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World Journal of Dermatology

Contents

Quarterly Volume 5 Number 2 May 2, 2016

DIAGNOSIS ADVANCES

REVIEW

MINIREVIEWS

World Journal of Dermatology
Volume 5 Number 2 May 2, 2016

Contents

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CD34+ dermal dendritic cells and mucin deposition in dermatomyositis

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Abstract

Dermal mucinosis is often associated with collagen diseases such as rheumatoid arthritis, lupus erythematosus, and dermatomyositis, in addition to autoimmune thyroiditis. We report eight cases of dermal mucin deposition secondary to typical dermatomyositis with cutaneous lesions known as heliotrope rash and Gottron's papules. Striking mucin deposition was observed in both the papillary dermis and reticular dermis of all biopsy specimens. Immunohistochemical analysis showed that CD34+ dermal dendritic cells (DDCs) in the perilesional area in combination with vimentin+ cells within the mucinous lesion might be important in giving rise to abnormal deposition of dermal mucin. On the other hand, numbers of factor ⅩⅢa+ DDCs and tryptase+ mast cells were reduced within and surrounding the mucin deposition, as compared with those in the dermis of normal controls. A pathogenic mechanism of dermal mucin deposition is proposed.

Key words: Mucin deposition; Dermatomyositis; CD34+ dermal dendritic cell

Core tip: Immunohistochemical analysis of skin biopsy specimens with dermatomyositis showed the involvement of CD34+ dermal dendritic cells, α-smooth muscle actin+ myofibroblasts and possibly mast cells, as well as vimentin+ fibroblasts for abnormally dermal mucin production. Further pathophysiological studies are required to more precisely clarify secondary cutaneous mucin deposition by CD34+ dermal dendritic cells. CD34+ dermal dendritic cells and mast cells might be important in giving rise to deposition of dermal mucin in dermatomyositis.

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INTRODUCTION

Dermal mucin deposition has been seen in several skin diseases, including granuloma annulare, autoimmune thyroiditis, and collagen diseases (dermatomyositis, scleroderma, and lupus erythematosus). These observations led us to imagine dermal mucinosis as a heterogeneous group of pathologies showing a common factor of dermal mucin deposition.

We have previously reported a rare case of self-healing papular mucinosis (SHPM) in a patient with rheumatoid arthritis[1]. We suggested that CD34+ or Factor XIIIa+ (FXIIIa+) dermal dendritic cells (DDCs) and tryptase+ mast cells (MCs) in the perilesional area in combination with vimentin+ cells in the mucinous lesion might have been involved in the dermal deposition of mucin. DDCs and MCs would then presumably play a key role in the development of mucinosis.

The present study tentatively defined DDCs as all the cells in connective tissue morphologically showing a dendritic shape. These fibroblast-like cells in the connective tissue have been classified into the following groups[2-8]: (1) true fibroblasts; (2) myofibroblasts; (3) CD34+ DDCs; (4) FXIIIa+ DDCs; and (5) others. Fibroblasts are regarded as those cells positive only for vimentin, and myofibroblasts as those positive for both vimentin and α-smooth muscle actin (α-SMA)[2,8]. DDCs are divided into CD34+ and FXIIIa+ DDCs[2-7]. Other fibroblast-like cells (*i.e.,* not categories 1-4) are not specified further, and are collected as other fibroblast-like cells.

The aim of the present study was to elucidate the involvement of DDCs and MCs in the dermal mucin deposition seen in dermatomyositis.

DIAGNOSIS

Participants comprised 8 patients who had been clinicopathologically diagnosed with dermatomyositis. This study followed eight cases of dermatomyositis showing clear mucin deposition in biopsied skin tissues taken at the time of the first medical examination. Fifteen volunteers who underwent removal of nevus cell nevi (including normal skin) were used as site-matched controls. Mean (± standard deviation) ages in the patient and control groups were 53 ± 26 years (range, 34-86 years) and 22 ± 20 years (range, 12-64 years), respectively. Male-to-female ratios were 3:5 in the patient group and 6:9 in controls.

Skin biopsy specimens from the 8 patients with dermatomyositis were obtained from the thigh in 3 cases, from the chest in 3 cases, and from the dorsum of the hand in 2 cases. Normal skin consisting of the remaining unaffected portion of surgically removed nevus cell nevus was derived from various corresponding control sites. Informed consent was obtained from all subjects prior to participation in the present study.

RSEARCH

Archival paraffin embedded tissues from dermatomyositis and normal skin were utilized for this study. In each case, formalin-fixed, paraffin-embedded, 4-μm-thick sections were stained by the periodic acid-Schiff (PAS) technique, with Alcian blue (pH 2.5). Fibroblast-like cells were immunohistochemically recognized using antibodies for vimentin, CD34, FXIIIa, α-SMA, and desmin. MCs were identified by immunohistochemical staining for tryptase.

Table 1 Antibodies used in immunohistochemical analysis

Antibody	Type	Source	Dilution
Vimentin	Mouse	Dako	1:40
CD34	Mouse	Nichirei	1:1
Factor XIIIa	Rabbit	Biogenesis	1:50
α-smooth muscle actin	Mouse	Dako	1:50
Desmin	Mouse	Dako	1:1
Tryptase	Mouse	Dako	1:50

Sections from all cases were stained with an avidin-biotin peroxidase technique, using an ENVISION kit (Dako, Carpinteria, CA). Antibodies used in the present study are shown in Table 1. Cells were stained with mouse monoclonal and rabbit polyclonal antibodies. Sections were deparaffinized in xylene and rehydrated in a graded alcohol series. Endogenous peroxidase activity was removed by immersion in methanol with 3% hydrogen peroxide for 10 min. Non-specific binding was blocked by incubation for 5 min at room temperature with non-immune goat serum. Primary antibodies were then applied to sections and incubated for 45 min at room temperature. Secondary rabbit anti-mouse immunoglobulin (Ig) was applied for 45 min at room temperature. Finally, specimens were developed with 3,3'-diamino benzidine solution and 1% hydrogen peroxide, then counterstained with Mayer's hematoxylin.

DDC and MC counts were assessed as the number of positive cells per 10 high-power fields (× 400) on each skin specimen by a single observer. Statistical significance was analyzed using Student's *t*-test. Student's *t*-test was applied for comparisons of mean numbers of positive cells between dermatomyositis and normal skin samples. Values of $P < 0.05$ were considered significant.

RESULTS

The profiles of eight patients with dermatomyositis are shown in Table 2. No patients had yet received any treatments (including steroids) for dermatomyositis at the time of biopsy. The interval between observation of the first skin symptom to first medical examination ranged from 1 to 6 mo (1 mo, $n = 2$; 5 mo, $n = 2$; 6 mo, $n = 1$; 3 mo, $n = 1$; 2 mo, $n = 1$; unknown, $n = 1$). Three cases (cases 2, 3 and 6) had muscle weakness, two cases (cases 3 and 7) had arthralgia, and one case (case 1) developed respiratory failure. Only one case (case 8) showed lung cancer; this patient died after 1 year. None of the other seven patients had internal malignancy.

Table 2 Profiles of eight patients with dermatomyositi

No	Age	Sex/period	Clinical findings	Sight of skin biopsy	Pathological findings
1	86	Male One month	Rash erythema of whole body respiratory failure	Right tight	Vacuolar change, mucin in papillary and reticular dermis
2	59	Female One month	Lilac rash of eyelids, erythema rash of limbs, dorsal hands of Gottron's papules arthralgia	Right tight	Vacuolar change, subepidermal blister, mucine in papillary dermis
3	53	Female Two months	Dorsal hands of Gottron's papules, scary erythema of face, chest, limbs, arthralgia, muscle weakness	Light tight	Vacuolar change, periadnexal infiltration mucin in papillary and reticular dermis
4	63	Female Five months	Lilac rash of eyelids, dorsal hands of Gottron's papules, scary erythema of face, neck, chest	Chest	Vacuolar change, periadnexal infiltration mucin in papillary and reticular dermis
5	46	Male Unidentified	Dale reddish erythema of face, edematous erythema of neck	Limbs	Vacuolar change, melanine incontinen mucin in papillary and reticular dermis
6	34	Female Five months	Dorsal hands of Gottron's papules rash erythema of eyelid, nasal grooves muscle weakness	Chest	Hyperkeratosis, vacuolar change, mucin in papillary dermis
7	46	Female Three months	Dorsal hands of Gottron's papules, scary erythema of knee and hip, arthralgia	Light dorsal hand	Hyperkeratosis, vacuolar change, mucin in papillary and reticular dermis
8	57	Male[1] Six months	Edematous erythema of face, neck, chest and shoulder	Chest	Vacuolar change, mucin in papillary and reticular dermis

[1]Only the 57-year-old male (case 8) was found lung cancer, the other seven patients had no internal malignancy.

Table 3 Number of positive cells in normal skin and dermatomyositis

	Normal skin (n = 15) mean ± SE cells/high-power field (× 400)	Dermatomyositis (n = 8) mean ± SE cells/high-power field (× 400)	P value
Mast cells tryptase	12.320 ± 0.997	5.788 ± 0.805	0.000270
Dendritic cells			
Vimentin	9.654 ± 1.374	16.0125 ± 3.257	0.0524
CD34	10.933 ± 1.131	14.937 ± 3.257	0.177
Factor XIIIa	8.708 ± 2.172	4.40 ± 1.619	0.166
α-SMA	0	0.488 ± 0.447	0.141
Desmin	0	0	

In terms of histopathology, mucin deposition was in the papillary dermis in two cases, and in the papillary and reticular dermis in six cases. All cases showed vacuolar change and one had subepidermal blistering (case 2). Two cases (cases 3 and 4) had periadnexal infiltration.

Our findings are shown in Figures 1 and 2 and Table 3. PAS-negative and Alcian blue-positive mucin deposition was identified in all 8 skin samples from dermatomyositis patients. Histologically, mucin deposition demonstrable with Alcian blue staining was distributed diffusely but not focally in the papillary dermis, and to a lesser extent between collagen bundles of the reticular dermis with or without sparse lymphocytic infiltrates. Vimentin+ fibroblasts (16.01 ± 3.23 in dermatomyositis *vs* 9.65 ± 1.37 in controls; P = 0.052), CD34+ DDCs (14.94 ± 3.35 in dermatomyositis *vs* 10.93 ± 1.13 in controls; P = 0.18), and α-SMA+ myofibroblasts (0.48 ± 0.45 in dermatomyositis *vs* 0 in controls; P = 0.14) tended to be moderately increased in numbers, whereas numbers of FXIIIa+ DDCs were decreased in dermatomyositis skin, compared to normal skin (4.40 ± 1.62 in dermatomyositis *vs* 8.71 ± 2.17 in control; P = 0.17), although no significant differences were evident between diseased and control groups. In contrast, significant differences between the two groups were only seen for numbers of tryptase-positive MCs (5.79 ± 0.81 in dermatomyositis *vs* 12.32 ± 1.00 in controls; P = 0.00027). MCs were diffusely scattered without forming cell clusters. DDCs and MCs were counted separately in areas of periadnexal matrix and interstitial portions of the dermis. However, no significant differences were seen between groups. Furthermore, histopathological examination revealed no increase in vascularization within the dermis among the 8 patients with dermatomyositis. We examined the tryptase(+) MC count according to progress before performing a biopsy after the onset of exanthema (Figure 3). For 3 mo, a tendency to increase was seen, followed by a gradual decrease, and, for 1 mo, it is with a low value most in 6 mo. Unfortunately, the extremely limited number of cases adversely impacted the statistical power of our comparisons.

DISCUSSION

The present immunohistochemical analysis of dermatomyositis showed a moderate increase in CD34+ DDCs and vimentin+ cells lacking CD34 or FXIIIa related to mucin deposition in the dermis. We have previously reported a rare case of self-healing papular mucinosis (SHPM) in a patient with rheumatoid arthritis[1]. In that lesion, well-circumscribed mucin deposition was

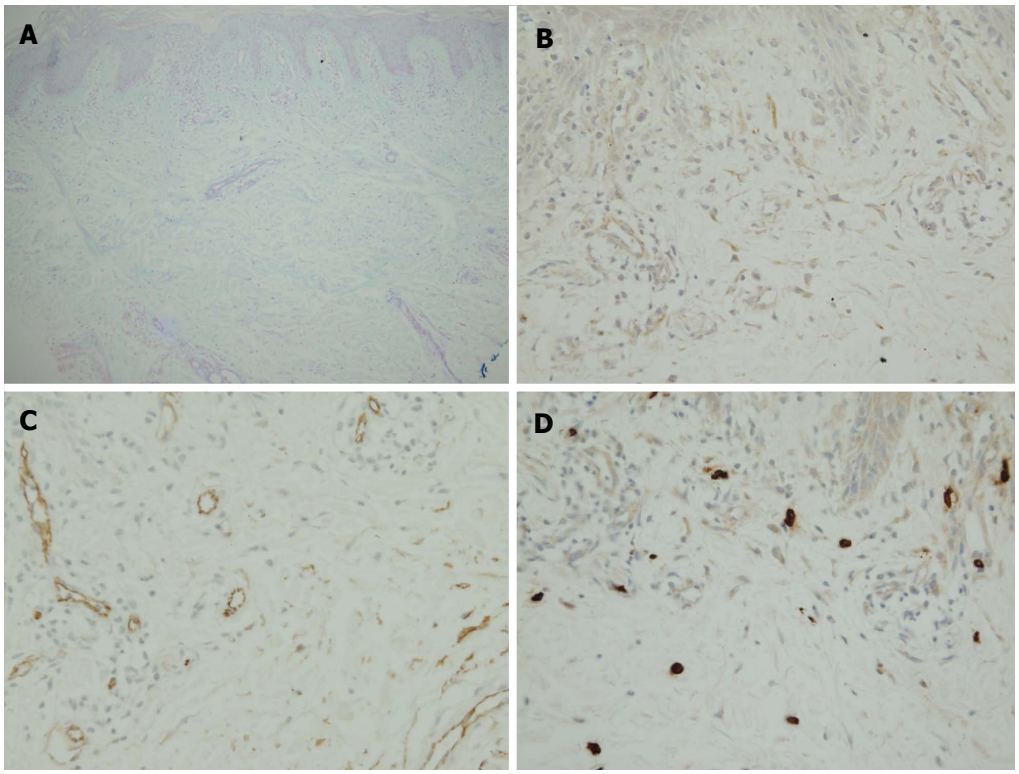

Figure 1 Representative histological findings in active skin lesions of dermatomyositis. A: Alcian blue (pH 2.5); B: Vimentin; C: CD34; D: Tryptase for mast cell staining.

demonstrated in the papillary dermis with Alcian blue staining. The overlying epidermis showed the formation of an epidermal collarette. On the other hand, in the case of dermatomyositis, diffuse mucin deposition was demonstrated with Alcian blue staining in the papillary dermis and between collagen bundles of the reticular dermis with or without sparse lymphocytic inflammatory infiltrates. Mucin deposition was particularly prominent in the papillary dermis. At the time of clinical diagnosis of dermatomyositis and immunohistochemical study, seven of the patients with dermatomyositis had no internal malignancies such as gastric or breast cancer, while one 57-year-old male patient showed lung cancer. There was also no evidence to support thyroid abnormalities among any of the eight patients.

Interstitial mucin deposition is a well-known occurrence in dermatomyositis[9]. However, the pathogenic mechanisms responsible for dermal mucin deposition remain unclear (Figure 4). Mucin is normally produced in small amounts by dermal fibroblasts, and chemically consists of acidic glycosaminoglycans. Rapoport *et al*[10] hypothesized that the overproduction of mucin results from autoantibodies against thyroid-stimulating hormone receptor stimulating dermal fibroblasts to produce deposition of mucin, mainly as hyaluronic acid. However, our cases showed no evidence of thyroid dysfunction. Another hypothesis is that interleukin (IL) 1β can induce glycosaminoglycan synthesis by fibroblasts *via* the prostaglandin E2 pathway through cyclooxygenase-2, an enzyme responsible for prostaglandin E2 synthesis[11]. IL1β can be produced by many cells, including fibroblasts, myofibroblasts, and MCs[12]. In our study, a small number of α-SMA+ DDCs were observed in dermatomyositis, whereas none were present among normal controls. The possibility that α-SMA+ myofibroblasts could produce mucin thus remains plausible. A third hypothesis is that Tominaga *et al*[13] observed an increased hyaluronan content in lesional skin compared to non-lesional skin in a patient with reticular erythematous mucinosis and proposed that the cells responsible for the deposition of hyaluronan in lesional skin were FXIIIa+/hyaluronan synthase 2+ DDCs rather than dermal fibroblasts. However, we found no evidence for an increase in FXIIIa + DDCs in the patient group with dermatomyositis (Figure 2).

Finally, Pugashetti *et al*[14] noted that local tissue hypoxia in response to chronic venous insufficiency could potentially increase the biosynthetic activity of fibroblasts and thus dermal mucin deposition. Our data offered no clinicopathological evidence for venous insufficiency. Since the numbers of vimentin+ spindle-shaped cells were increased in our cases, mesenchymally derived vimentin+/CD34- fibroblasts, histologically indistinguishable from CD34+ and FXIIIa+ DDCs, appeared likely to represent the source of mucin deposition.

What are the CD34+ cells? In the present study, numbers of CD34+ DDCs tended to be increased, although no significant difference was evident between the patient and normal control groups at the 5% level.

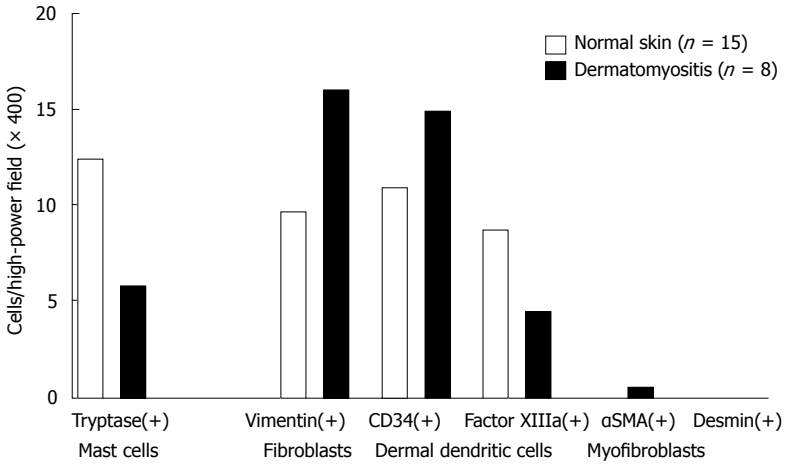

Figure 2 Number of positive cells in active skin lesions of patients with dermatomyositis. Vimentin+ fibroblasts, CD34+ DDCs and αSMA+ myofibroblasts are increased, but factor XIIIa+ DDCs are decreased in diseased skin compared to normal skin. A significant difference is evident for tryptase-positive mast cells between the diseased and control groups ($P < 0.0003$). DDCs: Dermal dendritic cells; α-SMA: α-smooth muscle actin.

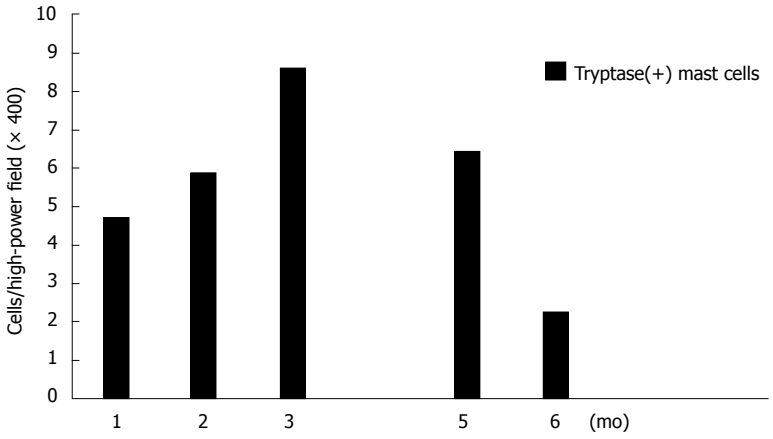

Figure 3 Progress at monthly intervals and mast cell count after occurrence of exanthema.

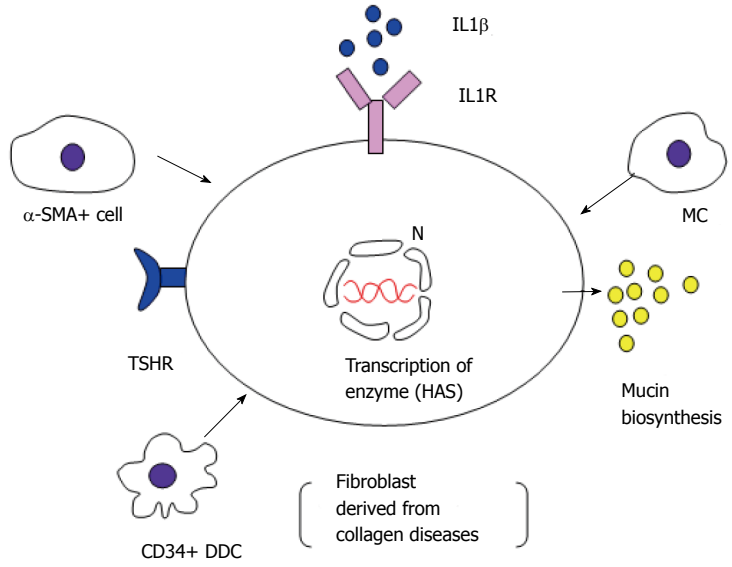

Figure 4 Proposed pathogenic mechanism underlying dermal mucin deposition in dermatomyositis. α-SMA: α-smooth muscle actin; N: Nucleus; TSHR: Thyroid-stimulating hormone receptor; HAS: Hyaluronan synthase.

Immunohistochemically, CD34 is a human progenitor cell antigen expressed not only on vascular endothelial cells but also on a population of dendritic fusiform cells around cutaneous appendages and in the interstitium, principally in the deep dermis[2,6]. In contrast, FXⅢa immunoreactivity is noted on populations of dendritic cells in the upper portion of the dermis and around blood vessels and cutaneous appendages. Taken together with our data regarding collagen disease involving dermatomyositis and rheumatoid arthritis[1], CD34+ DDCs seem to play important supportive functions in the production of mucin within diseased skin.

Much remains to be learned about CD34-expressing cells in the skin regarding the functional relationships of dermal mucin production between CD34+ DDCs and other cells (FXⅢa+ DDCs, α-SMA+ myofibroblasts, vimentin+ fibroblasts, and tryptase+ MCs). Although we did not identify the DDCs in dermatomyositis more

precisely, use of specific antibodies for DDCs such as blood dendritic cell antigens [BDCA-1 for myeloid DCs, BDCA-2 for plasmacytoid DCs (PDCs)] might be valuable for subtyping DDCs, as Shrestha *et al*[15] recently reported. Using juvenile patients with dermatomyositis, they suggested that increased numbers of mature PDCs with CD34 markers as well as MCs are the major producers of interferon (IFN)α, in which IFNα itself can conversely modulate DCs subsets. The major infiltrating DDCs around mucin-deposited skin lesions in dermatomyositis might plausibly represent PDCs, subsequently influencing the subsequent effector functions of T cells.

