, to indicate if a more aggressive treatment should be started.

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