MCs positive for tryptase were frequently seen in the perilesional area of predominantly the papillary dermis, although a significant reduction in total numbers of tryptase+ MCs were seen compared to numbers in normal controls. With respect to quantification of MCs, our data did not show any significant increase in the number of MCs at sites of dermatomyositis, as compared with the skin of controls. However, the present study also found greater numbers of MCs in the papillary dermis than in the reticular dermis for both control subjects and patients with dermatomyositis having mucin deposition. Abd El-Aal *et al*[16] reported that increased numbers of MCs could stimulate dermal fibroblasts to produce mucin in lichen myxedema. Martins *et al*[17] speculated mucin production from fibroblasts derived from patients with cutaneous mucinosis through the interaction of elevated serum levels of IgE between MCs bearing FcεRIα. We cannot discard this possibility, because we did not examine serum IgE levels for our 8 patients with dermatomyositis.

According to Smith *et al*[18], colloidal iron stain-positive mucin is present in 97% of skin biopsy samples from dermatomyositis cases and is a characteristic finding on views of dermatomyositis examining the pathological organization, but is not seen in all cases. Mucin deposition can represent an important sign of dermatomyositis, and its association with convalescence is unknown. This study examined the presence of MCs and DDCs in clear cases of mucin deposition with dermatomyositis.

The dermatomyositis and normal skin groups in this study showed similar results, with only MCs counts showing a significant difference. MCs tended to be decreased in our 8 dermatomyositis cases, who had not received treatment as of the time of biopsy. MCs may thus decrease at some stage during the progress of dermatomyositis. We showed this in the tryptase(+)MC count according to progress before performing biopsy after exanthem appeared. A tendency toward an increase was seen for three months after presentation, followed by a decrease.

CONCLUSION

Immunohistochemical analysis of skin biopsy specimens with dermatomyositis showed the involvement of CD34+ DDCs, α-SMA+ myofibroblasts and possibly MCs, as well as vimentin+ fibroblasts for abnormally dermal mucin production. Further pathophysiological studies are required to more precisely clarify secondary cutaneous mucin deposition by CD34+ DDCs.

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REVIEW

P2X7 receptor in skin biology and diseases

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Abstract

The P2X7 receptor is a trimeric ligand-gated cation channel present on immune and other cells. Activation of this receptor by its natural ligand extracellular adenosine triphosphate results in a variety of downstream responses, including the release of pro-inflammatory mediators and cell death. In normal skin, P2X7 is present on keratinocytes, Langerhans cells and fibroblasts, while the presence of this receptor on other cutaneous cells is mainly inferred from studies of equivalent cell types present in other tissues. Mast cells in normal skin however express negligible amounts of P2X7, which can be upregulated in cutaneous disease. This review discusses the potential significance of P2X7 in skin biology, and the role of this receptor in inflammatory skin disorders such as irritant and chronic dermatitis, psoriasis, graft-versus-host disease, as well is in wound healing, transplantation and skin cancer.

Key words: P2X7 receptor; Purinergic receptor; Extracellular adenosine triphosphate; CD39; Skin biology; Skin immune system

Core tip: The P2X7 receptor is present on immune, stromal and epithelial cells. Activation of this receptor by its natural ligand, extracellular adenosine triphosphate, causes a variety of downstream effects including release of inflammatory mediators and growth factors, as well as cell death. P2X7 has various functions on skin cells, and studies of mouse models of disease and of human cells and tissues highlight emerging roles for this receptor in common skin disorders.

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INTRODUCTION

Overview

The skin fulfils important roles such as barrier protection, thermoregulation, sensation, vitamin D synthesis[1] and immunological protection[2]. Extracellular nucleotides

Table 1 Events downstream of P2X7 receptor activation

RONS formation
Shedding of CD23, CD27, CD62L and E-cadherin
Up-regulation of CD80 and CD86 expression
PGE-2 synthesis and release
IL-1β and IL-18 maturation and release
IL-6 release
IL-2 and IL-17 synthesis and release
VEGF release
Killing of intracellular pathogens
Cell death

IL: Interleukin; PGE-2: Prostaglandin E2; RONS: Reactive oxygen and nitrogen species; VEGF: Vascular endothelial growth factor.

and nucleosides function through a signalling network comprising cell-surface purinergic (P2X, P2Y and adenosine) receptors and ecto-nucleotidases[3]. This network plays important roles in both physiology and pathophysiology, and as such is an emerging therapeutic target to combat many diseases[3]. Evidence indicates that the extracellular nucleotide adenosine triphosphate (ATP) and cell surface purinergic receptors and ecto-nucleotidases play important roles in skin biology[4,5]. Within this context the P2X7 receptor has a major role. This review aims to describe the cellular distribution of P2X7 in skin, and the potential significance of this receptor in skin biology and diseases.

Purinergic signalling

Purinergic signalling comprises a complex network of cell-surface receptors, where activation is mediated by extracellular signalling molecules such as ATP, which can act as a danger associated molecular pattern (DAMP) when released into the extracellular milieu after cell stress, damage or death[6]. Extracellular ATP or other nucleotides can subsequently lead to activation of two purinergic P2 receptor subtypes; P2X and P2Y receptors. P2X receptors are a family of seven trimeric ATP-gated cation channels (P2X1-7); while P2Y receptors are a group of eight G protein-coupled receptors (P2Y1, 2, 4, 6, 11-14). P2 receptors are expressed on numerous cell subtypes, and activation of these receptors by extracellular ATP, or other nucleotides for some receptor subtypes, are important in inflammation and immunity[7]. Activation of P2 receptors by ATP is regulated by the ecto-nucleotidases CD39 and CD73. CD39 degrades ATP into adenosine diphosphate (ADP) and subsequently adenosine monophosphate (AMP) before AMP is converted to adenosine by CD73[8]. Adenosine can then activate P1 receptors; a family of purinergic receptors selective for adenosine[3].

The P2X7 receptor

The P2X7 receptor belongs to the family of P2X receptors, which as noted above, are trimeric ATP-gated cation channels. Each P2X7 subunit is composed of intracellular amino and carboxyl termini, as well as two transmembrane domains connected by a long glycosylated extracellular loop, containing the ATP-binding site[9]. Activation of the P2X7 receptor by extracellular ATP results in K^+ efflux, and Na^+ and Ca^{2+} influx, as well as the flux of organic cations and anions including dyes[10]. P2X7 is present on leukocytes, but is also found on other cell types including epithelial cells and fibroblasts[7]. P2X7 activation results in the stimulation of numerous pathways including the release of various pro-inflammatory mediators, modulation of various cell-surface receptors, formation of reactive oxygen and nitrogen species, killing of intracellular pathogens and cell death[11] (Table 1). As a result of various studies in humans and animals, P2X7 is emerging as an important molecule in various biological processes[12] and is attracting considerable interest as a therapeutic target in a wide-range of diseases[13]. Due to this, and the increasing knowledge about the expression and function of P2X7 within the skin (Figure 1), there is a growing interest in the role of P2X7 in skin biology and related disorders.

P2X7 IN SKIN BIOLOGY

Keratinocytes

Keratinocytes comprise the majority of cells within the epidermis to provide a physical and immunological barrier[14]. It is well established that human and rodent keratinocytes express P2X7. Immunohistochemistry reveals that P2X7 is expressed in the upper layer of human and rat skin[15,16] suggesting that this receptor may be involved in the death of terminally differentiated keratinocytes. Consistent with this concept, human keratinocyte P2X7 co-localises with markers of apoptosis[16], while P2X7 activation induces human keratinocyte death *in vitro*[17] and increases murine keratinocyte death *in vivo*[18]. P2X7 has been reported to be present on human HaCaT keratinocytes[19] and can mediate ATP-induced death of these cells[20], although the presence of P2X7 in these cells has not been confirmed in all studies[21]. Nevertheless over-expression of protein kinase C alpha (PKCα) can result in increased expression of P2X7 in these cells[19] indicating that this kinase may be involved in the up-regulation of keratinocyte P2X7 in the upper layers of the epidermis. Despite the apparent localisation of keratinocyte P2X7 to the upper layers of the epidermis, functional studies (using ATP-induced dye uptake measurements) show that the majority of human and murine keratinocytes express P2X7[22,23]. Thus, these immunohistochemistry and functional studies combined suggest P2X7 may be present in all layers of the epidermis, with receptor expression increasing with keratinocyte differentiation and its upregulation resulting in the death of terminally differentiated keratinocytes.

In addition to cell death, P2X7 activation can induce interleukin (IL)-6 release from human keratinocytes[24], and can mediate ultraviolet radiation-induced IL-1β release from both human and murine keratinocytes[25,26]. P2X7 activation on HaCaT keratinocytes has also been implicated in the activation of disintegrin-like metalloprotease-mediated shedding of E-cadherin and transforming growth factor alpha (TGF-α) induced by the major bee venom

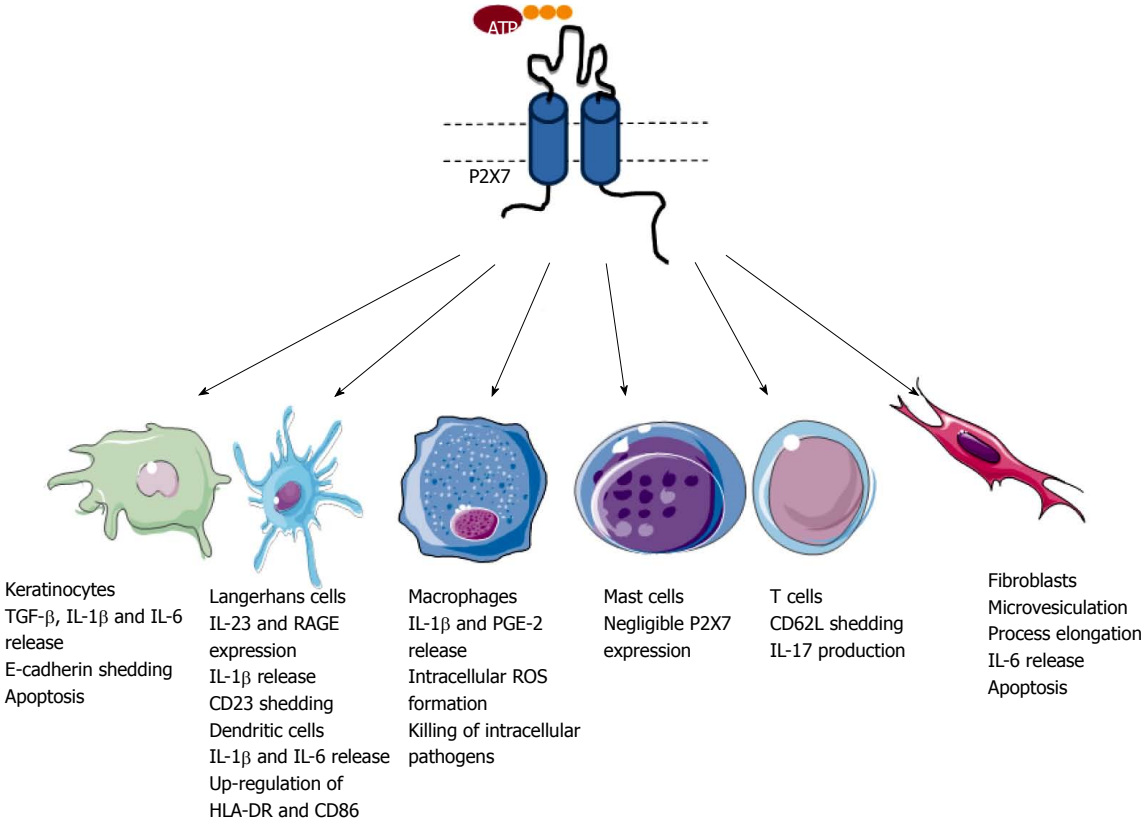

Figure 1 Expression and function of the P2X7 receptor on skin cells. P2X7 is present on keratinocytes, Langerhans cells, dermal dendritic cells, dermal macrophages, skin T lymphocytes and dermal fibroblasts. P2X7 activation on these cells induces a number of downstream events as indicated. P2X7 is absent on mast cells in normal skin, but can be upregulated during cutaneous disease. P2X7 may also be present on skin B cells, neutrophils, eosinophils and basophils (not shown), but direct evidence is lacking. Cell images were obtained from Servier Medical Art (www.servier.com). ATP: Adenosine triphosphate; HLA: Human leukocyte antigen; IL: Interleukin; PGE2: Prostaglandin E2; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; TGF: Transforming growth factor.

component melittin[27]. Collectively, these results indicate that P2X7 on keratinocytes may also be important in inflammatory and immune functions of these cells.

Langerhans cells

Langerhans cells (LCs) are professional antigen-presenting cells located in the epidermis, and are important in the establishment of adaptive immunity and the maintenance of peripheral tolerance[28]. P2X7 is present on both human and murine LCs from skin[22,23,29], as well as on migratory LCs [langerin$^+$ dendritic cells (DCs)] from human skin explants[30]. Although functional studies of P2X7 on LCs are largely limited to ATP-induced dye uptake measurements[22,23,29], P2X7 activation of migratory LCs causes increased cell-surface expression of the IL-23 receptor and the alarmin receptor for advanced glycation end products (RAGE)[30]. Further, P2X7 is present on human LCs derived from monocytes *in vitro* and activation of this receptor results in the rapid shedding of CD23 (the low affinity IgE receptor) from these cells[22]. Finally, P2X7 is present on the murine LC-like line, XS106, and activation of this receptor results in the release of IL-1β from these cells[31]. Collectively, these studies support a role for P2X7 activation on LCs in promoting inflammation and immunity.

The relative amount of P2X7 activity on LCs appears to be negatively modulated by the ecto-nucleotidase CD39 (Figure 2). It has long been known that LCs express high ecto-ATPase and ecto-ADPase activities[32], which is almost completely due to CD39[33]. Comparison of human monocyte-derived LCs and monocyte-derived DCs generated from the same subjects reveals that the relative P2X7 activity is lower on monocyte-derived LCs compared to monocyte-derived DCs despite similar amounts of cell-surface P2X7 expression[22]. This difference in activity between these two cell types is inversely associated with cell-surface CD39 expression[22]. These observations are consistent with the negative regulation of P2X7 activation by CD39 on murine peritoneal macrophages[34] and murine bone marrow-derived mast cells[35] (Figure 2). Notably, CD39 on LCs has been implicated in facilitating a protective or tolerogenic role for these cells in dermatitis[33,36]. Collectively, variations in CD39 activity may play important roles in the regulation of P2X7 activation on LCs, and in determining the relative contribution of these cells in immunity or peripheral tolerance.

Dermal DCs

Dermal DCs are a heterogeneous population of professional antigen-presenting cells, and like LCs are important in the establishment of adaptive immunity and the maintenance of peripheral tolerance[37]. It is well documented that

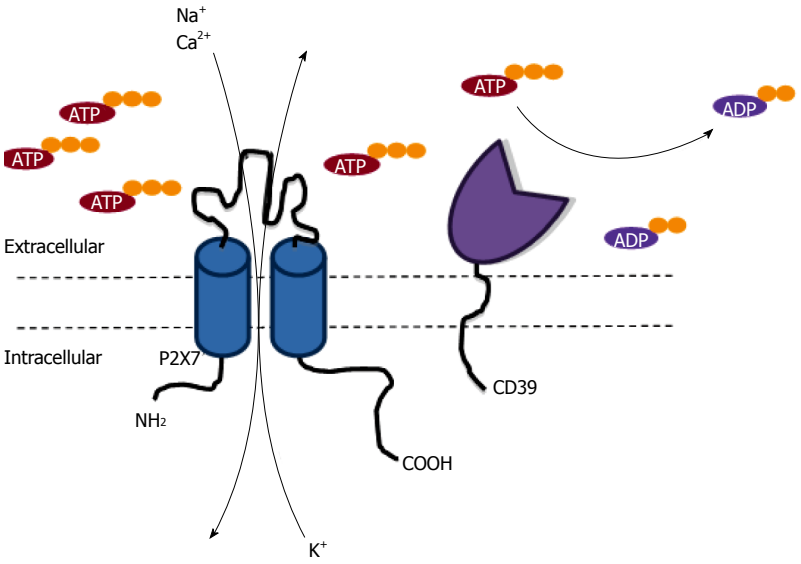

Figure 2 Activation of the P2X7 receptor and its regulation by CD39. Activation of P2X7 by extracellular ATP causes an influx of Ca^{2+} and Na^{+}, and efflux of K^{+}. Extracellular ATP can be degraded by cell surface CD39 to limit P2X7 activation on Langerhans cells, macrophages and mast cells. ATP: Adenosine triphosphate.

P2X7 is present on human and murine DCs derived from monocytes[38-41] or within lymphoid tissues[42,43], but direct evidence for P2X7 on dermal DCs is limited. P2X7 is present on foetal skin-derived DCs, where it may be involved in T cell stimulation[44], however direct evidence for DC P2X7 in this process is not well established. Interpretation of these results is complicated by subsequent findings that extracellular ATP can induce human and murine T cell proliferation *via* P2X7 in an autocrine fashion[45]. Thus, the role of P2X7 in T cell stimulation by dermal DCs remains to be elucidated.

P2X7 is also expressed on migratory DCs from human skin explants[30]. Activation of P2X7 on skin migratory DCs resulted in the release of IL-1β and IL-6, as well as the up-regulation of IL-23 and vascular endothelial growth factor (VEGF) mRNA and cell-surface expression of HLA-DR, and the co-stimulation molecule CD86[30]. Finally, P2X7 activation on these cells promotes the development of T helper 17 (Th17) cell responses[30].

Dermal macrophages

Dermal macrophages are a heterogeneous population of cells important in innate and adaptive immunity, as well as in tissue homeostasis and wound healing[37]. Direct evidence for P2X7 on dermal macrophages is lacking, but it is well established that this receptor is present on human and murine macrophages derived from monocytes[46-48] or isolated from tissues[49,50]. P2X7 activation on human and murine macrophages results in the release of pro-inflammatory mediators such as IL-1β and prostaglandin E_2[51], as well as the production of reactive oxygen species[52], and killing of intracellular mycobacteria[53], chlamydia[54] and toxoplasma[55]. Of note, P2X7 activation eliminates *Leishmania amazonensis*, the causative agent of human cutaneous leishmaniasis[56], within murine peritoneal macrophages[57], supporting the potential importance of macrophage P2X7 in skin biology.

Mast cells

Mast cells are present in the dermis, and play important roles during inflammation and immunity[58]. In contrast to other tissues, mast cells in normal human and murine skin express negligible amounts of P2X7[59,60], and ATP incubation of these cells fails to cause IL-1β release despite inducing IL-1β release from murine bone marrow-derived mast cells[61]. This negligible P2X7 expression on skin mast cells is due to fibroblasts expressing the retinoic acid-degrading enzyme Cyp26b1[61]. Although the exact mechanism by which these fibroblasts prevent P2X7 expression on skin mast cells is not known, exogenous retinoic acid upregulates P2X7 expression on bone marrow-derived mast cells[61]. This suggests that Cyp26b1-expressing fibroblasts in mice regulate retinoic acid concentrations to suppress P2X7 expression on skin mast cells. Whether this same inhibitory mechanism operates for human skin mast cells or limits P2X7 expression on other dermal cell populations remains to be determined.

Granulocytes

Granulocytes (neutrophils, eosinophils and basophils) are circulating innate immune cells that infiltrate the skin to promote inflammation and immunity[62]. Small numbers of neutrophils also circulate through normal skin, where they are presumed to function as sentinels[63]. Direct evidence for P2X7 on granulocytes within the skin is lacking, but P2X7 is present on human blood eosinophils[64,65] and murine bone marrow-derived basophils[66]. P2X7 activation on human eosinophils results in cation fluxes, increased expression of the integrin CD11b and reactive oxygen species formation, as well as chemotaxis of these granulocytes[64,65]. P2X7 activation is involved in the IgE-dependent activation of murine bone marrow-derived basophils[66], which may have implications for cutaneous allergic inflammation. Collectively, these results suggest P2X7 may play important roles in the pro-inflammatory actions of these granulocytes.

In contrast to eosinophils and basophils, P2X7 appears to be absent on neutrophils. Repeated evidence demonstrates that P2X7 is not present in human blood

neutrophils[67,68]. Neutrophil infiltration however is reduced by P2X7 deficiency in murine models of skin inflammation[69] suggesting that P2X7 may be present on murine neutrophils or that P2X7 activation on other skin cells indirectly promotes neutrophil infiltration. Nonetheless future studies are required to determine if P2X7 is present on murine neutrophils or on neutrophils within skin.

T cells

Both human and murine skin contains populations of tissue-resident and recirculating T cells, which are key cellular mediators of adaptive immunity[70]. Direct evidence for P2X7 on these skin T cells is lacking, however it is well known that human and murine T cell subsets from blood and lymphoid tissue express P2X7[71]. P2X7 activation induces the rapid shedding of CD62L (L-selectin) from both human and murine $CD4^+$ and $CD8^+$ T cells[72,73]. This cell adhesion molecule can regulate the migration of certain T cell subsets to sites of skin inflammation[74]. Thus, the possibility remains that P2X7-induced CD62L shedding may regulate T cell migration within the skin. There is also evidence that P2X7 activation promotes Th17 cell development in humans[75] and mice[76]. Thus, a further possible role for P2X7 on skin T cells is in the generation of cutaneous Th17 responses.

Dendritic epidermal T cells (DETCs) are resident T cells found in the epidermis of mice, but not humans, and have important roles in inflammation, immunity and wound healing[77]. Murine DETCs express low amounts of P2X7 mRNA[26] but an earlier study, using an anti-P2X7 monoclonal antibody and ATP-induced dye uptake measurements, failed to observe P2X7 on DETCs, despite the presence of P2X7 on keratinocytes and LCs[23]. Nevertheless ATP, released from keratinocytes, can enhance IL-17 release from CD3-activated DETCs[26]. A direct role for P2X7 activation on DETCs in this process was not established, and these cells express high amounts of mRNA for P2X1, P2X2, P2X3 and P2X5[26], thus it remains to be established if DETCs express functional P2X7. It also remains to be established if P2X7 is present on resident T cells in human skin, which are considered to be the equivalent cell type to murine DETCs[77].

B cells

B cells are key cellular mediators of adaptive immunity, but their role in the skin immune system is poorly understood. Emerging evidence indicates the presence of B cells in normal skin, although it is unknown if they are skin-resident or circulating B cells[78]. Further evidence indicates roles for B cells in cutaneous immunity and inflammation, and skin cancer[78]. As for T cells, evidence for P2X7 on skin B cells is lacking, but P2X7 is present on human and murine B cells from blood and spleen[79,80]. P2X7 activation results in the rapid shedding of CD62L from human B cells[79] suggesting that this mechanism may regulate B cell migration within the skin. P2X7 activation also results in the rapid shedding of CD23 from human and murine B cells[80]. Although the functional significance of this process is yet to be established, soluble CD23 can regulate IgE production[81]. Thus, P2X7-mediated release of soluble CD23 may regulate the development or severity of atopic dermatitis.

Fibroblasts

Fibroblasts are a heterogeneous population of cells located in the dermis with a variety of functions including tissue homeostasis, wound healing and inflammation[82]. Human skin fibroblasts express P2X7[83,84]. In addition to cation fluxes, dye uptake and membrane depolarisation, P2X7 activation in these cells results in microvesiculation, process elongation, IL-6 release and apoptosis[84]. High concentrations of glucose potentiate these P2X7-mediated responses[84]. This effect of glucose is attributed to a redistribution of P2X7 on the cell surface rather than increased expression of this receptor[84]. Of note, skin fibroblasts from type 2 diabetic subjects demonstrate enhanced P2X7-mediated responses compared to skin fibroblasts from normal subjects[85]. This enhanced P2X7 activity is suggested to be an important mechanism in the pathogenesis of vascular damage in diabetic subjects[85], but this concept is yet to be developed. P2X7 may also be expressed on murine skin fibroblasts, but observations are limited to the subcutaneous fibroblast cell line L929[86]. This study demonstrated that P2X7 activation mediates cation fluxes, membrane depolarisation and cytotoxicity in these cells.

P2X7 IN SKIN DISEASES

Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a type IV delayed-type hypersensitivity (DTH) reaction characterised by a T cell-mediated response to allergens[87]. A role for P2X7 in ACD in humans is supported by the up-regulation of this receptor in the epidermal basal layer of inflamed skin of atopic dermatitis patients compared to normal human skin[88], while other experimental evidence supports a role for P2X7 in murine models of ACD. ACD is commonly studied using animal models of contact hypersensitivity (CHS)[87]. Both pharmacological blockade and genetic deficiency of P2X7 impairs CHS responses in mice[89]. This impaired CHS response is due to the absence of P2X7-mediated IL-1β release from DCs abrogating the sensitising capacity of these cells[89]. Intradermal injection of the hydrolysis-resistant nucleotide, adenosine gamma-thiotriphosphate (ATPγS), can also enhance the CHS response in mice[31] indirectly supporting a role for P2X7 in ACD. However, ATPγS cannot activate murine P2X7 *in vitro*[90] despite activating other mammalian P2X7[90,91]. This raises the possibility that ATPγS acts on other P2 receptors in this model of murine CHS[31]. Notably, non-metal haptens can induce ATP release from primary human and HaCaT keratinocytes[92] providing a possible

source for extracellular ATP in ACD.

Irritant contact dermatitis

Irritant contact dermatitis (ICD) is an inflammatory reaction to chemical irritants involving cells of the innate immune system[93]. Experimental evidence in mice supports a role for P2X7 in ICD. Both pharmacological blockade and genetic deficiency of P2X7 impair oedema, IL-1β production and neutrophil infiltration in croton oil-induced ICD[69]. Furthermore, clodronate-depletion of DCs and macrophages, or pharmacological inhibition of caspase-1 reduced ICD in this model[69] suggesting that P2X7 on DCs and macrophages may contribute to the pathogenesis of ICD through IL-1β production. In addition to a role for P2X7 on DCs and macrophages in ICD, P2X7 on mast cells is involved in retinoid-induced ICD. This form of ICD is mediated by aberrant release of ATP within the skin and increased P2X7 expression on skin mast cells[61]. A role for mast cell P2X7 in chemical-induced ICD remains to be determined.

Consistent with a role for P2X7 in ICD, chemical irritants can induce ATP release from murine and human keratinocytes[33,94,95], and genetic deficiency of CD39 exacerbates croton oil-induced ICD in mice[33,94]. Croton oil also decreases ATPDase activity in mice[20] indicating that chemical irritants may further potentiate P2X7-mediated responses by causing a sustained increase in ATP concentrations during chemical irritant exposure. Of note, zinc deficiency, which is often associated with increased cutaneous inflammation, enhances ICD in mice and augments chemical irritant-induced ATP release from murine keratinocytes and in murine skin[36]. Further, zinc deficiency in murine ICD is associated with loss of LCs[36], which play a protective role in ICD through CD39 expression[33]. This suggests that both increased ATP release from keratinocytes and impaired hydrolysis of ATP by LCs may contribute to the pathogenesis of ICD.

Psoriasis

Psoriasis is a chronic inflammatory disorder manifesting as plaque or pustular-like lesions of the skin. Psoriasis emerges due to excessive keratinocyte renewal, caused by an innate immune cell response and subsequent engagement of the adaptive immune response, resulting in a feed forward mechanism of inflammation[96]. Although the role of P2X7 has not been investigated in animal models of psoriasis, *in vitro* studies support a role for P2X7 in psoriasis pathogenesis. Interferon gamma (IFN-γ), a pro-inflammatory cytokine implicated in psoriasis development[96] can upregulate the expression of P2X7 in primary keratinocytes[88]. Moreover, injection of the P2X7 agonist 2′,3′-O-(4-benzoyl)benzoyl ATP (BzATP) into normal human skin explants induces increased expression of cytokines and other molecules commonly associated with psoriasis, including IL-1β, IL-6 and TNF-α[30]. Importantly, these responses could be prevented through pharmacological blockade of P2X7[30]. Of note, P2X7 expression in this model also caused the functional maturation of cutaneous DCs and promoted the development of Th17 responses[30], both of which are important contributors to psoriasis pathogenesis[96].

Cutaneous graft-vs-host disease

Graft-*vs*-host disease (GVHD) is a common complication following bone marrow transplantation used to treat haematological malignancies[97]. Two types of GVHD develop in patients; acute GVHD emerges early after transplantation, while chronic GVHD is a persistent long-lasting inflammation, with both forms causing inflammatory damage to the skin, as well as the gastrointestinal tract, liver and lungs[97]. Pharmacological blockade and genetic deletion of P2X7 attenuates the development of disease in murine models of allogeneic GVHD[98,99]. Additionally, experimental evidence establishes a model whereby ATP released at the site of tissue damage causes upregulation of the co-stimulatory molecules, CD80 and CD86 on DCs to promote T cell responses[98]. P2X7 deficient mice receiving allogeneic bone marrow transplants demonstrated reduced serum concentrations of the pro-inflammatory cytokines IFN-γ, TNF-α, and IL-6[98], which was replicated through blockade of the P2X7 receptor *in vivo* using the nucleoside reverse transcriptase inhibitor stavudine[99]. Although the effect of P2X7 deficiency or blockade on acute skin GVHD was not directly reported in either study[98,99], skin is a known target organ of GVHD in these models of allogeneic bone marrow transplantation[100]. Of note, P2X7 blockade failed to prevent the development of chronic skin GVHD[98], suggesting P2X7 may not play a role in skin inflammation in chronic GVHD, or longer periods of P2X7 blockade are required for prevention of chronic skin GVHD.

Wound healing

Wound healing is classically defined by the disruption of haemostasis, migration of platelets resulting in blood clotting, followed by inflammation, cell proliferation and tissue remodelling[101]. Studies both *in vitro* and *ex vivo* have demonstrated a role for P2X7 in the process of wound healing. P2X7 is important for early cell migration and infiltration of immune cells required for wound healing, with P2X7 deficient cells showing a reduced migratory ability in an *in vitro* wound repair model suggesting that lack of P2X7 affects chemotaxis[102]. P2X7 also promotes the release of VEGF from primary monocytes, important for control of angiogenesis and wound healing[103]. Conversely, P2X7 is down-regulated on keratinocytes during wound healing[104], suggesting that this reduced expression may be linked with reduced apoptosis of keratinocytes to promote healing of the epidermis. Mast cells also play an important role in wound remodelling and repair[105], but express negligible P2X7 in normal skin[59,60]. It remains to be determined if P2X7 on mast cells is upregulated during wound healing.

Skin transplantation

Transplantation is an important therapy for many end-stage diseases and rejection of transplants remains

Table 2 Roles of the P2X7 receptor in mouse models of skin disease

Disease	Observations
Allergic contact dermatitis	P2X7 blockade or deficiency impairs CHS[89]
Irritant contact dermatitis	P2X7 blockade or deficiency impairs croton oil-induced oedema, IL-1β production and neutrophil infiltration[69]
Psoriasis	ND
Cutaneous graft-*vs*-host disease	P2X7 blockade or deficiency increases survival and reduces disease severity, serum concentrations of IFN-γ, TNF-α and IL-6 in allogeneic mouse models[98,99]
Wound healing	P2X7 deficient macrophages display reduced migration in an *in vitro* wound repair model[102]
Skin transplantation	P2X7 blockade or deficiency prevents allogeneic skin transplant rejection[109]
Melanoma	ATP injection impairs A375 melanoma cell growth in immuno-compromised mice[120] P2X7 blockade inhibits B16 melanoma cell growth in immuno-competent mice[121,122] P2X7 deficiency impairs B16 melanoma cell migration *in vitro*[102] P2X7 deficiency in host leads to increased B16 melanoma growth and metastasis[102]
Basal cell carcinoma	ND
Squamous cell carcinoma	P2X7 deficiency in host enhances chemical-induced carcinogenesis[18] BzATP injection led to tumour apoptosis[18]

ATP: Adenosine triphosphate; BzATP: 2',3'-O-(4-benzoyl) benzoyl ATP; CHS: Contact hypersensitivity; IFN: Interferon; IL: Interleukin; ND: Not determined; TNF: Tumour necrosis factor.

Table 3 Roles of the P2X7 receptor in human skin diseases

Disease	Observations
Allergic contact dermatitis	Increased P2X7 expression in atopic dermatitis lesions[88]
Irritant contact dermatitis	ND
Psoriasis	Increased P2X7 expression in psoriatic skin lesions[30,88]
Cutaneous graft-*vs*-host disease	ND
Wound healing	P2X7 activation promotes VEGF release from monocytes[103]
Skin transplantation	ND
Melanoma	P2X7 is present on melanoma cells[117,118] and cell lines[119], with increased expression compared to normal melanocytes[119] P2X7 activation induces A375 melanoma[118] but suppresses HT168-M1 melanoma cell death[119]
Basal cell carcinoma	P2X7 is present in necrotic tumour centres and apoptotic tumour cells, and correlates inversely with tumour aggressiveness[123]
Squamous cell carcinoma	P2X7 is present in apoptotic tumour cells and its activation causes A431 SCC cell death[123]

ND: Not determined; SCC: Squamous cell carcinoma; VEGF: Vascular endothelial growth factor.

a major problem. Studies in transplantation have shown upregulation of P2X7 expression on infiltrating lymphocytes in transplanted hearts in human patients[106]. Pharmacological blockade and genetic deletion of P2X7 in murine models leads to a delay in allograft rejection, which has been demonstrated in several transplant models including models of islet[107], heart[106] and lung[108] transplantation. However, with the exception of one preliminary report[109], there are limited studies investigating P2X7 in skin transplants. In this study[109], ATP is released in allogeneic but not syngeneic skin grafts. This ATP release involved macrophages and the pannexin-1 hemichannel, and was impaired by pharmacological blockade or genetic deletion of P2X7. This inhibition or absence of P2X7 delayed allogeneic skin graft rejection. Collectively, these results support a role for P2X7 in ATP release and tissue rejection in allogeneic skin graft transplantation.

Skin cancer

Skin cancers are common cancers within humans and include three main forms: Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma[110]. Ultraviolet radiation is the major causative factor of these skin cancers[110]. P2X7 is emerging as an important receptor in many forms of cancers, with various and contradictory roles attributed to this receptor in tumour biology[111]. These include but are not limited to tumour cell proliferation[112], death[113], and invasiveness[114], as well as anti-tumour immunity[115] and cancer pain[116].

The role of P2X7 in skin cancer has been studied most widely in melanoma. Immunohistochemistry reveals expression of P2X7 in human melanoma[117,118] and in various melanoma cell lines[119]. Further, this receptor is expressed at higher quantities in melanoma cells compared to normal melanocytes[119]. Importantly, P2X7 in melanoma and melanoma cell lines is functional[118,119]. Paradoxically, P2X7 activation promotes and suppresses ATP-induced apoptosis in human A375[118] and HT168-M1 melanoma cells[119], respectively. These differences remain to be reconciled, but opposing effects with P2X7 have also been observed in murine models of melanoma. ATP injection impairs the growth of A375 melanoma cells in (athymic) immuno-compromised mice[120] supporting an anti-tumour effect for P2X7 presumably through ATP-induced cell death.

Conversely, injection of P2X7 antagonists inhibits the growth of murine B16 melanoma cells (which express P2X7[121]) in immuno-competent mice[121,122]. Additional data from these studies demonstrated that this pro-tumour effect of P2X7 was due to enhanced ATP-induced proliferation of B16 melanoma cells[121,122]. P2X7 on immune cells also plays an important role in preventing melanoma progression by promoting anti-tumour immune responses. B16 melanoma growth and metastasis is increased in P2X7 deficient mice or wild-type chimeric mice transplanted with P2X7-deficient bone marrow compared to control mice[102].

P2X7 may also play an important role in BCC and SCC. Immunohistochemistry of human samples reveals expression of P2X7 in the necrotic centre of BCCs and within apoptotic cells in both BCCs and SSCs, suggesting that P2X7 activation may mediate killing of malignant cells within these tumours[123]. Evidence for this process in BCC is wanting, but P2X7 can mediate the killing of the human A431 SCC line[123]. Another report however attributed this cytolytic effect to adenosine resulting from ATP hydrolysis rather than ATP directly[124]. Thus, the role of P2X7 in this cell line remains uncertain. As noted above, P2X7 is also present on immortalised HaCaT keratinocytes[19] and mediates ATP-induced death in these cells[20]. Notably, ultraviolet B irradiation down-regulates P2X7 expression in HaCaT keratinocytes, potentially leading to survival of cells with a reduced ability for ATP-induced apoptosis, and allowing for malignant transformation and survival of malignant cells[125]. Consistent with this concept, in BCC patients, more aggressive tumours have lower P2X7 expression, suggesting that loss of P2X7 can act as a marker for increased tumour aggressiveness[123]. Finally, in a murine model of chemically-induced skin papilloma/SCC carcinogenesis, injection of BzATP reduces the frequency and size of papillomas and skin cancers, a response that is absent in P2X7 deficient mice, indicating a role for P2X7 in this process[18]. P2X7 activation in these tumours is associated with apoptosis[18]. Of note, P2X7 expression is reduced in papillomas and skin cancers compared to normal skin[18], suggesting that down-regulation of P2X7 in skin tumours is a possible escape mechanism to avoid ATP-induced apoptosis.

Summary

In summary, P2X7 is present on immune, stromal, epithelial and malignant cells in diseased skin, and is up-regulated in some skin disorders. Activation of P2X7 cells and the resulting downstream effects are implicated in numerous skin diseases including allergic and irritant contact dermatitis, psoriasis, cutaneous GVHD, as well as in skin transplantation and skin cancer. In some instances the role of P2X7 in skin disease is supported by mouse models (Table 2) and human studies (Table 3), but for other skin diseases evidence is limited to only one species. Nevertheless, P2X7 represents a potential biomarker and target for treatment of various skin disorders, but further studies are required before the clinical value of P2X7 can be utilised.

CONCLUSION

The P2X7 receptor is present on numerous immune and other cell types in the skin including keratinocytes, Langerhans cells, and dermal dendritic cells, and may be present on T and B cells. P2X7 expression is negligible on mast cells, but can be upregulated in skin disease. Activation of P2X7 by ATP results in numerous downstream effects including cytokine release and apoptosis. P2X7 may play a role in homeostatic skin biology and has been implicated in a number of skin disorders, including contact dermatitis, psoriasis, cutaneous GVHD, and is involved in other skin processes including transplantation and wound healing. Thus, P2X7 represents a potential target for therapy of skin diseases.

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REVIEW

Unraveling oral psoriasis and its relationship with geographic tongue: A literature review

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Abstract

Differentiating between oral psoriasis and geographic tongue is difficult and controversial because some patients with geographic tongue do not necessarily have psoriasis. Furthermore, the number of clinical studies, reporting histopathological and genetic evidence for the definitive diagnosis of oral psoriasis, is limited. The aim of this literature review was to obtain data for supporting the diagnosis of oral psoriasis with particular emphasis on the relationship between psoriasis and geographic tongue. Based on the current data, it can be concluded that geographic tongue is the most common oral lesion in psoriasis, and histopathological, immunohistochemical, and genetic similarities have been observed between the two diseases. This review also emphasizes the importance of conducting oral examinations in patients with psoriasis and skin examinations in patients with geographic tongue.

Key words: Psoriasis; Geographic tongue; Oral psoriasis; Benign migratory glossitis

Core tip: The occurrence of oral lesions in psoriasis is rare; however, some authors consider geographic tongue as an oral manifestation of psoriasis. Furthermore, the number of clinical studies, providing histopathological and genetic evidence for the definitive diagnosis of oral psoriasis, is limited. The aim of this literature review was to investigate the current data on oral psoriasis with an emphasis on the relationship between psoriasis and geographic tongue.

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INTRODUCTION

Psoriasis is a chronic, inflammatory, cutaneous-articular disease that affects 1%-3% of the world's population[1,2]. The occurrence of oral lesions in psoriasis is rare, and the relationship between these lesions and the disease is controversial because of a limited number of cases with definitive histopathological diagnosis[3-7]. Schultz first reported oral lesions in psoriasis in 1898; he presented three cases of psoriasis on the buccal mucosa[8]. Subsequently, Oppenhein provided evidence of oral psoriasis in 1903 when he confirmed a clinical diagnosis by histopathology[9]. There is substantial variability in the location and presentation of these lesions, and they are often described as plates or white patches, ulcers, pustules, papules, and erythematous lesions[8,10-17]. In general, oral lesions in psoriasis can be divided into the following two categories: the first category includes true psoriatic lesions (confirmed by biopsy) accompanied by a parallel clinical course of skin lesions[3,18,19] and the second category, which includes majority of oral findings in psoriasis, contains non-specific lesions, including fissured tongue and geographic tongue[3,4,7,18-20]. Patients with psoriasis frequently exhibit geographic tongue, showing clinical, microscopic, and genetic similarities between the two diseases. However, the condition still does not have a well-defined etiology[21-24]. The diagnosis of geographic tongue as oral psoriasis is controversial and difficult as some patients with geographic tongue do not suffer from psoriasis[3]. Additionally, the number of clinical studies, providing histopathological and genetic evidence on a plausible definitive diagnosis of oral psoriasis is limited[3,18,22]. Considering the importance of obtaining accurate data, the aim of this literature review was to assess the current data on oral psoriasis with particular emphasis on the relationship between the disease and geographic tongue.

LITERATURE RESEARCH

A systematic literature search was conducted using PubMed and the Cochrane Library. The search terms used were "geographic tongue", "oral psoriasis", "psoriasis", and "benign migratory glossitis". In total, 65 relevant studies were included in the review.

ORAL MANIFESTATIONS OF PSORIASIS

Although psoriasis affects up to 3% of the world's population, there are a limited number of studies that focus on involvement of the oral mucosa[1,5].

Psoriatic lesions have mostly been observed in the jugal mucosa, labial mucosa, skin of the lips (vermilion), hard and soft palate, floor of the mouth, gums, and tongue. The presentation of these lesions is highly variable, and they have been described as striae, white plaques, grayish white spots, white scales, mottled erythema, brown plaques, ulcers, pustules, papules, and atrophic lesions (Table 1)[8,10-17]. In 1933, Usher examined 100 patients with cutaneous psoriasis and found that the oral mucosa was affected in two of them. Years later, Pisanty and Ship[10] (1970) described a case of a male patient who exhibited an asymptomatic white plaque in the upper and lower lips for a duration of 2 mo. The patient had a personal and family history of psoriasis. Using histopathological analysis, the authors confirmed a diagnosis of oral psoriasis.

DeGregori *et al*[25] described a 53-year-old psoriasis patient with a family history of the disease and diffused erythema on the gingiva and tongue, symptoms that were histopathologically compatible with oral psoriasis. The authors demonstrated that up to the date of publication of their study, only 15 cases of oral psoriasis had been reported, and only two of them showed involvement of the gingival tissue.

Salmon *et al*[9] reported a case of psoriasis with oral involvement where the patient reported pain and itching in the lips and tongue. The tongue and lips exhibited irregular ulcers with erythematous borders, and a diagnosis of oral psoriasis was confirmed by histopathology.

White *et al*[12] described a case of a 43-year-old patient with psoriasis and erythematous lesions in the attached gingiva, labial mucosa, and soft palate, whereas Cataldo *et al*[26] described a case of a 47-year-old patient with white and raised lesions on their tongue and lips.

Hietanen *et al*[21] evaluated the oral mucosa of 200 patients with psoriasis, most of whom presented with disseminated skin psoriasis. Amongst these, fissured tongue was present in 9% of the patients, geographic tongue was observed in 1%, and angular cheilitis in 3%. Biopsies were performed in 20 patients, four of which had outcomes that were consistent with psoriasis.

Hubler[27] reported five cases from three families who presented with generalized pustular psoriasis and tongue injuries. The author concluded that geographic tongue was an oral manifestation of generalized pustular psoriasis and that the two diseases were polygenic and episodic, had identical clinical histopathology, and manifested due to the influence of external factors.

Sklavounou *et al*[28] reported a case where intraoral examination revealed white lesions with erythematous areas that were slightly raised, well circumscribed, and located on the dorsum of the tongue. Lesions similar to geographic tongue were also observed on the lateral edge of the tongue. Although no skin disorder was diagnosed until the evaluation, the daughter was a carrier of psoriasis. A biopsy and HLA typing were performed, and the results of the microscopic analysis and the presence of B13 antigen confirmed a diagnosis of oral psoriasis.

Younai *et al*[29] reported an unusual case of oral lesions with the characteristics of psoriasis. The intraoral

Table 1 Oral psoriasis - case reports

Ref.	Age (yr)	Sex (M/W)	Affected areas	Clinical aspects	Histopathological diagnosis	Cutaneous psoriasis
Pisanty *et al*[10]	47	Man	Labial mucosa	White plaques	Yes	Yes
DeGregori *et al*[25]	53	Man	Tongue gingiva	Diffuse erythema	Yes	Yes
Salmon *et al*[9]	45	Woman	Tongue labial mucosa	Erythematous ulcers	Yes	Yes
White *et al*[12]	43	Woman	Gingiva labial mucosa soft palate	Erythematous spot	Yes	Yes
Cataldo *et al*[26]	47	Woman	Tongue lip	White plaques	Yes	Yes
Sklavounou *et al*[28]	42	Woman	Tongue	White plaque with erythematous areas	Yes	No[1]
Younai *et al*[29]	65	Woman	Tongue lip	Multiple pustules within the atrophic and erythematous areas	Yes	No
Rozell *et al*[30]	18	Man	Gingiva	Erythematous lesions	Yes	No[1]
Brice *et al*[14]	77	Man	Tongue, palate and gingiva	Erythematous lesions	Yes	Yes
	51	Man	Labial mucosa and gingiva	Erythematous plaques with withe border		
Ariyawardana *et al*[31]	11	Woman	Buccal mucosa	Erythematous plaque	Yes	Yes
Binmadi *et al*[15]	72	Man	Tongue	Ulcers associated with fissured tongue	Yes	Yes
Reis *et al*[32]	35	Woman	Gingiva palate	Erythematous patches	Yes	No
Mattsson *et al*[33]	52	Woman	Buccal mucosa and gingiva	Diffuse patchy erythema	Yes	Yes
	40	Man	palate	red areas		

[1]Patient with familiar history of psoriasis.

examination revealed geographic and fissured tongue, as well as an injury on the upper lip that was covered by a crust which could be easily removed by scraping to reveal a surface with minimal bleeding and white dots. No skin lesions were observed in the extra-oral examination. Lip biopsies were performed and the histopathological results were suggestive of psoriasis.

Rozell *et al*[30] showed that the presence of skin lesions was not necessary for the manifestation of oral psoriasis in some cases. For example, an 18-year-old male who was studied for 12 years showed no clinical signs of cutaneous psoriasis during this period, although he exhibited erythematous lesions in the gums. An initial biopsy performed when he was 6 years old yielded classic histopathologic results of psoriasis. A second biopsy performed 12 years later gave the same result. His family history was positive for psoriasis, but none of the family members with dermal psoriasis presented any oral manifestations.

Brice *et al*[14] reported two cases with an initial diagnosis of cutaneous psoriasis who exhibited injuries in the attached gingiva. Histopathological examination revealed signs that were compatible with psoriasiform mucositis. Although rare, oral involvement of psoriasis may occur and the correct diagnosis depends on clinical and histopathological evaluation.

Ariyawardana *et al*[31] reported a case of intraoral psoriatic psoriasis in an 11-year-old child with red lesions in the jugal mucosa, and psoriasis was histopathologically confirmed in this case.

Binmadi *et al*[15] described a case of a psoriasis patient presenting with painful ulcers and fissured tongue for 5 wk. Histopathological examination revealed evidence supporting a diagnosis of psoriasis. In this study, the authors emphasized the importance of an oral examination in patients with psoriasis.

Yesudian *et al*[5] concluded that oral lesions are rare, with evidence found in fewer than 100 publications in the literature. They also suggested that it is unclear whether oral psoriasis is a distinct entity, or if, indeed, it exists at all.

Reis *et al*[32] reported a case of a non-psoriatic patient with diffuse erythematous taint on their gums and palate. A histopathological examination of the lesions revealed a diagnosis of psoriasis.

Mattsson *et al*[33] described two cases of lesions in the gums and jugal mucosa with psoriasiform histopathological characteristics, which clinically presented as erythema and serpiginous white areas, respectively. These patients reported a history of cutaneous psoriasis.

In 1993, Gonzaga *et al*[34] concluded that the prevalence of oral lesions in patients with psoriasis would be much greater if a rigorous intraoral examination was carried out. Similarly, Picciani *et al*[4] studied the prevalence of oral lesions in 203 psoriatic patients and found a high frequency of nonspecific oral lesions, thereby demonstrating the relationship between geographic tongue/fissured tongue and psoriasis.

Despite the aforementioned reports of lesions where clinical and histopathological examinations were compatible with oral psoriasis, the most common oral manifestations include nonspecific lesions such as geographic tongue and fissured tongue. Therefore, additional studies are required in order to define geographic tongue as a true oral lesion

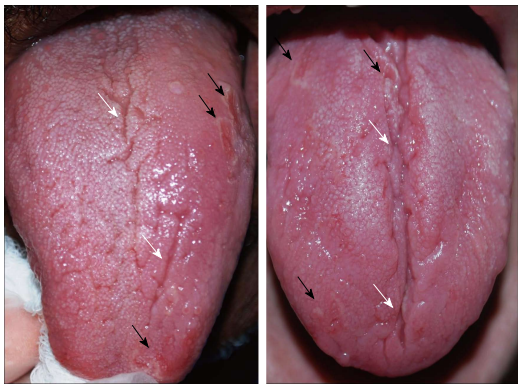

Figure 1 Clinical aspects of geographic tongue (black arrow) and fissured tongue (white arrow).

of psoriasis[4,35].

ASSOCIATION OF GEOGRAPHIC TONGUE AND/OR FISSURED TONGUE WITH PSORIASIS

Clinical aspects

Several authors suggest an association between psoriasis and geographic tongue or fissured tongue (Figure 1)[4,7,18,19,22,36]. Approximately 10% of patients with psoriasis present with geographic tongue[4], and it is more commonly associated with the pustular form of the disease[37].

Fissured tongue is the oral condition most commonly associated with geographic tongue, and the prevalence of the condition is increased in patients with psoriasis. Although most injuries in psoriasis are transient, some lesions can have a more permanent course. Therefore, it is possible that geographic tongue is a transient expression of oral psoriasis, while fissured tongue is a delayed and more permanent expression of the disease. However, a common genetic marker for the three conditions is yet to be found[38].

Previous studies have demonstrated that the prevalence of fissured tongue ranges from 9.8% to 47.5%, whereas that of geographic tongue ranges from 5.6% to 18.1%[4,7,19,20,24,36,37].

Geographic tongue, also known as benign migratory glossitis, was first described by Reiter in 1831. Although this condition has no defined etiology, it has a chronic profile with inflammatory and immune-mediated elements. It affects approximately 0.6%-4.8% of the world's population, and occurs most commonly in children and women[39-41]. It is clinically characterized by erythematous lesions (due to loss of filiform papilla) with whitish irregular edges, particularly on the dorsum and side edges of the tongue. The white border consists of filiform papilla on regeneration and a mixture of keratin and neutrophils. The lesions tend to change location, pattern, and size over time due to epithelial peeling at one location along with simultaneous proliferation elsewhere. There are periods of exacerbation as well as remission, the latter being asymptomatic and not requiring treatment. Some patients complain of pain or burning, particularly during intake of spicy or acidic foods. Diagnosis of geographic tongue is based on patient history and a physical examination. However, histopathology may be necessary in unusual cases[41-44].

Very rarely, other sides of the tongue may be affected, and this is known as geographic stomatitis or benign migratory erythema[45,46].

Gonzaga *et al*[47] examined the association between alcohol, tobacco, and stress in 129 patients with psoriasis, 399 patients with geographic tongue, and 5472 healthy individuals. Their results showed high levels of alcohol consumption in psoriatic patients and a strong relationship between psoriasis and geographic tongue and psychosomatic factors. They concluded that the interactions between environmental factors and psoriasis differed from those that occur with geographic tongue, and they suggested that these differences accounted for the different manifestations of the two diseases. However, they considered both conditions to be part of the same disease.

Daneshpazhooh *et al*[37] conducted a case-control study, studying oral lesions in 200 psoriasis patients; These patients were divided into the following two groups: patients with psoriasis (n = 87, 43.5%) and the control group (n = 39, 19.5%). Fissured tongue was more frequently seen in the psoriatic group (n = 66, 33%) than the control group (n = 19, 9.5%). Geographic tongue was observed in 28 cases (14%) from the psoriatic group and 12 cases (6%) in the control group.

Zargari[36] conducted a prospective study examining the prevalence of lesions on the tongue of patients with psoriasis. The author observed that 47 patients (15%) had tongue lesions, 25 (8%) had fissured tongue, and 17 (6%) had geographic tongue (of which 7% of patients had early psoriasis and 1% with late psoriasis). The author concluded that the incidence of geographic tongue in early psoriasis was an indicator of disease severity.

Hernández-Pérez *et al*[24] examined 80 patients with psoriasis and 127 healthy individuals and found that the number of patients with fissured tongue was more in patients with psoriasis (47%) than that in the control group (20%). Geographic tongue was present in 12% and 5% of patients in the psoriasis and control groups, respectively. The authors concluded that these lesions may be a predecessor of psoriasis or a marker of severity.

Picciani *et al*[4] also reported that the prevalence of geographic tongue was at its highest in early psoriasis, whereas the prevalence of fissured tongue was highest in late psoriasis.

Singh *et al*[7] evaluated 600 patients with psoriasis and concluded that prevalence of geographic tongue is increased in these patients and is related to the severity of the disease.

Picciani *et al*[48] also examined the relationship between disease severity and the presence of geographic tongue in 284 patients with psoriasis through the PASI. They

found that severe psoriasis occurred in 25% of patients without geographic tongue and in 58% of patients with this oral lesion. The authors concluded that geographic tongue could be considered a marker for the severity of psoriasis.

Gonzaga *et al*[49] conducted a study with 118 psoriasis carriers and 88 patients with benign migratory glossitis, and their results suggested that this lesion is a preceding manifestation of the cutaneous condition. They also identified the similarity between the fundamental lesions and symptoms of these diseases. In this tongue lesion, the erythematous lesions correspond to dermal peeling and, similar to psoriasis, follow a chronic course presenting periods of remission and exacerbation[49]. The chewing and speech processes, which are constant trauma factors in the tongue that could correspond to the Koebner phenomenon, may stimulate the emergence of geographic tongue. The authors concluded that the prevalence of oral lesions of psoriasis may be much higher than currently reported because, in general, patients are not subjected to a thorough oral examination[49].

Histopathological aspects

For several authors, the clinical and histopathological similarities between psoriasis and geographic tongue support the theory that the latter is an oral manifestation of the former (Figure 2)[13,17,18,24].

The histopathological features of psoriasis include uniform elongation of the rete ridges, dilated blood vessels, thinning of the supra-papillary plate, intermittent parakeratosis, perivascular infiltration of lymphocytes, and the presence of occasional neutrophil aggregates in the epidermis. Histopathological diagnosis is made by comprehensively evaluating these findings[50].

Since the diagnosis of geographic tongue is based on clinical examination, few histopathological studies have been conducted on this condition, and this has hindered the general understanding of the etiopathogeny of the oral lesion and its relationship with psoriasis.

Femiano[18] conducted a histopathological comparison of 40 patients with geographic tongue: 20 with psoriasis and 20 without the cutaneous disease. In the psoriasis group, all the fragments showed the histopathological features of psoriasis, while only 80% of the patients in the non-psoriasis group exhibited these characteristics. Thus, the author concluded that geographic tongue is an oral lesion of psoriasis and can exist as a subclinical form of the condition.

Picciani evaluated and compared the histopathological aspects of geographic tongue lesions as well as dermal lesions in patients with and without psoriasis. The study found that most of the classic histopathological features of psoriasis were observed in all cases as parakeratosis, acanthosis, suprapapillary epithelial atrophy, spongiosis, basal layer hyperplasia, crest fusion, exocytosis, and the presence of papillary superficial and inflammatory infiltrate. However, remarkable differences were observed in the peripheral areas of the geographic tongue lesions in the two groups, with the oral lesions of patients with psoriasis showing hyperplastic, inflammatory, and vascular changes in the periphery. Examination of these peripheral changes could perhaps help distinguish geographic tongue from true oral psoriasis[51].

The importance of angiogenesis in the pathological process of psoriatic lesions is well recognized. The balance between pro- and anti-angiogenic factors regulates the genesis of new blood vessels. Angiogenesis facilitates the disease progress in pathological processes such as tumor growth or chronic inflammation[52]. The vascular system is increased due to vasodilation and lengthening of existing vessels and also by the formation of new vessels. These morphological changes are observed even before epithelial hyperplasia of the psoriatic plaques[52]. Santos[53] qualitatively compared the geographic tongue lesions in patients with and without psoriasis and found that vascular ectasia associated with vascular tortuosity were the major changes associated with psoriasis accompanied by frequent geographic tongue lesions.

The evaluation of these aspects, especially in the peripheral areas of oral lesions, could perhaps help distinguish between geographic tongue and true oral psoriasis[53].

Munro's micro-abscess (neutrophil collections in the corneal layer) is present in over 75% of psoriasis cases, whereas pustule of Kogoj (also a collection of neutrophils, but in the spinous layer) is mainly present in pustular psoriasis cases[54]. Picciani[51] recently demonstrated a high prevalence of pustules of Kogoj in geographic tongue injuries, and this finding strengthens the theory that geographic tongue represents a pustular manifestation of psoriasis[37]. Evaluating oral and cutaneous lesions in patients with pustular psoriasis could help improve the current understanding of this relationship.

Immunogenetic similarities

Although there is a paucity of studies examining immunogenetics in geographic tongue, the results of those that exist demonstrate that it is the oral lesion most commonly associated with psoriasis.

The inflammatory infiltrate in psoriasis consists mainly of T cells: $CD4^+$ in the dermis and $CD8^+$ in the epidermis. Macrophages are the major antigens observed in psoriatic cells, and the infiltrate in oral psoriatic lesions consists of macrophages and T cells, especially CD4. The few immunohistochemical studies conducted in patients with geographic tongue showed a similar abundance of $CD4^+$ cells[13,17,55].

An immunohistochemical study of patients with geographic tongue demonstrated the presence of dilated and tortuous capillaries and intense cell proliferation (as evidenced by antibody Ki-67), similar to psoriatic lesions. However, a diagnosis of oral psoriasis was not established because of the absence of cutaneous manifestations[17].

Espelid *et al*[55] conducted an immunohistochemical study in geographic tongue lesions with CD3, CD4, CD8, CD22, and CD11c antibodies and HLA-DR. They demonstrated

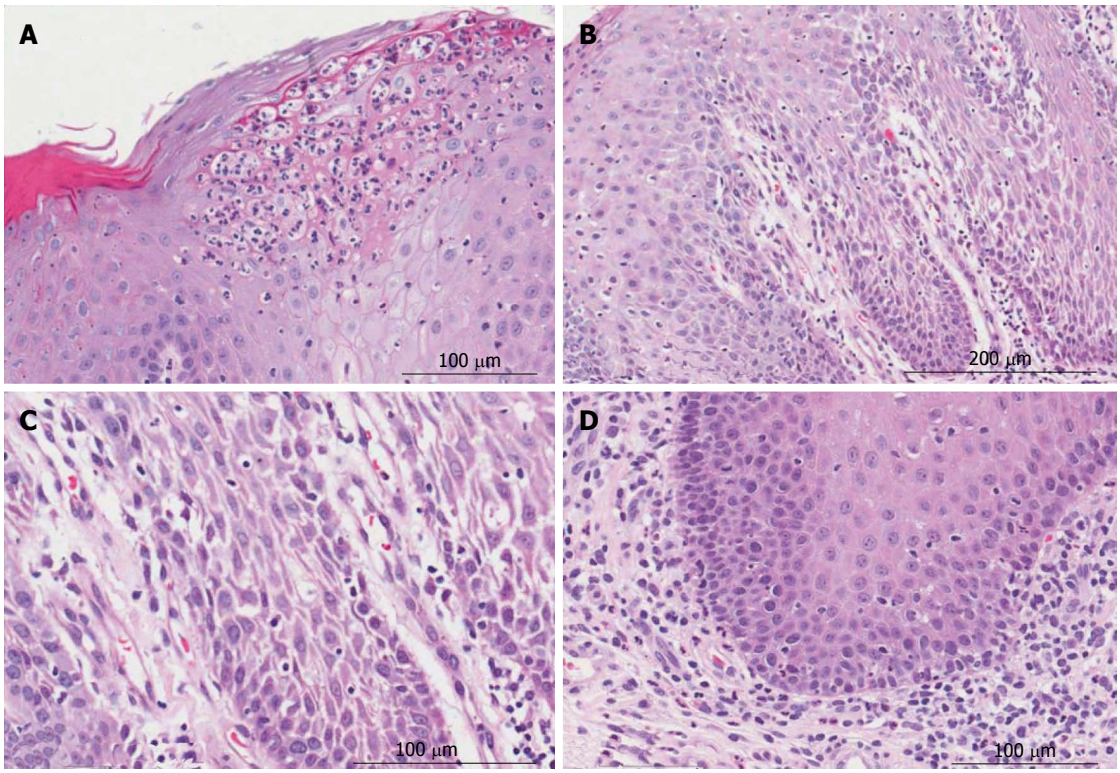

Figure 2 Histopathological aspects of geographic tongue. A: Histopathologic appearance exhibiting parakeratosis, exocytosis of polymorphonuclear leukocytes, and Munro micro-abscesses; B: Acanthosis, elongation, and fusion of rete ridges; C: Dilated tortuous vessels and espongiosis; D: Basal layer hyperplasia and superficial lymphocytic chronic inflammatory cells (hematoxylin and eosin).

that sub-epithelial inflammatory infiltrate is predominantly composed of $CD4^+$ T lymphocytes, along with the presence of macrophages.

Ulmansky *et al*[13] showed that $CD4^+$ T lymphocytes are the main cells in the inflammatory infiltrate from geographic tongue.

Based on this, the authors of the aforementioned studies concluded that there was a connection between geographic tongue and psoriasis[13,55].

Picciani[51] investigated the inflammatory responses of patients with geographic tongue who either did or did not have psoriasis (using CD1a, CD3, CD4, CD8, CD20, and CD68 antibodies). They found that the oral and cutaneous lesions had similar qualitative and quantitative standard markings, regardless of the antibody used. Oral and skin lesions of patients with psoriasis revealed a higher prevalence of TCD3, CD4, and CD8 T cells.

With psoriasiform lesions such as geographic tongue causing difficulties in diagnosis, the measurable difference in the amount and pattern of distribution of $CD4^+$ and $CD8^+$ cells could aid diagnostic decision making, especially in cases with very similar histopathological features[56].

In a recent study, the concentration of TNF-α and IL-6 in the saliva of patients with geographic tongue and healthy individuals was examined. The results showed an increase of both proteins in patients with geographic tongue, and this finding strengthens the link between this condition and psoriasis[57].

In the past decade, Th1 cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) were considered to play a major role in psoriasis, but recent evidence points toward a greater role of IL-23 and IL-17A in the physio-pathogenesis of psoriasis[58].

Domingos[59] (2015) conducted an analysis of the immunopositivity to antibodies directed against IL-6, IL-17, and IL-23 in skin lesions of psoriasis and geographic tongue lesions of patients with and without the cutaneous disease. The three antibodies showed a similar pattern of cytoplasmic labeling, predominantly basal and parabasal, in psoriasis as well as geographic tongue. In the sections where the basal layer hyperplasia was most significant, the markings were longer and more prominent[59].

Cytokeratins are the main structural component of keratinocytes in various groups, and they are expressed during various stages of cellular differentiation[60,61]. In psoriasis, the present cytokeratins change in the pattern of expression, and they have been identified by immunohistochemical methods as differentiation markers and hyper-proliferation of keratinocytes[61]. Activated keratinocytes express keratins that differ from normal skin, such as CK6, CK16, and CK17. Santos[53] also evaluated the correlation between the patterns of distribution of CK6, CK16, and CK17 in skin lesions of psoriasis and in oral lesions of geographic tongue, and the immunohistochemical analysis showed a similar distribution in both lesions. A greater quantitative similarity was observed between geographic tongue lesions and skin lesions in patients with psoriasis, reinforcing the

association between the diseases.

In 1996, the association between psoriasis and geographic tongue was supported by genetic analysis for the first time when a common genetic marker, the human leukocyte antigen (HLA-Cw6) was determined. Thus, these two conditions apparently have a common genetic basis[22]. The genetic determinant of geographic tongue pathogenesis is under-reported in the literature, with only five papers correlating this oral lesion to HLA genes which are known to be important for susceptibility to psoriatic disease. Specifically, relationships were demonstrated with the HLA-B13, -B15, -B58, -CW6, -DR5, and -DRW6 alleles[22,62-65].

Picciani *et al*[65] conducted the first study using molecular methodology for HLA typification. They found associations between HLA-B × 57 and psoriasis vulgaris and HLA-B × 58 and geographic tongue. Both alleles are serological divisions of HLA-B17. The findings of this study strengthen the link between the two conditions.

The same authors[17] evaluated an isolated case of a patient with a family history of psoriasis and geographic tongue in association with benign migratory erythema and found histopathological, immunohistochemical, and immunogenetic features similar to those observed in dermatitis. However, a diagnosis of oral psoriasis was not completed because of the absence of cutaneous lesions in the patient.

Historically, the difficulty in accepting a diagnosis of geographic tongue as oral psoriasis arose from the fact that some patients with geographic tongue did not have psoriasis[3]. However, a detailed family analysis of these patients, including insights into the family history of psoriatic disease, may introduce new genetic markers that show increasingly significant correlations between the two conditions.

CONCLUSION

Geographic tongue is the most prevalent oral lesion in psoriasis, with histopathological, immunohistochemical, and genetic similarities observed between the diseases. In order to confirm the relationship between geographic tongue and psoriasis, it will be necessary to conduct new studies that combine histopathology and immunogenetic analysis. This review also highlights the importance of conducting oral examinations in patients with psoriasis and skin examinations in patients with geographic tongue.

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REVIEW

Review of narrowband ultraviolet B radiation in vitiligo

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Abstract

Vitiligo is a common, acquired pigmentary disorder of unknown etiology with great impact on patient's appearance and quality of life. It presents a therapeutic challenge to many dermatologists. Photochemotherapy using psoralen and ultraviolet A (UVA) therapy, topical and oral immunosuppresants, as well as cosmetic camouflage are also commonly employed with varying clinical efficacy. Phototherapy is a popular treatment option, which includes both of the generalized ultraviolet B (UVB) therapies, broadband UVB and narrowband UVB (NB-UVB). It has been used favorably, both alone as well as in combination with other agents like topical calcineurin inhibitors, vitamin-D analogs. Combination therapies are useful and may provide quicker regimentation and treat vitiligo with an additive mechanism of action than UVB phototherapy. Advances in technology may lead to the continuing use of UVB phototherapy as a treatment for vitiligo through the development of sophisticated devices and delivery systems as well as innovative application methods. These will provide increased therapeutic options for all vitiligo patients, particularly those with refractory disease. In this article, I have reviewed the available data pertaining to efficacy and safety issues for NB-UVB as monotherapy, its comparison with psoralen plus UVA and other modes of phototherapy, combination regimens that have been tried and future prospects of NB-UVB in vitiligo.

Key words: Narrow-band ultraviolet B; Phototherapy; Vitiligo

Core tip: Vitiligo is a procured depigmentation issue with great effect on patient's appearance and his satisfaction. Till date, the etiology of vitiligo remains elusive, which makes it difficult to have curative therapies. Narrowband ultraviolet B (UVB) phototherapy is generally utilized and delivers great clinical results. In this manuscript, I review the excursion of narrowband UVB from its prior days of advancement until this time as monotherapy, its comparison with psoralen and ultraviolet A and other modes of phototherapy and in combination with other therapies in the management of vitiligo.

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INTRODUCTION

The principal investigation of the use of light in the therapy of dermatologic issue dates from 1400 BC when patients with vitiligo were taken sure concentrates of the plants Psoralea corylifolia in India and Ammi majus linnaeus in Egypt as topical application or ingestion, trailed by introduction to the sun[1]. The genuine enthusiasm for the utilization of ultraviolet (UV) light in the remediation of different cutaneous illnesses began in the nineteenth century when Niels Finsen got the Nobel Prize in 1903 for his helpful outcomes with UV illumination in lupus vulgaris[2].

In 1977, Fischer[3] observed that light at a wavelength of 313 nm was viable in clearing psoriatic plaques. Diffey and Farr[4] in the wake of concentrating on the impacts of UV radiation (UVA, UVB and UVC), recommended that more drawn out wavelengths added nothing to the helpful event, that shorter wavelengths really cheapened the adequacy of remediation, and that UVB was practically viable at 311 nm.

A couple of years after the fact it was resolved that the best wavelengths were somewhere around 295 and 313 nm; inside of that range, the proportion of the most reduced viable every day dosage to the negligible erythema measurement was littlest for 313 nm, demonstrating that this wavelength might have the ideal "phototherapy index" for clearing psoriasis[5]. These ponders prompted the advancement of the Phillips TL-01 fluorescent light, which radiates a slender crest around 311-312 nm (Figure 1)[6].

Narrowband UVB (NB-UVB) is a subset of the UVB wideband or broadband range. The UVB band includes the scope of wavelengths between 290 nm and 320 nm while UVB narrowband has a restricted range of emanation (310-315 nm) wavelengths with a crest at 311 nm[7].

NB-UVB phototherapy lodges comprise fluorescent TL-01 (100 W) tubes as the wellspring of light. The expense of a chamber and lights show extensive varieties in the middle of nations and wholesalers. NB-UVB lodges accessible industrially either join TL-01 alone or in blend with UVA tubes. Blend chambers take more time to control a medication measurements. Along these lines, in spite of the fact that they give adaptability, they might speak to an unacceptable tradeoff for a bustling phototherapy unit[8].

Smaller containers of NB-UVB have additionally gotten to be accessible in little range treatment types of gear (hand and foot unit, NB-UVB brush) for the treatment of restricted body sites[9].

NB-UVB calendars can be customized by skin sort and neighborhood experience. Two methods are most generally utilized; one includes definition of the person's minimum erythema dose (MED) by method for a different bank of TL-01 tubes[10]. Another approach, as commonly practiced is the tight band skin sort convention. It involves standard initial dose according to Fitzpatrick skin phototype (Table 1) with stepwise increments (typically 20%) contingent upon patient's erythema response. This plan has demonstrated colossally compelling and has been generally circulated and utilized as a part of an expansive choice of phototherapy practices[8].

Minimum erythema dose determination includes uncovering little characterized ranges of sun-ensured, clinically unaffected skin to expanding dosages of UV light, the measurements to every zone normally being 1.4 times the past measurement. A layout of UV-hazy, glue plastic with eight 2.3 cm^2 gaps (ports), fastened to the lower back of the patient might be utilized, with every port presented to an alternate illumination dose from a board of TL-01 fluorescent tubes. Whatever remains of the patient's skin is secured amid these UV exposures[11].

The dose for each port for NB-UVB photo-testing is reliant on the subject Fitzpatrick skin type. For skin types Ⅰ-Ⅲ, initial doses of 400, 600, 800, 1000, 1200, 1400 mJ/cm^2 are utilized while for skin sorts Ⅳ-Ⅵ, 800, 1000, 1200, 1400, 1600 and 1800 mJ/cm^2 are utilized. The patients are instructed not to receive any natural or artificial UV light to this region of the skin during the next 24 h and asked to return to the phototherapy center in 24 h. The area of the photo-testing should be identified by ink marking at the different dosage sites. A positive perusing is believed as recognizable erythema inside of the edges of the photo-testing port. If bright red erythema develops or blistering occurs at the site of any of the phototesting sites, topical corticosteroids can be used to treat the area[12].

When MED has been detected, the treatment convention is typically "percent based". Regularly 70% of the MED worth is utilized for the first treatment; from there on treatment is given three times or all the more week by week with 40%, 20% or 10% increases relying upon neighborhood experience, erythema response and skin sort resistant[13,14].

A semi-automated small hand-held MED tester (Durham MED tester) has gotten to be accessible which produces a settled arrangement of UV dosages, taking into account constricting foils. The Durham MED analyzer lessening arrangement approximates a geometric arrangement with a variable of 1.26. Beginning from the open gap (100%), each consequent gap is lessened by a variable of around 1.26[15].

METHODS OF NB-UVB RESEARCH

NB-UVB as monotherapy

NB-UVB phototherapy has been observed to be powerful and alright for vitiligo[16]. The consequences of monotherapy with NB-UVB have been exceptional in Asian skin. Roughly 75% of cases in a previous study accomplished more prominent than 75% to finish repigmentation after NB-UVB therapy for a greatest time of 12 mo[17]. The average length of time of sickness was fundamentally shorter in the individuals who had stamped to finish pigmentation contrasted and the individuals

Table 1 Fitzpatrick's skin phototypes

Phototype	Sunburn and tanning history (defines the photo type)	Immediate pigment darkening	Delayed tanning	Constitutitve color (unexposed) buttock skin	UVA MED (mJ/cm^2)	UVB MED (mJ/cm^2)
I	Burns easily, never tans	None	None	Ivory White	20-35	15-30
II	Burns easily, tans minimally with difficulty	Weak	Minimal to weak	White	30-45	35-40
III	Burns moderately, tans moderately and uniformly	Definite	Low	White	40-55	30-50
IV	Burns minimally, tans moderately and easily	Moderate	Moderate	Beige-olive, lightly tanned	50-80	40-60
V	Rarely burns, tans profusely	Intense brown	Strong, intense brown	Moderate brown or tanned	70-100	60-90
VI	Never burns, tans profusely	Intense (dark brown)	Strong, intense brown	Dark brown or black	100	90-150

UVA: Ultraviolet A; UVB: Ultraviolet B; MED: Minimum erythema dose.

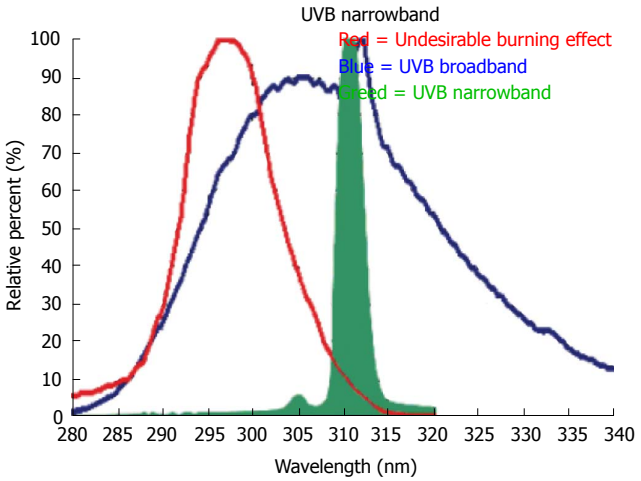

Figure 1 Narrowband ultraviolet B phototherapy (Bandow and Koo[6]). UVB: Ultraviolet B.

who had weaker reaction. Likewise with any treatment methodology for vitiligo, the best results were seen in lesions on the face and neck, trailed by the proximal limbs and trunk. Pigmentation around the hair follicles was the more widely recognized kind of starting repigmentation that was seen in around seventy five percent of cases.

It was focused on impact of NB-UVB and the impact of influenced destinations, individual's age and duration of illness on the response[18]. Full pigmentation was all the most ordinarily seen in facial sores and sores situated on the neck and trunk in diminishing request of recurrence (68, 57.9, half, individually). Age did not impact the reaction to treatment for facial sores, while in different extents aggregate pigmentation was significantly more ordinarily seen in more youthful patients (under a twenty years). Injuries over the neck and extremities (arms and legs) demonstrated a high percent of total pigmentation (83.3%, 33.3% and 28.5%, separately) in those with illness of late onset (less than two years).

Likewise as the time span of the lesion is prolonged, the sores over the face reacted better. Creators suggest early therapy, as the excellent outcomes were accomplished by youthful patients with late onset vitiligo.

In a randomized, controlled, side-to-side correlation survey, the average change in the NB-UVB was 42.9% contrasted and 3.3% in the untreated side, with the seriousness of malady having been surveyed by VASI[19]. The response changed extraordinarily between distinctive body areas, with the excellent reaction occured over the lower furthest points and most exceedingly terrible reaction on the foot. While all cases did not get therapy for their face, 37.5% of the individuals who decided on therapy of this area had more than seventy five percent repigmentation.

In India, an extensive, open, forthcoming study, just around a quarter of patients could accomplish more than seventy-five percent repigmentation[20]. This poor response can be credited to bring down initial estimation and twice-week after week therapy. In those patients who had huge pigmentation, it was ascribed to great consistence, a more prominent number of medicines and expanding total measurements. Albeit introductory repigmentation was darker, great shading coordinating could be accomplished with proceeded with treatment (Table 2).

NB-UVB vs psoralen and UVA

In a previous study contrasting twice-week after week, local psoralen and UVA (PUVA) against NB-UVB, authors reported return of pigmentation in 67% of cases in the NB-UVB bunch contrasted and 46% in the local PUVA bunch following four months of therapy[21]. Following three months of NB-UVB therapy, 8% of cases indicated more than 75% repigmentation, though following 1 year of NB-UVB usage, 63% had such repigmentation. In another review, permanent pigmentation following 12 mo of therapy consummation was seen in 78.5% of patients in the NB-UVB bunch and 60% in the PUVA bunch[22].

In the initially randomized, twofold visually impaired, fake treatment controlled study, change in body area territory influenced by vitiligo was more noteworthy with NB-UVB than fake treatment after 48 sittings[23]. Following 1 year of end of treatment, predominance as far as adequacy for NB-UVB was kept up, in spite of the fact that it was not measurably huge. No relationship between length of time of malady and accomplishment

Table 2 Studies of narrowband ultraviolet B in treatment of vitiligo (monotherapy)

Ref.	Study component	Study design	Patient's No.	Mode of each treatment	Dosimetry	Degree of pigmentation	Incidence of side effects
Njoo *et al*[134]	NB-UVB	Prospective, open, uncontrolled	51	Twice a week	0.25 J/cm^2 followed by 20% increments until minimal erythema	After a maximum of 1-yr treatment: > 75% repigmentation in 53%	Pruritus: 8% Xerosis: 4%
Scherschun *et al*[16]	NB-UVB	Retrospective	7	Three-times a week	280 mJ/cm^2; followed by 15% increments until mild erythema or pruritus	70% patients achieved > 75% repigmentation after a mean 19 treatments	Mild asymptomatic erythema: 58% Pruritus: 14%
Hamzavi *et al*[19]	NB-UVB	Randomized, controlled side to side	22	Three-times a week	70% of MED on depigmented skin followed by 10% increments until onset of repigmentation	Mean improvement after 6 mo or 80 exposures: 42.9% (treatment side) *vs* 3.3% (control side)	
Kanwar *et al*[17]	NB-UVB	Open uncontrolled	14	Three-times a week	280 mJ/cm^2 followed by 20% increments	After 1 yr: > 75% repigmentation in 71.4%	Burning and pruritus: 28.6% Xerosis 3nd thickening of lesional skin: 21.4%
Kanwar and Dogra[27]	NB-UVB	Prospective, open, uncontrolled	20	Three-times a week	280 mJ/cm^2 followed by 20% increments	After a maximum of 1 yr treatment: > 75% repigmentation in 75% patients	Lesional burning and pruritus: 20%. Xerosis 3nd thickening of skin: 15%
Brazzelli *et al*[18]	NB-UVB	Open, uncontrolled	60	Twice or three times a week	180-200 mJ/cm^2 followed by 50 mJ/cm^2 increments until mild erythema	Complete repigmentation or up to maximum 2 yr: 68% (face) 57.9% (neck). 50% (trunk), limbs poorer results	
Kishan Kumar *et al*[20]	NB-UVB	Prospective, open, non-randomized	150	Twice a week	250 mJ/cm^2 (150 mJ/cm^2 for children) followed by 20% increments until perceptible erythema	> 75% repigmentation after maximum 1 yr treatment: 17.4%	Erythema, burning, pruritus: 7%. Xerosis: 6%

NB-UVB: Narrowband ultraviolet B.

of treatment was watched. Albeit some levels of repigmentations were seen in the total series of the NB-UVB bunch and 92% of those in the PUVA bunch, shading match was astounding in whole patients in NB-UVB, however it was so weaker with PUVA. The cosmetic prohibited shading planning had a tendency to bear notwithstanding taking after 12 mo of phototherapy discontinuance.

In a side-to-side examination work, a precisely break even with number of patients accomplished 0%-40%, 40%-60% and 60%-75% repigmentation following 60 sittings[24]. The distinction in the frequency of symptoms, for example, erythema and rankling was not significant between the gatherings.

In a little review investigation, 70% of patients accomplished > 75% repigmentation following an average of 19 remedy sittings. Authors watched that more drawn out ailment length of time associated contrarily with reaction to therapy[16]. In the same sitting, NB-UVB gave higher response contrasted and PUVA in bestowing strength in vitiligo and in pigmentation in both dynamic and permanent illness[25].

Vitiligo for the most part starts in youth with half of the affected persons having ailment onset before the age of twenty years[26]. Be that as it may, experience of NB-UVB in youth vitiligo is constrained. In a planned work, enlisted twenty six youngsters, of whom twenty finished the search. Following therapy for a most extreme of 12 mo, three quarters of the studied group had more than 75% repigmentation. After an average introduction of 34 times, half repigmentation was accomplished. Median length of time of illness before treatment start was less for patients who had stamped to finish repigmentation contrasted and the individuals who had negligible or mild change. Excellent reaction was seen on the face and neck, trailed by the upper arms, thighs and trunk. In spite of the way that the makers assumed that NB-UVB is convincing and all around persevered in youngsters with vitiligo, the whole deal result for dermatologic issues when in doubt is unknown[27].

NB-UVB offers significant points of interest over PUVA which might be essential in picking treatment for patient. It is less tedious, less demanding to perform, and does not require the associative organization of a photograph sensitizer that might bring about queasiness, waterfalls, phototoxic responses, and undesirable medication reactions[25]. Different points of interest additionally incorporate the sheltered use in pregnant ladies and youngsters and truant medication expenses[28,29].

However, short remission rate is one of the best disservices of NB-UVB contrasted and PUVA, regarding infirmities on palms and soles does not react to NB-UVB albeit such sickness can now and again react in youthful youngsters. In correlation, PUVA treatment is regularly viable at these locales as NB-UVB is less infiltrating than UVA radiation[30,31].

NB-UVB vs broadband-UVB

NB-UVB has a moderately monochromatic range of

emission when contrasted and broadband-UVB (BB-UVB)[32]. Erythema is more usually delivered by BB-UVB than NB-UVB, as NB-UVB is compelling at negligible erythema dosages considerably less than those utilized as a part of BB-UVB treatment[33]. The TL01 light is around 5-10 overlay less strong than BB-UVB for erythema incitement, hyperplasia, edema, sunburn cell arrangement and langerhans cell exhaustion from the skin[34].

NB-UVB is viewed as more powerful with fewer side effects contrasted and BB-UVB in treating a few ceaseless incendiary skin infections as psoriasis and vitiligo. Recently it has been ended up being better than BB-UVB in treatment of HIV-related eosinophilic pustular folliculitis with impressive achievement, particularly against the extreme tingle[35].

Targeted NB-UVB treatment

Targeted phototherapy implies delivering light to localized diseased areas of skin involving less than 10% body surface area (BSA) and it can be combined with systemic treatments if needed[36]. Since only the affected area is presented to radiation, more doses of radiation can be utilized to achieve better and faster results with lower total cumulative dose and hazards of phototoxicity. Also, it can be used to treat difficult to reach areas like skin folds.

Recent UV devices that discharge light successful for the improvement of vitiliginous patches in a targeted fashion are becoming popular. Among targeted phototherapy devices currently available, excimer laser has been shown to induce the most rapid onset of repigmentation in vitiligo. In addition to excimer laser a monochromatic excimer lamp has also been utilized in the treatment of vitiligo with almost comparable results[37,38].

As far as the targeted UVB devices are concerned, the UV spectrum delivered varies from one machine to another. These devices include "BClear" that delivers BB-UVB, "multiclear" or "dualight" providing UVA and UVB combination and lastly "Bioskin", which gives a NB-UVB waveband peaking at 311 nm[39].

Xenon chloride laser, popularly known as an excimer laser (EL), is a 308 nm laser that was initially used for treating psoriasis[40]. Be that as it may, as its operational wavelength is near that utilized as a part of NB-UVB, it is utilized to regard vitiligo too. This laser offers the benefit of conveying high measurements of light to limited areas[41,42].

It was initially utilized effectively in vitiligo by Baltás *et al*[43] in 2001. In 2002 Spencer *et al*[42] presumed that the level of repigmentation in a time of 2-4 wk is much higher than that accomplished with whatever other current vitiligo treatment. Taneja *et al*[44] and Choi *et al*[36] likewise demonstrated helpful results with excimer laser with non acral lesions reacting the best. Two reports contrasted the viability of excimer laser with NB-UVB, and found that the former brought about more huge and faster repigmentation[45,46]. However, neither of these two studies was controlled nor used a standardized scoring method.

The monochromatic excimer light (308 nm MEL) might introduce a few preferences over the laser. Firstly, it gives a bigger illumination field that empowers to treat bigger ranges at once. Secondly, bring down force thickness prompts diminished danger of mishaps because of overexposure, recommending a superior wellbeing profile. The excimer light was found to give proportional pigmentation as contrasted and an excimer laser. In 2003, Leone *et al*[38] reported that 35/37 (95%) patients hinted at repigmentation inside of initial eight sittings of MEL and excellent and good repigmentation in 18 and 16 patients, respectively. They likewise demonstrated that 3 of their series who were resistant to NB-UVB phototherapy, indicated astounding repigmentation after 308 nm MEL treatment. They suggested this may be conceivable because of the distinction in the method of activity of these two sources, with 308 nm MEL gadget conveying higher vitality fluences to the objective tissue in less time when contrasted with NB-UVB devices.

The repigmentation rate was somewhere around 25% and half over the whole body, and somewhere around half and 75% for vitiligo injuries not situated at hard prominences or extremities[47]. Interestingly, agents additionally noticed that MEL impelled more erythema than EL recommending that regardless of indistinguishable 308 nm crest wavelength, EL and MEL may have diverse photobiological properties.

Additionally, Shi *et al*[48] likewise found that the repigmentation rates with excimer light were same as those with laser (79% *vs* 87.5%, $P > 0.05$). A review investigation of 80 patients with segmental vitiligo (SV) treated with EL demonstrated that 75%-99% repigmentation was accomplished in 23.8% of cases and 50%-74% repigmentation in 20% of cases[49]. This report shows that other than surgical systems, EL may be a possibility for SV patients, with the level of repigmentation absolutely connecting with treatment span, combined measurements, and shorter malady duration[49].

A recent study was conducted in 40 patients of "stable" vitiligo including under 5% BSA who were resistant to conventional oral/topical treatment options. They were treated with a focused on NB-UVB gadget twice-week by week for a most extreme of 30 sessions or until 100% repigmentation, whichever was come to first. Seventy-seven point five percent of cases accomplished pigmentation at a rate from half to hundred percent. Pigmentation started as ahead of schedule as the 3rd dosage now and again and by the 10th measurements in all responders. Best reaction was seen on the face and neck with 20 of the 31 injuries accomplishing 90%-100% repigmentation around there. There was not a correlation between the Length of time of the disease and the repigmentation accomplished. Focused on NB-UVB phototherapy is by all accounts a viable treatment choice in restricted lesion with a quick onset of repigmentation

appeared as right on time as 2nd week of therapy[50].

Targeted BB-UVB vs targeted NB-UVB therapy

Very few studies utilizing broadband UVB exist. Asawanonda *et al*[51] analyzed the repigmenting viability of targeted BB-UVB therapy with that of NB-UVB in an equi-erythemogenic manner. Twenty similar vitiliginous lesions from 10 patients were arbitrarily distributed to get either targeted BB-UVB or targeted NB-UVB treatment. Ultraviolet fluences were begun at half of the insignificant erythema measurements detected within the vitiliginous patches, then increased gradually, in the same manner, to ensure equi-erythemogenic comparison. Medicines were completed twice week after week for 12 wk. The outcomes demonstrate that review 1, *i.e.*, 15%-25% repigmentation, to review 2, 26%-50% repigmentation, happened in 6 of 10 subjects. Responses in terms of repigmentation, de-pigmentation, or lack thereof, were similar between lesions receiving broadband and NB-UVB phototherapy. Beginning of repigmentation happened as ahead of schedule as 4 wk of treatment in many subjects. Medicines were all around endured, with just negligible erythema and hyperpigmentation. They concluded that targeted BB-UVB produces comparable clinical reactions to targeted NB-UVB in the treatment of the non-segmental kind of vitiligo.

Combination therapy

The points of combination treatment are to lessen the reactions of phototherapy, by possibly encouraging a lower UVB combined measurements or number of medicines, and to enhance adequacy; this includes the simultaneous utilization of a specialists that might offer an added substance or synergistic effect[52]. Similarity between medicines must be considered, as topical operators might have UVB blocking impacts; thus, it is for the most part exhorted that if topical specialists are utilized, they ought to be connected post-UVB presentation[53].

Vitamin D analogs and NB-UVB

The blend of vitamin D simple and NB-UVB was utilized first by Dogra and Parsad[54]. Decreased levels of vitamin D3 were observed in vitiligo patients and other co-morbid autoimmune conditions. A significant body of data suggests that vitamin D3 is strongly immunosuppressive and improves many Th1 triggered diseases, *i.e.*, it inhibits the Th1 phenotype and potentiates the Th2 phenotype; and that low levels are associated with autoimmune conditions including vitiligo. However, the cause of low vitamin D3 in patients with autoimmune conditions remains unknown[55]. Some authors[56] watched considerably better reaction with the blend contrasted and NB-UVB alone (in spite of the fact that not critical) in a side-to-side examination study. Likewise, others reported the adequacy of mix treatment of NB-UVB with calcipotriol in vitiligo and they recommended that phototherapy with NB-UVB in blend with topical calcipotriol might prompt prior pigmentation with lower beginning aggregate NB-UVB radiation in subjects with vitiligo[57,58].

On the other hand, some authors couldn't discover empowering contrasts in the rate of repigmentation[59].

Topical calcineurin inhibitors and NB-UVB

Autoimmunity is most likely the major cause suggested for vitiligo. Its part in the disease is supported by discovery of organ-particular antibodies in the patients[60]. Topical immunomodulators are discovered valuable in the treatment of vitiligo alone, and in addition in mix with NB-UVB. It was proposed that cooperation in the middle of pimecrolimus and keratinocytes, making a positive environment for melanocyte development and movement[61].

Castanedo-Cazares *et al*[62] and Nordal *et al*[63] reported the viability of the combination in the treatment of vitiligo through the initiation of pathways impacting melanocyte movement and melanogenesis. They recommended that expansion of topical tacrolimus to NB-UVB ought to be further researched, considering its lower carcinogenic profile contrasted and systemic organization. Additionally, the utilization of tacrolimus might be valuable to counteract UVB-instigated erythema by restraining early-stage occasions of the provocative process[64]. Most of the reports consolidating local calcineurin inhibitors with NB-UVB proved that the blend might expand the adequacy, and likely rush the reaction, just for facial sores.

Afamelanotide and NB-UVB

Afamelanotide, is a potent and longer-lasting synthetic analogue of naturally occurring α-MSH. Grimes *et al*[65] showed in 4 vitiligo patients that combined treatment of NB-UVB and afamelanotide is likely to promote melanoblast differentiation, proliferation and eumelanogenesis leading to faster and deeper repigmentation (at least > 50%) in each case within 2 d to 4 wk.

In another recent study, patients with skin phototypes, Ⅲ through Ⅵ and an affirmed conclusion of NSV that included fifteen percent to half of aggregate body area range were subjected to combination treatment (n = 28) *vs* NB-UVB monotherapy (n = 27). Following 30 d of NB-UVB therapy, 16 mg of afamelanotide was directed subcutaneously to the blend treatment amass month to month for 4 mo while NB-UVB therapy proceeded with; the second gathering kept on getting NB-UVB monotherapy. A blend of afamelanotide insert and NB-UVB phototherapy brought about clinically obvious, measurably critical predominant and speedier repigmentation contrasted and NB-UVB alone. Reaction was highly discernible in patients with skin types Ⅳ to Ⅵ[66].

Fluorouracil and NB-UVB

In a recent study, various sessions of intradermal 5-fluorouracil have likewise appeared to enhance NB-UVB adequacy, with 48% of patients accomplishing > 75% repigmentation contrasted with 7% of patients

treated with NB-UVB alone[67].

Oral or topical antioxidants and NB-UVB

The part of increased oxidative anxiety in the etiology of vitiligo has prompted the utilization of antioxidants orally and topically in the treatment of vitiligo[68,69]. Topical preparations containing catalase and superoxide dismutase have been concentrated on with NB-UVB in a few case arrangement. Topical utilization of pseudocatalase (Mn/ethylenediaminetetraacetic acid-bicarbonate complex) and calcium in mix with decreased-measurements BB-UVB brought about total repigmentation on the face and dorsum of the hands in ninety percent of cases[69]. Elgoweini and Nour El Din[70] concluded that mean number of medicines required to accomplish > half percent repigmentation was diminished (sixteen *vs* twenty sessions) by adding oral antioxidants to NBUVB. Dell'Anna *et al*[71] found that a tablet containing vitamins E and C, alpha-lipoic corrosive, polyunsaturated unsaturated fats and cysteine monohydrate brought about more subjects accomplishing > 75% repigmentation contrasted with NB-UVB alone (47% *vs* 18%, $P < 0.05$). In another report, NB-UVB was joined with oral organization of polypodium leucotomus separate, which is known not anti-oxidative and immune-modulating characters. In the blend therapy bunch, a pattern towards an expanded repigmentation in the head and neck zone was watched, that almost came to measurable significance[72].

Oral minipulse and NB-UVB

A previous study contrasted four different treatment gatherings of vitiligo patients with progressive course: Steroid oral minipulse (OMP) alone, betamethasone in a dose of 0.1 mg/kg body weight twice weekly on two continuous days for three months took after by decreasing of the dosage by 1 mg consistently over the accompanying three months, OMP with PUVA, OMP with NB-UVB, and OMP with BB-UVB. The outcomes demonstrated that OMP was not helpful all alone but rather had some quality as an enhancer treatment for PUVA and NB-UVB[73].

Laser

Erbium laser dermabrasion has been speculated to bring about a more noteworthy profundity of radiation infiltration into the dermis, where it can animate melanocyte undifferentiated cells furthermore bring about conveyance of more prominent measurements of radiation[74]. This standard was demonstrated successfully when generally UV-safe destinations on the hands, feet and hard protuberance were treated with NB-UVB with former Erbium laser dermabrasion. Measurably critical results were acquired with 46% of sores accomplishing > 50% repigmentation with going before 2940-nm erbium:YAG laser contrasted with 4.2% of control sores ($P < 0.0001$). Furthermore, unfavorable impacts like postponed recuperating (up to 21 d in 1 patient), edema going on for two through fifteen days when limits were dealt with, and hypertrophic scarring hampered the general patient satisfaction[74].

This study proposes a need to investigate the synergistic part of lasers with NB-UVB in the therapy of vitiligo, particularly on generally UV-safe locales.

Newer trends

Recently, home based NB-UVB regimens, using instruments like SS-01 UV phototherapy instrument, Dermfix 1000™ NB-UVB and Waldmann™ NB-UVB 109, have been attempted effortlessly of use at home, along these lines, maintaining a strategic distance from incessant visits to a healing facility based phototherapy unit more than a while. This modality makes phototherapy available to individuals who cannot afford this treatment because of logistical reasons; however, it may not be financially affordable by patients in resource poor developing countries. It is a useful option for localized lesions and can be used to target new lesions at the earliest. Shan *et al*[75] reported excellent repigmentation in 27 of 36 cases with face and neck lesions, 16 of 43 cases with truncal vitiligo and 9 of 34 patients with limb lesions following treatment with SS-01 UV phototherapy. Lesions on the acral parts were, nonetheless, impervious to treatment.

Newer forms of unconventional phototherapy were endeavored in the management of vitiligo with changing outcomes. In a previous research, the authors[76] looked at the response of skin taking after illumination with UVA1 (340-400 nm) and broadband noticeable light in typical people with skin sorts IV-VI. Utilizing diffuse reflectance accessories, the examiners demonstrated that melanin esteem expanded in a measurements subordinate way taking after UVA1 or noticeable light introduction. Be that as it may, in a late study, El-Zawahry *et al*[77] contrasted UVA1 phototherapy and NB-UVB and reasoned that UVA1 was less effective than NB-UVB and along these lines had a constrained worth as a monotherapy in vitiligo.

A planned study utilizing a new multi-wavelength focused on Intense Pulse Light System UVA1-UVB in relationship with fluticasone cream was embraced. Eight of the ten patients who took an interest in the survey finished it. Four patients had grade 1 change (1%-25%); one had grade 3 (51%-75%); two had intensifying of the injuries after sun presentation; the last showed no response. The fundamental favorable circumstances of this strategy are that it is anything but difficult to do and it is focused to the skin lesions[78].

It was demonstrated that unmistakable light created by a helium-neon laser (633 nm) could actuate melanocyte relocation and expansion[79]. Few years later, Lan *et al*[80] utilized the same laser light source to bring about repigmentation in SV. It is trusted that the dermatomal dispersion of SV suggests a neural dysregulation, forcing it somewhat diverse to cure than NSV. The helium-neon laser has been found to adjust the adrenergic dysregulation of cutaneous blood stream seen in SV[81]. Taking after treatment with helium-neon laser, more than half repigmentation was noted in 60% of patients with

head and neck SV, repigmentation starting after 16-17 medications[79,81].

Recently, Yu *et al*[82] utilized 635 nm low-vitality laser for treating SV with the principle objective to distinguish components anticipating therapy result. In this study, 7 of 14 patients reacted to the treatment (reaction was characterized as accomplishing no less than 25% of repigmentation) accordingly affirming the effectiveness, albeit constrained, of noticeable light in SV remediation. Imperatively, the creators inferred that assessment of noninvasive cutaneous blood stream with and without earlier unmistakable light illumination on frosty focused on SV sores might serve as a treatment reaction indicator[82].

Hartmann *et al*[83] as of late attempted UVB extreme heartbeat light source with top outflow at 311 nm (Relume-Mode, Lumenis) in a right-left similar study where phototherapy was given once week by week on left side and tacrolimus was connected twice every day on right side. They reasoned that long haul treatment with both of the two modalities turned out to be equivalently compelling.

DISCUSSION

NB-UVB may exert its effects in vitiligo in a two-step process. Both may occur simultaneously. The first being the stabilization of depigmentation process and the second, the stimulation of residual follicular melanocytes[84]. It is likely that NB-UVB, similar to PUVA therapy stimulates the dopa-negative, amelanotic melanocytes in the outer hair root sheaths, which are activated to proliferate, produce melanin, and migrates outward to adjacent depigmented skin resulting in perifollicular pigmentation[85].

The helpful activity includes a mix of impacts in cell cycle energy, modifications in cytokine expression, impact on melanocytes and immunomodulation[86,87].

MOLECULAR ASPECTS OF NB-UVB IRRADIATION

Urocanic acid

NB-UVB has been appeared to impel isomerization of urocanic corrosive (UCA), "a cutaneous photoreceptor", from trans to cis structure, which might be essential in the immunomodulatory impacts of TL-01[86]. Cis-UCA has been appeared to stifle human natural killer cell action in a measurements subordinate manner[56]. The safe concealment properties of cis-UCA might be because of tweak of cytokines, for example, tumor necrosis factor (TNF)-α, interleukin (IL)-10 and IL-12, and also LC depletion[88]. A furthermore effort in the system of activity of cis-UCA incorporates the incitement of prostaglandins E2 (PGE2) generation[89].

CELLULAR ASPECTS OF NB-UVB

NB-UVB induced apoptosis

The progress in using NB-UVB for treatment of numerous provocative skin diseases is intellect to be through the inciting of apoptosis and incredible consumption of T cells. DNA harm is one of the real sub-atomic triggers for UVB-actuated apoptosis[90]. Caspases, which are apoptosis related serine proteases inside of the cell, are enacted and give rise to a course of occasions which stimulate atomic buildup, DNA fracture, and breaking down of the cell[87,91].

In caspase-dependent apoptosis, there are two primary pathways included: The natural pathway (mitochondrial/apoptosome pathway) in which cell passing happens through mitochondrial crumbling and the extraneous pathway (death-receptor pathway) in which coordinate enactment of death receptors by UVB is included in UV-prompted cell demise (Figure 2)[92].

Demise receptors have a place with a super group of receptors communicated on any cell and are described *via* conveying an intracellular passing domain[93]. This family involves CD95 (Fas), the TNF receptor and the TNF-related apoptosis-affecting ligand receptor[94].

Impelling of apoptosis by UVB, in any case, is not particular for keratinocytes but rather influences different cells also including lymphocytes and macrophages[95]. Little information has been created in regards to NB-UVB in keratinocytes. NB-UVB affects apoptosis in T lymphocytes more effectively than BB-UVB[91].

It is conceivable that UVB-prompted lesional T cell apoptosis is interceded by implication by CD95L expression on neighboring keratinocytes or by direct cytotoxic effect of UVB[96].

NB-UVB induced immunosuppression

Antigen presenting cells: Janssens *et al*[97] showed that the impact of UVB on the capacity of epidermal langerhans cell (LCs) demonstrated a checked concealment of blended epidermal cell lymphocyte response (MECLR) which is utilized as a measure of insusceptible responsiveness. The decrease in MECLR was not paralleled by the progressions in LCs numbers or HLA class 2 expression. On the other hand, Aufiero *et al*[91] affirmed that different exposures of NB-UVB diminished the thickness of LCs by 20% however on introduction to BB-UVB, LCs morphology was unaffected. Thus, NB-UVB decreases the quantity of both T lymphocytes and LCs.

Natural killer cells: NB-UVB radiation causes a measurement subordinate hindrance of natural killer cell action, in relationship with a lessening in NK-associated cytokines[98-100].

Cytokine induction

Intense presentation to high measurements of NB-UVB appears to smother sort 1 (IFN-γ) and associatively incite sort 2 (IL-4) cytokine expression while incessant introduction to low dosages of NB-UVB comes about prevalently in the concealment of IFN-γ expression[101]. Piskin *et al*[102] also, confirmed that the declaration of IFN-γ actuating cytokines (IL-12, IL-18, IL-23 and IL-27) was diminished after chronic NB-UVB presentation.

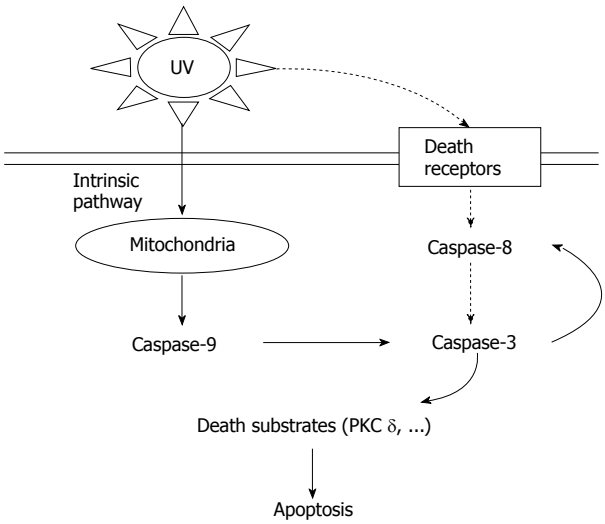

Figure 2 Proposed signaling pathway for ultraviolet-induced apoptosis in human keratinocytes (Sitailo *et al*[92]). UV: Ultraviolet.

UVB also fortifies keratinocytes to discharge the immunosuppressive solvent cytokines including IL-10 which repeals the capacity of LCs to present antigens to Th1 clones and even tolerizes them. Therefore, IL-10 moves the resistant reaction from a Th1 into a Th2 reaction[34].

Lebwohl and Ali[103] suggested that UVB-prompt concealment of Th2 chemokine creation proposes that UVB introduction to the skin smothers invasion of Th2 cells to the epidermis, along these lines, both BB-UVB and NB-UVB are thought to be viable for the treatment of different Th2-interceded or Th2-penetrating skin illnesses. What's more, the impacts of NB-UVB on constituent cells of skin other than keratinocytes might take an interest in the aggregate restorative activity.

UVB radiation has been appeared to be an intense inducer of TNF-α quality expression which intervenes motioning by human keratinocytes[104]. It is recommended that NB-UVB modifies the creation of cytokines and chemokines as a joined consequence of its immediate and aberrant TNF-α-interceded effects[105].

NB-UVB phototherapy expands union of IL-1, TNF-α and LTC-4, which incite melanocyte proliferation and relocation and melanin formation[16]. Furthermore, the parts of IL-1 and TNF-α in synthesis of melanin are disputable and opposing, as reported in a few researches[104,106].

It was suggested that TNF-α hinders the appearance and movement of tyrosinase, the main chemical in melanin blend. It also provoke limitation of pigment formation which is optional to initiation of atomic variable κB. IL-1 animates combination of endothelin-1, which is mitogenic and melanogenic[107]. The disagreement is that IL-1β has been found to lessening expansion of melanocytes and melanogenesis, while IL-1β diminishes melanocyte tyrosinase movement with no impact on multiplication[108]. Imokawa *et al*[109] watched expanded articulation of endothelin-1, IL-1 and tyrosinase in human keratinocytes *in vivo* and *in vitro* after UVB illumination, recommending the conceivable component of repigmentation. Arrival of PGE2 and PGF2 is other system of activity of phototherapy[110]. PGE2 is incorporated in the skin and manages melanocyte and Langerhans cell work, and advances melanocyte proliferation[111].

Skiba *et al*[112] inspected the impact of UVB light on cytokines (TNF-α, IL-10, IL-1β, FasL) by illuminating the unconstrained changed human epidermal cell line HaCaT to UVA (2000 and 8000 J/cm^2) or UVB (200-2000 J/cm^2) irradiation. RNA was removed from cells at 0, 4, 8, 12, 16, 24, 48 h post light for consequent ongoing PCR enhancement. They found that, TNF-α mRNA amount were promptly up managed (0 h) next light ,with highest incitement at 8 h post 2000 J/m² UVA and 200 J/m² UVB illumination.

Hino *et al*[105] explored the impact of NB-UVB on creation of chemokines and proinflammatory cytokines by keratinocytes in examination with BB-UVB. They utilized the same method as that of Skiba *et al*[112] and affirmed the past consequences of the expanded generation of TNF-α after UVB light however the increased impact of NB-UVB was not as much as that of BB-UVB.

Immuno-histochemical examination was done, to evaluate the TNF-α expression in lesional and perilesional skin when contrasted with ordinary control skin, prior and then afterward NB-UVB treatment. At standard, there was a critical increment of TNF-α in vitiligo injuries contrasted and perilesional and solid skin which proposes a conceivable inclusion of this substance in the loss of pigmentation in vitiligo. The expansion in TNF-α expression after NB-UVB phototherapy recommends another part in repigmentation[106].

Effects on pigmentary system

Introduction to UV light results in expansion in the quantity of dynamic melanocytes, the rate of melanin combination, and the exchange of shade granules to encompassing keratinocytes[113].

Sunlight exposure causes expanded levels of coursing MSH and ACTH with expanded skin darkening[114]. It was watched that UVB and MSH act synergistically to build melanin content in the skin[115].

UVB light causes lipid peroxidation took after by era of free radicals and consumption of the intracellular pool of diminished glutathione (GSH), bringing about oxidative anxiety. There is confirmation that the dynamic oxygen species created by UVB light might assume a part in melanogenesis and directs the epidermal melanin unit by expanded articulation of melanogenic α-MSH and ACTH peptides[116].

NB-UVB might apply its belongings in vitiligo in a two-stage process. Both might happen all the while. The primary being the adjustment of depigmentation procedure and the second, the incitement of leftover follicular melanocytes[84]. However, the molecular mechanisms of these processes remain unraveled[117].

In ordinary melanocytes, the coupling of development

components, for example, bFGF HGF, and ET-1, to receptors on melanocyte results in the quick actuation of the mitogen-enacted protein kinase (MAPK) and ribosomal S6 kinases[118]. In melanocytes, a solitary development element is adequate to stimulate the MAPK course however is not ready to support melanocyte expansion or reasonability. No less than two distinctive development variables in mix are important to affect melanocyte expansion[118].

Wu *et al*[119] showed that NB-UVB irradiation stimulated the proliferation of melanocytes with a critical increment in the arrival of bFGF and ET-1 by keratinocytes. bFGF has been perceived as a characteristic mitogen for melanocytes, which improves the development and survival of them. ET-1 invigorates DNA union in melanocytes, and has a synergistically stimulatory impact on bFGF-animated DNA amalgamation of these cells.

Kawaguchi *et al*[120] reported that NB-UVB is viable in stimulation of proliferation and differentiation of functioning melanocytes in epidermis. The precursor melanocytes seem to proliferate into mature pigmented melanocytes after UV exposure. They differentiate into TRP-2 positive melanocytes by the activation of c-kit receptor then become TRP-1 positive melanocytes.

NB-UVB animates expanded articulation of the POMC quality which is joined by creation and arrival of α-MSH[119,121] .

ADVERSE EFFECTS OF NB-UVB

Acute effects

Erythema: NB-UVB is moderately sheltered, and this is one of the fundamental purposes behind it being viewed as the first decision of treatment of summed up vitiligo in grown-ups, and also in youngsters. Erythema is the most critical intense symptom of NB-UVB, and the frequency differs somewhere around 10% and 94% according to the pharmaceutical style and meaning of erythema[120]. Be that as it may, asymptomatic powerless redness is relied upon to be basic, as this is the final stage for NB-UVB in vitiligo. A more noteworthy extent of cases create erythema as contrasted and PUVA, yet they are less inclined to pulsate therapy because of a smaller span of NB-UVB-prompted redness.

Blistering: Lesional blistering following NB-UVB treatment is extraordinary, depicted for the most part in psoriatic plaques, and amid treatment of pityriasis rubra pilaris. The instrument of rankling is misty. George and Ferguson[122] proposed that inside psoriatic plaques might be because of fast loss of scales, presenting lesional skin to a "phototoxic" measurements in connection to contiguous moderately photograph shielded skin causing rapid loss photoprotection from the lesions thus exposing them to a big dose of radiation.

Pruritus: Albeit additionally a typical symptoms of TL-01 treatment, it now and again mirrors the hidden infection forms[123]. Wallengren[124] explained this phenomenon by the possibility of the role of prostaglandin E2 which induces itch and potentiates itch induced by histamine release.

Infection: Reactivation of herpes simplex infection can happen with NB-UVB therapy and safety oriented procedures ought to be brought in those with a background marked by this condition[125]. The possible impacts of NB-UVB on the eyes, specifically presentation related conjunctivitis or keratitis; should be considered if treating patients with periocular skin inflammation, despite the fact that treatment can be performed deliberately with the eye close as opposed to with goggles in this circumstance[126].

Chronic effects

Photoaging: Constant NB-UVB introduction is liable to increment photoaging. There is an expanded era of ROS in skin upon introduction to NB-UVB. These ROS are accepted to be basic go betweens of the photoaging process. ROS can adjust proteins in tissue to frame carbonyl subsidiaries, which aggregate in the papillary dermis of photodamaged skin[127].

Carcinogenesis: Actuation of the decay brought on by UVB is settled. This light is a completed disease bringing about specialists and TL-01 has been seemed to provoke DNA hurt in individual's tissues and animal examples. In a final knockout mouse case, change of hurtful cutaneous neoplasms were essentially more noteworthy for NB-UVB than BB-UVB taking after similar dose presentation[128]. The development of cyclobutane pyrimidine dimers (CPD) was basically ascending with NB-UVB, however those of radiation inducing and 8-oxoguanine were on a very basic level more after BB-UVB. These discoveries recommended the nearby connection in the middle of CPD and the higher cancer-causing capability of NB-UVB. In any event in the setting of psoriasis, it is suggested this hindrance of NB-UVB opposite BB-UVB could be offset the way which the aggregate measurements wanted for leeway of psoriasis is less than that for BB-UVB. The main accessible creature information required perception for a long time[129].

However, there were conflicting data that NB-UVB has been appeared to be less[5] just as[130], and more cancer-causing than BB-UVB[6]. Likewise NB-UVB related skin tumor danger might be not as much as that with PUVA[22]. Rivard and Lim[131] reported that the danger of improvement of nonmelanoma skin growth has been assessed to be under 2% every year which is not as much as that of PUVA. Black and Gavin[132] have recommended that at present, NB-UVB has all the earmarks of being a moderately safe treatment methodology; in any case, consistent long haul follow-up is crucial.

The world writing was methodically explored to upgrade data on the skin tumor hazard with UVB phototherapy, and strategies suggested to reduce carcinogenicity during phototherapy[133].

Skin sparing strategy: Parts of the body where no sores are available (particularly the face) ought to be protected amid medications. Likewise, parts that have repigmented palatable ought to, if conceivable, be protected amid consequent medications (for instance by wearing trousers when in doubt, don't react to phototherapy)[134]. Privates ought to be likewise protected in light of the fact that these regions, when in doubt, don't react to phototherapy and genital tumors have been seen after PUVA treatment[22].

Prevention of pointless presentation to characteristic daylight on both treatment and non treatment days and the utilization of UV-blocking specialists on sun uncovered ranges. Also, the use of combined treatments with other modalities to reduce the cumulative dose[135].

Proper patient selection: And using protocols suitable to each patient with lower cumulative doses[132].

Chemoprevention: This term is used to minimize the risk of carcinogenesis to UV therapy by using non toxic diet with antitumour properties. For example, black teas extract which contains dimeric faranols, and polymeric polyphenols. These are effective in reducing UVB and UVA mediated DNA damage and expression of early response genes[136].

Light dose adjustment: This may be the best appr-oach to obliging the carcinogenesis of NB-UVB. Close erythemogenic measurements of NB-UVB clear psoriasis quicker than lower dosages of NB-UVB, but the later regimen is similarly powerful with just somewhat more medicines[6].

Less frequent doses: Dawe *et al*[137] thought about thrice-weekly and five times week after week medications utilizing half body correlation study. Notwithstanding no critical contrast in extent of patients who indicated skin clearing and time to freedom were found between the two regimens. Besides, the five week by week bunches got higher aggregate measurements and had more scenes of very much delineated erythema.

ADVANTAGES OF NB-UVB PHOTOTHERAPY

From the advantages of NB-UVB phototherapy over other phototherapeutics: No topical or oral drug, tests, or unique glasses are needed[34]. Quicker reaction than expansive band UVB and like PUVA[138]. Number of medicines required for clearing is by and large not as much as wide band UVB and PUVA[22]. Safe for youngsters, pregnant ladies and lactating mothers[139]. Eliminating erythemogenic wavelengths underneath 311 nm grants higher intensities and more presentation times bringing about most extreme advantage from phototherapy and a shorter course of treatment[22,32].

Longer reduction periods after treatment like those with PUVA treatment and particularly better than BB-UVB treatment[33]. Studies show 38%-40% of NB-UVB treated patients requires no extra treatment for no less than one year[140].

DISADVANTAGES OF NB-UVB PHOTOTHERAPY

Because of the diminished force of tight band contrasted with expansive band, more lights are expected to give auspicious treatment. Standard wide band frameworks have 8 to 16 lights, though limit band frameworks need 24 to 48 lamps[141]. Additionally NB-UVB lights seem to have a shorter future than expansive band and subsequently, require more continuous substitution. NB-UVB light lodges costs including the lights are a great deal more expensive[34]. Erythema is less unsurprising than with expansive band UVB, however it might be more extraordinary and steady. Frequently lesional just[8].

THE PERSONAL SATISFACTION AFTER NB-UVB TREATMENT

Vitiligo is an illness with significant restorative and ensuing psychological sway, instead of physical inability. Most of the researches carried out yet have evaluated the viability of NB-UVB in the change of restorative distortion - that is, a diminishing in the range of depigmentation. In spite of the fact that it is normal to trust that repigmentation taking after NB-UVB would enhance the personal satisfaction in vitiligo patients, there is insignificant target appraisal to such an impact. In an investigation of review configuration, Tjioe *et al*[142] surveyed the personal satisfaction in vitiligo individuals after therapy with NB-UVB. Despite the fact that the patients evaluated their wellbeing to be by and large great to fantastic, phototherapy represented just a little change in a minority of patients as a rule prosperity. The principle issue of phototherapy in reasonable cleaned people is conspicuousness of the vitiligo injuries resulting in pigmentation of the encompassing typical skin demanding a more noteworthy level of disguising unto total repigmentation is accomplished in the sores. In a report in youngsters, personal satisfaction evaluated by the Children's Dermatology Life Quality Index (CDLQI) did not lessen altogether in kids having under 25% repigmentation, whereas the diminishment was noteworthy in the individuals who had more than 25% pigmentation with a corresponding abatement in CDLQI with change evaluation of repigmentation[133].

CONCLUSION

Albeit various administration alternatives exist for vitiligo, UVB phototherapy is for the most part the treatment of decision as it is compelling as well as has a great danger to-advantage proportion. Ordinary BB- and NB-UVB is generally accessible and helpful especially in far reaching illness, despite the fact that NB-UVB has been all the

more broadly concentrated on with demonstrated viability. Combined treatments are likewise helpful and might give faster regimentation and treat vitiligo with an added substance system of activity than UVB phototherapy. Progresses in innovation might prompt the proceeding with utilization of UVB phototherapy as a remedy for vitiligo through the improvement of complex gadgets and conveyance frameworks and in addition creative application strategies. These will give expanded helpful choices to all vitiligo patients, especially those with recalcitrant disease.

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Pediatric ocular rosacea, a misdiagnosed disease with high morbidity: Proposed diagnostic criteria

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Abstract

Ocular rosacea is an important and underdiagnosed chronic inflammatory disorder observed in children. A clinical spectrum ranging from chronic eyelid inflammation, recurrent ocular redness, photophobia and/or hordeola/chalazions and conjunctival/corneal phlyctenules evolving to neovascularization and scarring may occur. Visual impairment and consequent amblyopia are frequent and corneal perforation although rare is the most feared complication. Ocular manifestations usually precede cutaneous lesions. Although few cases of pediatric ocular rosacea (POR) have been reported in the literature, many cases must have been underdiagnosed or misdiagnosed. The delay in diagnosis is greater than one year in the large majority of cases and may lead to serious ocular sequelae. This review aims to highlight the clinical features of POR, its epidemiology, easy diagnosis and effective treatment. We also propose new diagnostic criteria, in which at least three of the five clinical criteria must be present: (1) Chronic or recurrent keratoconjunctivitis and/or red eye and/or photophobia; (2) Chronic or recurrent blepharitis and/or chalazia/hordeola; (3) Eyelid telangiectasia documented by an ophthalmologist; (4) Primary periorificial dermatitis and/or primary features of rosacea; and (5) Positive familial history of cutaneous and/or ocular rosacea.

Key words: Ocular rosacea; Diagnostic criteria; Demodex folliculorum; Leukoma; Pediatric; Blepharoconjunctivitis; Chalazia

Core tip: Ocular rosacea is a chronic inflammatory disorder with a clinical spectrum ranging from chronic eyelid inflammation, recurrent ocular redness, photophobia and/or hordeola/chalazions and conjunctival/corneal phlyctenules. Although few cases of pediatric ocular rosacea (POR) have been reported in the literature, many cases must have been underdiagnosed or misdiagnosed. This delay in diagnosis may lead to serious ocular sequelae. This review aims to highlight the clinical features

of POR, its epidemiology, new diagnostic criteria, treatment and outcomes.

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INTRODUCTION

Rosacea is a chronic condition affecting the facial and ocular surface tissues, particularly common in the fair-skinned population[1-4]. The American National Rosacea Society developed a classification system that became the standard one. According to the patterns of signs and symptoms, four major clinical subtypes of rosacea are described: Erythematotelangiectatic, papulopustular, phymatous and ocular rosacea. In children, the phymatous type is not seen[1-4]. These subtypes may be discrete variants or may be progressive from one to another, and they can also coexist. Ocular rosacea is one of the four described types of rosacea, characterized by involvement of eyelids, conjunctiva and corneal tissue[1-4].

The prevalence of ophthalmic involvement in rosacea is probably higher than previously presumed and it varies considerably between ophthalmic and dermatological studies[2,3,5]. In most adult cases, ocular manifestations are preceded by cutaneous signs, making the diagnosis easier. However, in pediatric ocular rosacea (POR) the ocular involvement may precede dermatologic manifestations in more than half of the patients[5-8], delaying the diagnosis. The mean delay between disease onset and the diagnosis is greater than one year in most case series[6,8-11], and greater than two years in more than half of cases[6,8-10]. Before the established diagnosis, many patients are seen by multiple ophthalmologists and/or others clinicians and receive various types of therapy, including topical antibiotics, topical corticosteroids, lubricants and antiallergic drops, without success[6,8,12,13]. In fact, the management must be multidisciplinary, including dermatologists, ophthalmologists and pediatricians.

The non-recognition of POR can also be a result of the varied names adopted in the literature and the lack of overall consensus: Chronic blepharokeratoconjunctivitis[6,9-11,14-18], blepharokeratitis[10], chronic phlyctenular keratoconjunctivitis[8-10,18] phlyctenular blepharokeratoconjunctivitis[10,14,18], and meibomitis-related keratoconjunctivitis[19].

The main aim of this review is to make the children's health care providers aware of POR, by highlighting its clinical features, epidemiology, easy diagnosis and treatment. We also propose POR criteria.

EPIDEMIOLOGIC DATA

Few cases of POR have been reported in the literature. In 13 published series[5-17], a total of 259 patients were found and the number of patients in each varied between 3[16] and 51[15]. In another series, the largest ever published about POR, the sample included 615 cases, most of them described as mild, by Gupta *et al*[18] in 2010. In others studies, the number of cases was smaller probably because only severe cases were reported[5-17].

POR is mostly diagnosed by ophthalmologists[6,9,11,14,15], making this condition rare for other physicians and is underdiagnosed or misdiagnosed by them[5-13,15,16]. In two tertiary centers of ophthalmology, in Philadelphia[10] and in New Deli[18], chronic blepharokeratoconjunctivitis was the reason for referral in 15% and 12.3% of all children, respectively.

In the 259 patients of the 13 series[5-17], 162 are girls (62.5%) and 97 are boys (37.5%), the opposite of what was found by Gupta *et al*[18] (37.5% *vs* 62.5%).

The median age of onset in five of the 13 series (122 patients) varied between 3.2 years and 7.0 years, with extremes of 1 mo and 17 years[6,8,9,11,17]. There is a significant delay in diagnosis, often more than two years, justifying the median age at presentation in tertiary centers, between 4.6 years and 10.2 years[6,7,11,18].

A positive family history for rosacea was found in nine of the 34 patients of two series (26.5%)[5,8]. However, in most series family history wasn't reported. Since children with rosacea are more likely to have familial rosacea[1,8], it is important to obtain this clinical data, which can help suggesting the diagnosis.

Bamford *et al*[20] demonstrated that having a hordeolum during childhood predisposes for rosacea in adulthood, underlying the close relationship between ocular and cutaneous inflammation. Ocular rosacea may occur without cutaneous manifestations and in individuals with any subtype of rosacea, although it is noteworthy that 50% of patients with erythematotelagiectatic and papulopustular types have eye inflammation[1,5].

Fair-skinned children of European descent are more commonly affected, although any ethnic group can be afflicted[1,4,5,8,12].

OUR EXPERIENCE IN POR

Since July of 2009, we have diagnosed and treated eight cases of POR: Three males and five females. They were referred to our tertiary Pediatric Rheumatology and Ophthalmology Units due to chronic red eye of unknown etiology, most of them after a medical peregrination and multiple ineffective topical treatments.

Their median age was 10 years (3-16 years) with an established diagnosis two years after the first symptoms (0-7 years); the mean previous medical consultations was eight (0-30 consultations), including at least one evaluation for an ophthalmologist in each (maximum of 13 different ophthalmologists). Two children have evolved to leukomas (Figure 1) and a decrease in visual acuity (7/10 and 8/10 respectively), what are persistent sequelae. We have already published the first two cases diagnosed at our unit[21].

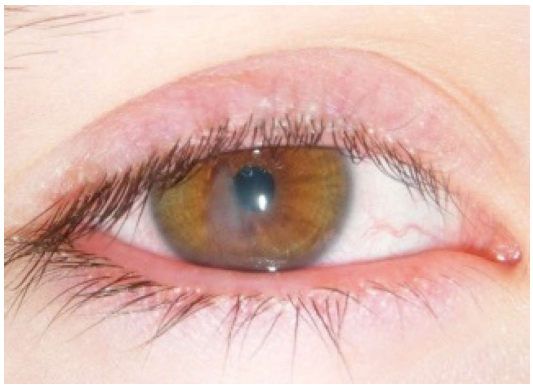

Figure 1 Sequelae of pediatric ocular rosacea: Leukoma.

Figure 2 Chronic conjunctivitis and chalazia in pediatric ocular rosacea.

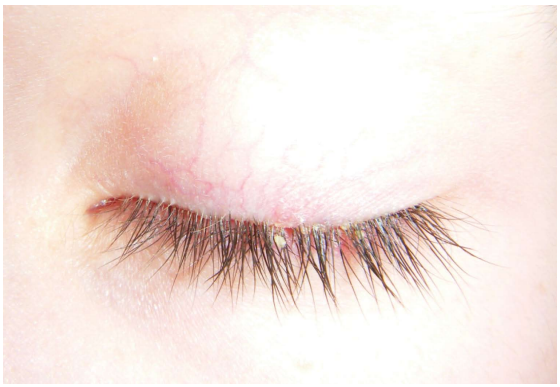

Figure 3 Blepharitis in pediatric ocular rosacea.

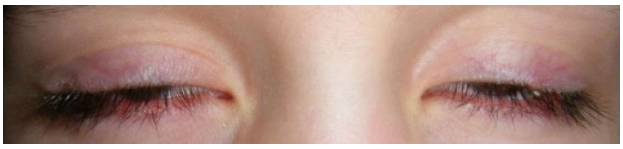

Figure 4 Telangiectasias and erythema of the lid margin in pediatric ocular rosacea.

ETIOLOGY, PATHOPHYSIOLOGY AND HISTOPATHOLOGY

The exact etiopathogenetic mechanism of rosacea and OR remains unknown. There are probably different regulatory systems involved[3-5,22]. The infection by microbial organisms may have an important role. In OR, *Demodex folliculorum* mites, a common inhabitant of normal human skin, possibly represents a contributing cofactor to the inflammatory reaction seen in both cutaneous and ocular disease[2-4,22,23].

Recently, bacterium *Bacillus oleronius* has been isolated from *Demodex folliculorum* mites and found to be responsible to trigger an immune system response. These seem to have a correlation with facial rosacea and OR[1,24].

Gastric coinfection with *Helicobacter pylori* has also been implicated, since this bacteria has the ability to produce flush-inducing toxins[3,4,7,22,23]. *Staphylococcus aureus* and *Staphylococcus epidermidis* are common organisms cultured from conjunctival or lid swabs, but their relationship with OR is questionable[7,11,12].

Recent studies focus on the role of bacterial lipases and interleukin-1 alpha and elevated concentrations of promatrix metalloproteinases in the blepharitis and corneal epitheliopathy, respectively[4]. Promatrix metalloproteinases are degrading enzymes responsible for the inferior corneal stromal thinning[4].

Rosacea induces vasodilation with increased blood flow and vessel permeability leading to erythema, telangiectasias and lymphedema of the affected tissues, especially in the eyelids[4]. The histopathological changes are unspecific, showing perifollicular infiltrates consisting of lymphohistiocytes, epithelioid and giant cells[16].

CLINICAL MANIFESTATIONS

The clinical spectrum and severity of POR is variable, depending on the involvement of eyelids, conjunctiva, cornea and other ocular findings[3,4,6]. The first manifestations of POR can be chronic conjunctivitis, recurrent hordeola and/or chronic chalazia (Figure 2)[5-8,11,16,20], which are quite frequent in childhood, explaining the common delay in the diagnosis of this condition. Nevertheless, POR is often silent, painless and has unspecific clinical manifestations[2-6,12,16]. Table 1 shows the different ocular findings in POR.

The most common manifestations are blepharitis (Figure 3), recurrent hordeola/chalazia (Figure 2), telangiectasias of the lid margin (Figure 4), dry eye, conjunctivitis and keratitis, frequently in association (blepharoconjunctivitis, blepharokeratoconjunctivitis)[2-6,8,10,15]. The typical clinical picture is a long history of hyperemic conjunctiva and intense photophobia associated with chronic blepharitis, explaining why POR is frequently called blepharoconjunctivitis[6,11,19].

Combining 12 series, including 245 patients, 185 (75.5%) had bilateral involvement, generally asymmetrical[5,6,8-17]. In the Gupta *et al*[18] series only 47.5% had bilateral involvement.

Eyelid involvement may precede the other features in months to years, because it is primarily an eyelid margin inflammation, such as blepharitis or meibomitis[4-6,8,11,13]. Corneal and conjunctival are secondarily involved.

The ocular symptoms include foreign body sensation, pain, burning, redness, photophobia and epiphora[3-6,8,11,19]. As a consequence of the long diagnostic delay, more than a half of the children have already corneal injuries at diagnosis, such as punctate epithelial erosions,

Table 1 Different ocular findings in pediatric ocular rosacea[1-8,10-19]

Eyelid: Telangiectasias and erythema of the lid margin, meibomian gland dysfunction, anterior blepharitis, recurrent chalazia/hordeola, madarosis (loss of eyelashes), trichiasis
Conjunctiva: Interpalpebral or diffuse hyperemia, papillary and/or follicular reaction, pinguecula, scarring
Cornea: Punctate erosions, pannus, superficial neovascularization, lipid deposition, spade-shaped infiltrate, scarring, thinning, ulceration, perforation, phlyctenula
Sclera: Episcleritis, scleritis
Insufficiency of tear film (dry eye) with abnormal Schirmer test
Uvea: Iritis (rare)

Table 2 Differential diagnosis of pediatric ocular rosacea[2-4,8,17]

Chronic conjunctivitis (viral, allergic, atopic)	Medication toxicity
Keratoconjunctivitis sicca	Interstitial keratitis
Meibomitis	Infectious keratitis (herpes simplex)
Recurrent hordeola/chalazia	Sterile or bacterial corneal ulcers
Staphylococcal blepharoconjunctivitis	Auto-immune diseases
Seborrheic blepharoconjunctivitis	Sarcoidosis

subepithelial infiltrates, corneal phlyctenules, marginal keratitis, ulceration and corneal opacity[8,11,13]. Pediatric corneal involvement tends to be central or paracentral[6].

Depending on the severity, conjunctival and/or corneal phlyctenules may be present in 5.5%[18] up to almost 40%[8, 11,15].

The primary features of pediatric facial rosacea are chronic facial flushing, non-transient erythema, papules and pustules (limited to the cheeks, chin and nasolabial areas), telangiectasias, idiopathic periorificial dermatitis and the ocular and periocular signs previously described[1,4,5,16]. Onset and severity of POR is not associated with the cutaneous signs[2,3,13].

DIFFERENTIAL DIAGNOSIS

As previously mentioned, symptoms of POR aren't always specific and other ophthalmic disorders may present with similar findings, so the differential diagnosis includes a broad spectrum: Chronic conjunctivitis (viral, allergic, atopic), keratoconjunctivitis sicca, meibomitis, recurrent hordeola/chalazia, staphylococcal or seborrheic blepharoconjunctivitis, medication toxicity, interstitial or infectious (herpes simplex) keratitis, sterile or bacterial corneal ulcers, auto-immune diseases, sarcoidosis, among others (Table 2)[2-4,8,17].

PROPOSED CRITERIA FOR POR

There are no specific clinical signs neither laboratory test nor histopathological markers for POR[2-5,12]. Chamaillard *et al*[5] and Hong *et al*[16] have proposed "dermatologic and ophthalmologic criteria for childhood rosacea". However, in these clinical criteria four of five are cutaneous manifestations[5,16]. Cetinkaya *et al*[13] have also proposed the "pediatric acne rosacea diagnostic criteria" as a combination of meibomian disease, chronic blepharitis, recurrent chalazia and chronic symptoms of photophobia, ocular irritation and redness, with or without corneal vascularization, that do not respond to routine medical treatment[13]. For Léoni *et al*[7], the diagnostic criteria of POR requires two ophthalmologic and/or two dermatologic criteria.

Considering the above mentioned publications[5,7,13,16], in Table 3 we propose a new diagnostic criteria for POR. As in the previous proposed diagnostic criteria[5,16], ocular redness may be absent. The diagnosis of POR should be multidisciplinary, with the contribution of dermatologists, ophthalmologists and pediatricians. The presence of lid margin telangiectasia and erythema, together with meibomian gland dysfunction (chronic chalazia) and a long history of ocular irritation should suggest the diagnosis of POR[8,9,12-14], especially if there is no response to routine medical treatment[13].

TREATMENT

The initial therapeutic approach should always include local measures, such as daily warm compresses, eyelid hygiene with neutral baby shampoo and liquefaction and removal of the thick meibomian gland secretions[1-4,8,10,11,13,15]. Prolonged topical erythromycin ointment or, more recently, azithromycin 1.5% eye drops may be useful and effective in mild cases and in association with other treatments[14]. Although very few publications support their efficacy and its administration in children is difficult, these eye drops are usually used[16]. Doan *et al*[14] described their experience with topical 1.5% azithromycin eye drops (monotherapy) being superior to systemic erythromycin and considered it as a first-line therapy.

Children that prove to be intolerant to prolonged topical treatment or with severe ocular involvement and/or both severe cutaneous and ocular rosacea must be treated with systemic antibiotics associated to topical care[3,5-7,12,13]. Tetracycline and doxycycline, normally used in adults, are inadvisable in children younger than 7-8 years due to their potential bone toxicity and dental staining[1,3-6,12]. Alternative safe and effective options are: Erythromycin (30-50 mg/kg per day, three times a day), clarithromycin (15 mg/kg per day divided in two doses) or azithromycin (10-12 mg/kg per day, one dose)[1,6,10,11,13,17]. Treatment with oral metronidazole is another possibility, but its frequent neurologic adverse effects, particularly peripheral neuropathy, forbids prolonged therapies[4,5,7,16]. Effective

Table 3 Proposed diagnostic criteria of Coimbra for pediatric ocular rosacea

Chronic or recurrent[1] keratoconjunctivitis and/or red eye and/or photophobia
Chronic or recurrent[1] blepharitis and/or hordeola/chalazia
Eyelid telangiectasia documented by an ophthalmologist
Primary features of pediatric rosacea (facial convex areas with chronic flushing and/or erythema and/or telangiectasia, and/or papule, pustules in cheeks, chin, nose or central forehead and/or primary periorificial dermatitis)
Positive familial history of cutaneous and/or ocular rosacea

Diagnosis: ≥ 3 criteria; [1]Chronic (≥ 2 mo); Recurrent (≥ 3 episodes lasting > 4 wk in 12 mo).

amoxicillin treatment has also been described[15].

In children older than eight years old the cyclines can be used as first systemic therapy: Minocycline, doxycycline[8,13,25]. After remission, prolonged treatment with doxycycline 40 to 100 mg once or twice daily is a good option[4,8,12,13,25].

The recurrence rate is high, especially within the first three months of treatment if systemic therapy is tapered too quickly[4,7,8,10,12]. Hence, therapeutic success is directly related to its duration, by reducing the number of recurrences. Prolonged treatments (over three months) may be required[6,8,10,13-16], with some publications recommending systemic antibiotic for at least six months[10] and others for a minimum of 12 mo[13]. Some patients will need oral antibiotics during several years, but most children may be tapered off within six months of treatment[6,10].

Intermittent treatments are necessary if shorter periods of systemic antibiotics are used[5,7,11]. Since long-term use of oral antibiotics may be problematic, it has been suggested that after six to twelve months of treatment oral therapy should be tapered slowly[4,8]. Some authors suggest that low maintenance dosages can be taken indefinitely[4], but this is questioned by others given its subtherapeutic dosages[16].

Topical (ocular) corticosteroids can prove useful for short-term exacerbations of eyelid disease and the management of inflammatory keratitis and episcleritis since they constrain eyelid and ocular inflammation[3,4,8,11-15]. However, its long-term use should be avoided due to their well-known potential side effects, such as increased intraocular pressure, glaucoma and cataracts. They should be discontinued as soon as possible. Furthermore, their discontinuation can frequently lead to rosacea exacerbations (topical steroid dependency)[1-4,7,13-15,17]. If indicated, topical corticosteroids must only be used during the initial weeks and the drops tapered by one drop per week[7,11,13].

Cyclosporine A 0.5% to 2% eye drops (four-six times per day) is an interesting approach for children with steroid-dependent disease and in phlyctenular blepharokeratoconjunctivitis[14,26]. Our experience shows that topic cyclosporine isn't well tolerated by children, probably due to the lack of a suitable preparation in Europe.

It was described the efficacy of ivermectin to the treatment of refractory cases of cutaneous ocular rosacea, as an antiparasitic drug effective against mites Demodex[27]. The treatment consist in an oral single-dose, and despite being proscribed to children under five years and under 7 kg, it has been used in pediatric age[27]. This drug has primarily been reported in the treatment of immunosuppressed patients, but there are reports of its success in immunocompetent patients[27,28].

Surgical care is needed in specific cases, like corneal perforation[2,15,25]. Other options under investigation are laser and intense pulsed light therapy. Dietary intake of omega-3 has recently proven to be effective as an anti-inflammatory and in clearing meibomian gland secretions[2,6]. Flaxseed oil (∝-linoleic acid) 2.5 mL once a day for up to 12 mo, with gradual reduction to an alternate day administration, can be an option in children intolerant or non-compliant with the use of long-term systemic antibiotics[7].

OUTCOMES/SEQUELAE

POR can wax and wane with a recurrence rate of 40%[10]. Affected children suffer from chronic conjunctivitis, corneal pannus, corneal neovascularization, generalized keratitis and meibomian gland disease. Chronic symptoms and frequent exacerbations may lead to tissue hypertrophy, extensive neovascularization, scarring, corneal opacification, corneal perforation and complications from secondary infections[1,4-8,11-13,15,18]. Some patients may develop raised intraocular pressure and cataract, possibly with relation to chronic topical steroid therapy[15].

The duration of the disease and the corneal involvement are the determining factors of severity[4,6,13]. Furthermore, a prolonged therapy regimen is required to minimize corneal scarring and visual loss. Gradual tapering is recommended to avoid relapses[4,6,13]. Thus, POR can be a source of significant visual morbidity in children[4,6,8,15,18].

In comparison to adults, children seem to be more susceptible to corneal damage imposed by the inflammatory and immune response to periocular bacteria. This may compromise vision development, which combined with the position of the opacities in the cornea may be complicated by secondary amblyopia[1,4,6,8,10,12].

TAKE HOME MESSAGES

OR is a subtype of rosacea, which is a chronic inflammatory disease; POR is frequently under and misdiagnosed, so it is probably more common than we previously thought; POR may be associated with high morbidity, development of sequelae and it is a possible cause of loss of vision;

The diagnosis is facilitated by the proposed POR criteria; An ophthalmologist observation is mandatory for the diagnosis, but it should be suggested by pediatricians or dermatologists; Treatment requires a minimum of three months' antibiotic therapy and a subsequent gradual tapering.

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MINIREVIEWS

Actinic keratosis and field cancerization

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Abstract

While actinic keratoses (AKs) have been considered precancerous until recently for being able to turn into squamous cell carcinomas (SCCs), it is now agreed that it would be more appropriate to call them cancerous. Although not all AKs turn into SCC and some of them may even have a spontaneous regression, there is an obvious association between SCC and AK. Approximately 90% of SCs have been reported to develop from AKs and AKs are the preinvasive form of SCCs. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. AK can be a single lesion or it can involve multiple lesions in a field of cancerization; thus, AK treatment is grouped under two headings: (1) Lesion-specific treatment; and (2) Field-targeted treatment. Lesion-specific treatments are practicable in patients with a small number of clinically visible and isolated lesions. These treatments including cryotherapy, surgical excision, shave excision, curettage and laser are based on physical destruction of the visible lesions. Field-targeted treatments are effective in the treatment of visible lesions, subclinical lesions and keratinocyte changes in the areas surrounding the visible lesions. Field targeted treatment options are topical imiquimod cream, 5% 5-fluorouracil cream, ingenol mebutate, diclofenac gel, resimiquimod and photodynamic therapy.

Key words: Actinic keratosis; Squamous cell carcinoma *in situ*; Field cancerization

Core tip: While actinic keratoses (AKs) have been considered precancerous until recently for being able to turn into squamous cell carcinomas (SCCs), it is now agreed that it would be more appropriate to call them cancerous. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. In this review, epidemiology, ethiopathogenesis, diagnostic approach and treatment options for AK and field cancerization have been evaluated in light of recent literature.

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INTRODUCTION

Actinic keratoses (AKs) are epidermal lesions characterized by skin-colored, red or red-brown crusty and squamous spots, patches or nodules with a potential to progress to squamous cell carcinoma (SCC). Being an indicator of cumulative ultraviolet (UV) exposure, AK lesions typically appear on the areas with chronic sun exposure such as the face, chest, hairless scalp, auricles, hands and dorsal regions of arms[1]. It has been reported that one of every 10 AKs progresses to invasive SCC in time. People with more than five AKs have a relatively increased risk of SCC. While AKs have been considered precancerous until recently for being able to turn into SCCs, it is now agreed that it would be more appropriate to call them cancerous. The term keratinocyte intraepithelial neoplasia (KIN) has been proposed for these lesions[2].

Although not all AKs turn into SCC and some of them may even have a spontaneous regression, there is an obvious association between SCC and AK. Approximately 90% of SCs have been reported to develop from AKs and AKs are the preinvasive form of SCCs[1]. About 20%-25% of the lesions regress in a year. In a similar period of time, 15% of the lesions will reemerge. It is very difficult to predict if any regression is permanent.

All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. It should be noted that subclinical lesions may also transform into SCC[3]. The histopathology of subclinical lesions is the same as that of clinically observable AKs. The number of subclinical spots in an area is more than 10 times that of visible AKs[1,3]. The risk factors of transformation from AK into SCC have been enumerated as endurance, bleeding, larger lesion diameter, fast growth, erythema and ulceration with minor risks including pain, palpability, hyperkeratosis, itching and pigmentation[4].

EPIDEMIOLOGY

The real incidence of AK is not known. The risk of having AK in a lifetime is estimated to be 50%. The World Health Organization has reported that the prevalence of AK is clearly associated with the location of the place of living. In smaller latitudes, both the prevalence of AK is high and multiple AKs are seen more frequently[5].

The rate of prevalence is reported to be 40%-60% on the average in Australia and between 11% and 25% in the northern hemisphere. They are seen more in males than females[6]. A study has reported the prevalence as 15.4% in men and 5.9% in women in the United Kingdom. These rates go up to 34.1% in men and 18.2% in women after 70 years of age[7]. In Australia, the prevalence was found to be 22% in men and 8% in women and 83% and 64% between the ages 60 and 69, respectively[8].

FIELD CANCERIZATION

Multiple AKs are usually seen in areas exposed to the sun and dysplastic keratinocytes or preclinical lesions can be seen histologically on the clinically lesion-free skin surrounding the AKs. Even if the keratinocytes on these areas appear to be normal histologically, they are candidates for a future tumor growth. This process is defined as field cancerization[1,9]. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. Photodamage is the earliest finding of the process progressing from AK to finally SCC[1]. The term field cancerization is defined as the presence of one or more areas created by genetically altered epithelial cells that lead to the prognosis of epithelial carcinogenesis. The effect of field cancerization is well-documented in squamous cell tumors[10].

The definition of field cancerization was first used by Slaughter *et al*[2] in 1953. Such areas are probably associated with exposure to carcinogens[2]. Multiple cancers that are associated with gene aberrations induced by carcinogens, that do not occur due to metastasis of tumor cells and that appear as tumors independent of, and in different distances from, each other are associated with field cancerization[11]. A cutaneous field cancerization refers to the histologically altered areas on the lesion-free skin tissues surrounding the non-melanocytic skin tumors on a chronically photodamaged skin[3].

ETIOPATHOGENESIS

UV

UV radiation seems to be the major player responsible for the process starting from photodamaging of the skin and progressing to actinic keratosis and SCC. The leading risks are intensive or cumulative UV exposure, open area activities, tanning efforts and longevity. The DNA lesions induced by UV are either repaired or if the damage is severe the cell enters apoptosis to protect itself from mutation. In case the cell cannot be fully repaired but it remains alive, the damaged nucleotides result in permanent somatic mutations and accumulation of such mutations may end up in cancer[6].

Gene mutations

In normal cellular growth, the p53 expression is suppressed. Its expression is activated during severe stresses in which the cell is caught between apoptosis and survival in the case of cytotoxic or mutagenic agents for instance. The gene that undergoes mutation most frequently in humans during AK is p53 (37%) and there is a strong relationship between TP53 mutations

and AK/SCC. Both the UVA and UVB wavelengths are among the causes of carcinogenesis in TP53 DNA mutations. The mutations of this gene appear at the early stages of carcinogenesis and also play a role in the progression of cancer[12]. The UV radiation induced TP53 mutation has been found in more than 90% of SCCs developing from AKs[7]. The clonal patches consisting of cells with TP53 mutations can also be found on normal skin. Jonason *et al*[13] have reported that these cell clones are 10 times more in number and are larger on a skin exposed to the sun than on a skin not exposed to sun. Brennan *et al*[14] have shown that tumor recurrence is significantly higher in the presence of mutations in peritumoral areas. No recurrence has been seen in the neighboring areas without any mutations[14]. In CDKN2A mutation, the risk of progression from AK to SCC increases significantly[6]. The other mutations associated with the progression of skin cancers are NOTCH1, NOTCH2 and SMO. Hu *et al*[15] have shown that the Notch/CLS signal is suppressed in the stromal area neighboring premalignant AK lesions. They have also shown that tissue changes such as stromal atrophy and inflammation occur when the Notch/CLS signal is eliminated. This is a potent stimulus for epithelial tumors[15].

Immune suppression

While the rate of progression from AKs to SCCs is 10% in immunocompetent persons, this rate is 50% in immunosuppressed people. Patients who underwent organ transplantations have 100-250 times increased risk of cutaneous SCC. UV and immunosuppressive drugs are effective in the occurrence of skin cancer. Because the immunosuppressive therapy used for transplant patients reduces peritumoral inflammation, the invasion of skin tumors can easily go unnoticed in clinical practice[16]. Trans-urocanic acid (UCA), which is a UVB chromophore, is expressed in stratum corneum in ample amounts. It is rapidly isomerized into a cis form by the effect of UVB. CisUCA is a potent immunosuppressant[6]. Another target of UV radiation is DNA. The keratinocyte and langerhans cells are also direct targets of UV for being located in the upper layers of the skin. Due to UV radiation, not only DNA is damaged but also the antigen presenting functions of LH are suppressed. At the same time, secretion of immunosuppressive inflammatory cytokines such as PG E2 and PAF becomes effective. In the end, UV acts in two ways in skin cancers, by causing genetic damage and by suppressing anti-tumor immunity. Both of these processes are important in the progression of preneoplastic AKs to SCCs[17].

Others

The risk is higher especially in persons whose Fitzpatrick skin type is Ⅰ or Ⅱ (easily having sunburn and hardly having any tan). The presence of freckles on the face, even if only a few, increases the risk significantly[1]. The HPV infections may play a role in the pathogenesis of non-melanoma skin tumors. HPV 38 has been found more frequently in AK lesions than in SCC lesions[18]. Chronic inflammation is an important indicator of tissue changes progressing to carcinogenesis. Cyclooxygenase-2 (COX-2) inhibiting anti-inflammatory drugs can reportedly prevent tumorogenesis, but cannot reverse tumorogenesis that has already started[19].

Mucin 1 (MUC 1), a transmembrane glicoprotein plays a critical role in human cancer. MUC 1 is not expressed by the normal epidermis in human skin. It is expressed by keratinocytes in some premalignant and malign lesions such as epidermolysis bullosa, Paget's disease, Bowen's disease, and Merkel's carcinoma. Arciniegas *et al*[20] found that MUC 1 was localised at the apical surface of some atypical keratinocytes of AKs, but was not detected in the epidermis of normal skin. This findings suggest that the expression of MUC 1 in AK may contribute to the progression of AK to SCC.

UVA in particular causes DNA mutations that are characterized by photo-oxidative stress. Longevity increases the risk due to factors such as increased cumulative UV exposure and decreased immune resistance. The prevalence of AK is higher in males. The rate of working in open areas being higher in men and AGA are risk factors for scalp AKs. The use of photosynthesizing medication and genetic diseases such as xeroderma pigmentozum are also risk increasing factors for AK development[1,2].

HISTOPATHOLOGIC CHARACTERISTICS

AK is characterized by atypia and dysplasia of the keratioctyes in the basal layer of epidermis. The atypical and dysplastic clusters grow in time and advance to upper layers. Alternating areas of parakeratosis and hyperkeratosis are present in the corneum layer[11]. The atypical changes in the epidermal keratinocytes may be in different sizes and shapes and involve nuclear pleomorphism. The neoplastic keratinocyte proliferation in AK is limited to the epidermis[2]. There are signs of lymphocytic inflammatory infiltration and solar elastosis in dermis. From epidermal changes, AK and SCC cannot be distinguished histologically. Molecular changes associated with cancer are present in both AK and SCC. Padilla *et al*[21] have shown that the genetic characteristics of AK and SCC lesions are closely associated with each other. This finding supports the fact that AK is of malign nature from the very beginning. Its lichenoid, hypertrophic, bowenoid, pagetoid and pigmented types have been defined histologically[3,10].

CLINICAL SIGNS

It is most frequently seen in the areas which are mostly affected by DNA damage caused by UV radiation including the head, face, ears, lower lip, dorsal region of hands, lower legs, décolleté region, neck and upper back. AK is the most widely seen skin cancer on a sun-damaged skin[1,22]. It appears as squamous, skin-

colored, pink or red-brown papules, macules or plaques with vague margins. It can be a single lesion, but more commonly there are multiple lesions on a photodamaged skin. A classical aspect of AK is the rough surfaces of lesions feeling like sandpaper[1]. The size of lesions can range from a few millimeters to 3-4 cm and larger. When the lower lip is affected, it appears as a dry, scaled and atrophic lesion, which is called actinic cheilitis[15]. Depending on its clinical appearance, AK may be of classical, hypertrophic, atrophic or pigmented type, or appear as cornu cutaneum or actinic cheilitis. The severity of AK was divided into 3 phases within itself: (1) Lesions not so visible, vaguely felt with palpation; (2) Lesions are of medium thickness, easily palpated and seen; and (3) Hyperkeratotic and thick lesions[23].

DIAGNOSIS

A typical AK lesion does not require any histopathologic analysis. The clinical and subclinical changes of AK and field cancerization on the skin can be diagnosed by way of examination. Alongside multiple AK presence, those areas of the skin with a chronic UV damage such as solar lentigines, pigmentation disorders, altered skin tissue, deep and superficial lines, telangiectasias, xerosis and solar elastosis are considered as a field of cancerization[3]. However, biopsies are required in patients suspected of having invasive SCC lesions including hyperkeratotic and hypertrophic lesions with a diameter larger than 1 cm, which involve induration, bleeding, inflammation, ulceration, fast growth, pain upon palpation, no response despite appropriate treatment or relapses in periods as short as 2-3 mo[24].

DERMOSCOPY

Dermoscopy is a very useful method in diagnosing AK with 98.7% sensitivity and 95% specificity[25]. The value of dermoscopy depends on the physician's experience and the AK's dermoscopic characteristics, of which superficial scurf/scales are the most common one. Sometimes, underlying structures cannot be discerned due to such scurf. The second most widely seen pattern is the red, artificial network structure, which is described by a strawberry appearance. The other dermoscopic signs include targetoid-like appearance, rosette sign, absent fissures/ridges, crypts and milia-like cysts[26].

TREATMENT

The goal of AK treatment is to treat the field of cancerization and prevent formation of new lesions rather than to ameliorate the clinical appearance of AK lesions. Although the evidences showing that this approach is useful are very few, treatment is a requirement when the clinical and histological characteristics of AK are taken into consideration[1]. The need for treatment also involves continuous monitoring of AKs with respect to patient complaints, AK's effect on quality of life and transformation into SCC[24].

AK can be a single lesion or it can involve multiple lesions in a field of cancerization; thus, AK treatment is grouped under two headings: (1) Lesion-specific treatment; and (2) Field-targeted treatment[2].

Lesion-targeted treatments

These are practicable in patients with a small number of clinically visible and isolated lesions. They are based on physical destruction of the visible lesions.

Cryotherapy: This is the first-choice treatment method when the lesions are few or isolated. It is a fast and cheap method. There is no standard protocol about the application time, frequency or cycle intervals of cryotherapy. The success of treatment depends on the experience of the applying person. The correct application method is to create an ice ball that freezes the epidermis. Afterwards, a bulla should occur indicating that the basal membrane is separated from the dermis. This method has been shown to be successful in 90% of thin lesions[2]. Applying it in two freeze-thaw cycles including an area of 1mm around the lesion is generally preferred. The rates of clearance with one or two applications have been reported to be between 68% and 75% at the end of a 3-mo period[24].

Oliveira *et al*[27] experimented the effect of cryotherapy on two lesions of similar character from 13 patients with multiple AKs. They applied a liquid nitrogen cryotherapy to one of the lesions in a single session for 10 s and 30 d later they compared the biopsies taken from the lesions that was and was not administered cryotherapy. They found distinct decreases in keratinocyte atypia, epithelial thickness, and lymphocyte infiltration in the corneum layer and dermis in the lesion which underwent cryotherapy. Thai *et al*[28] administered their cryotherapy in a way to exceed the lesion margin by 1 mm using different freeze times. A full response was obtained in 39% of those that were administered less than 5 s of cryotherapy, in 69% of those that had longer than 5 s and in 83% of those that had longer than 20 s. They reported that they had full response in 94% of the lesions and the cosmetic results were good to excellent.

The side effects are pain during application, development of bullas and scars, hypopigmentation and hyperpigmentation. Hypopigmentation is seen in 29% of the cleared lesions and hyperpigmentation in 6% of them[1,2].

Surgical excision, shave excision and curettage: Surgical methods are not the first-choice in AK treatment. They should be preferred in hyperkeratotic, treatment-resistant and invasive SCC suspected lesions[2]. Through curettage and shave excision, atypical cells are removed mechanically. Both of these two methods are usually completed with an electrodesiccation. In this way, both the remaining abnormal tissues are destroyed and bleeding is controlled. Their disadvantages include the necessity of local anesthesia and their applicability to

a few and only hyperkeratotic lesions. These methods are not useful in the treatment of subclinical lesions and broadly damaged areas. Their possible side effects are scars, wound site infections, dyspigmentation and anesthesia-related complications[29].

Laser treatments: Ablative ultrapulse Er:YAG and CO_2 lasers are indicated in isolated and a limited number of lesions. However, their effects have not been evidenced with double-blind randomized studies. Sherry *et al*[30] have reported that long-term efficacy continues in AK patients who were administered ablative CO_2 laser and the lesion-free period is 27.4 mo on the average. Their side effects include erythema, pain, irritation, itching, and secondary infection.

Non-ablative fractioned lasers (ER:YAG and CO_2) are able to improve skin quality, but they do not achieve a significant decrease in the number of AK lesions[24]. Although a decrease has been achieved in the number of facial AK lesions that had been treated using the fractioned photothermolysis method, it has been reported that the histological aspects of AK and/or SCC continue to exist in histopathological examinations[31]. Their disadvantages are higher cost than cryotherapy and the requirement for specially trained staff.

Field-targeted treatments

They are effective in the treatment of visible lesions, subclinical lesions and keratinocyte changes in the areas surrounding the visible lesions.

5-Fluorouracil cream: It is a pyrimidine analogue that was approved by the FDA in 1970. It impairs DNA formation by stopping conversion from deoxyuradilic acid to timidilic acid through inhibition of thymidilate synthetase. It disrupts cell proliferation, particularly in the fast reproducing cells of basal layer and AK, resulting in cell deaths. It is used in 5% cream form for 2-4 wk, applied once or twice daily[3]. The area of application should not exceed 500 cm^2 at a time. Erythema, burning, itching, pain, hyperpigmentation, wound site infection, bullas and ulceration may occur for about 4-6 wk after the treatment. Its photosensitivity effect limits its use in summer.

The long-term effects of 5% 5-fluorouracil (5-FU) cream applied for 4 wk, twice a day have been explored in a large-scale study published recently. The rates of being cleaned from AK of the patients who were checked every 6 mo in 2.6 years were found higher than the placebo group. Moreover, their spot treatment needs were found significantly less than the placebo group[32].

The 5-FU cream with a lower concentration of 0.5% is approved by FDA, but is not available in Europe. A 12-wk use applied once daily is recommended. The effect of 0.5% formulation has been found similar to that of 5% cream form, but the side effects were less and patient satisfaction was better[33]. The penetration of 5-FU, the biological active substance, is increased by combining low-dose 5-FU with salicylic acid (SA), taking advantage of the keratolitic effect of SA. The combined preparation is approved in Switzerland. Although the 0.5% FU and SA combination seems more effective with fewer side effects, there is a need for long-term studies[3].

The effectiveness of the combination of low-dose 5-FU with 10% SA has been compared to that of diclofenac gel and carrier base. The 5-FU and SA combination was found significantly more effective than diclofenac gel and carrier base with 72% histological cleaning and 55.4% complete cleaning. The application area reactions were seen more in the 5-FU and SA combination and the side effects were found mild and moderate[34]. In a prospective randomized study where it was compared to a two-session cryotherapy application, the 0.5% 5-FU and SA combination was found superior to cryotherapy[35]. In a meta-analysis, the 5% and 0.5% 5-FU formulations were rated superior to other field-targeted treatments[36].

Disadvantages of 5-FU cream include long treatment period, itching, prolonged erythema, pain, ulceration, erosion, secondary infection and depigmentation. It is teratogenic for impairing the DNA synthesis in fast dividing cells. It may have a systemic toxicity risk when used excessively and particularly when used for the areas with impaired barrier function[22].

Imiquimod: Imiquimod is an immune response regulator from the imidazoquinolone group. It is a Toll-like receptor agonist showing its effect on cytokine-producing cells such as monocytes, macrophages and dendritic cells[2,3,22]. It stimulates cytokine secretion by the TLR-7 induction, which improves cellular immunity. It is effective on both natural and acquired immune response, showing indirect antiviral and antineoplastic effect.

It was first approved by FDA in 2004 for the treatment of AK keratosis[37]. Imiquimod 5% cream and 3.75% cream forms are available. The 5% cream form is approved to be used on a hairless scalp and on areas up to 25 cm^2 in the face twice a week for 4 wk followed by a 4-wk resting period. The purpose of such alternating treatment is to reduce local skin reactions. The 3.75% cream form was approved in 2010 to be used every night in a 2-wk period followed by a 2-wk resting period. It can be applied to larger areas on the face and scalp and has a shorter treatment period compared to the 5% cream[2].

In both forms, subclinical lesions emerge together with inflammatory reactions at the beginning of the treatment, leading to an increase in the number of lesions. The rate of cleaning AKs is higher in people with severe local reactions. This supports the fact that inflammation is part of the action mechanism in AK[38]. Pruritus, burning, erythema, edema, pain, dryness, desquamation, erosion and ulceration may be seen locally. Systemic reactions such as myalgia, nausea and weakness are less frequent. Fewer reactions are seen during the second treatment cycle. It should be used carefully if there is an ongoing immunosuppressive

therapy in immunodeficient patients who had organ transplantation[24].

The effect of 3.75% imiquimod on the maximum number of lesions has been assessed in a placebo-controlled, double-blind study made with 319 patients and more than 90% decrease has been found in the number of lesions after 2 treatment cycles of 2 wk. The average and complete decrease in the number of lesions has been found significantly higher than placebo group[39].

Resiquimod: Resiquimod is an immune modulator structured as an imidazoquinoline amin whose phase 3 studies still continue in Switzerland. It is a TLR-7 and 8 agonist and stimulates cytokine secretion (IL-12 and TNF-α) more strongly than imiquimod. Its total cure rates have been found as 74.2% with 0.01% gel and 90.3% with 0.03% gel in patients who were given one more cycle of treatment after the phase 2 study using it 3 d a week, once a day for 4 wk followed by a no treatment period of 8 wk. Most frequently seen side effects are irritation at the application site[1,3].

Diclofenac: Diclofenac gel includes 3% diclofenac sodium in 2.5% hyaluronic acid carrier is a nonsteroidal anti-inflammatory drug which COX-2 inhibitor. UVB is known to induce COX-2 expression in human skin[22]. The production of prostaglandins from arachidonic acid plays a role in the skin cancer induced by UVB. The COX-2 inhibition with diclofenac probably shows its effect in AK treatment by impairing this cascade[2]. Diclofenac gel also plays a role in AK treatment by inducing apoptosis and inhibiting angiogenesis[1]. It is recommended to use it twice a day for 90 d. Side effects include itching, erythema and dryness. Diclofenac gel may rarely lead to photosensitivity in some patients. It is suggested to use it in combination with cryotherapy in hypertrophic lesions.

It was reported at the end of an analysis of 17 studies made with 3% diclofenac gel that there was 58% complete clearing of lesions a month after a 3-mo treatment, its efficacy continued at the end of one year and its effect was comparable to those of 5% imiquimod and 5% 5-FU. It has also been evidenced that it is safe in immunosuppressive patients, suitable to be used following cryotherapy and FDT, and more tolerable than the other treatment agents[40].

Ingenol mebutate (PEP005): Ingenol mebutate is a traditional treatment agent derived from the plant called euphorbia peplus. It was first approved by FDA in January 2012 for the treatment of AKs on the face, scalp, trunk and extremities in adult patients. It still has approvals in Europe, Australia and Canada[1,41]. It is an effective option in the topical treatment of AKs that are not hyperkeratotic. Ingenol mebutate shows its effect through two mechanisms: (1) Causing death of keratinocytes that underwent transformation; and (2) Causing death of remaining cancerous cells by increasing inflammatory reaction[41].

The mechanism of action primarily involves cell necrosis as a result of impaired structures of cell plasma membranes and mitochondria. This action takes place in 1-2 h after its application. In the following days, the remaining tumor cells are eliminated through neutrophile-antibody dependent cellular cytotoxicity[41].

It is recommended to apply its 0.015% gel formation on the face and scalp once a day for 3 consecutive days and its 0.05% gel formation on the trunk and extremities for 2 consecutive days. It can be washed away after keeping it at least 6 h on the application site[42]. Its major side effect is that the local skin reaction makes a peak on the 4th day at the application site, but then dies away after the 8th day. Its other side effects, pain, itching and irritation, are less frequent and milder[43].

The results obtained from the patient group that participated in the phase 3 study and received treatment with ingenol mebutate were assessed in terms of quality of life, patient satisfaction and clinical outcomes. Quality of life and treatment satisfaction were observed to improve significantly in the patients both in the face-scalp group and trunk-extremity group[44]. The advantages of ingenol mebutate therapy are that it is cheaper than other topical treatments, it is used for a short period of time and it does not cause photosensitivity[41,45].

The safety and tolerability of 5% 5-FU cream and 0.015% ingenol mebutate have been compared and the maximum local skin reactions have been found similar. Although the time of experiencing skin reactions has been found longer in the 5-FU group, both therapies have been found safe and tolerable in general[46]. Ingenol mebutate gel applied after cryotherapy increases the effect of cryotherapy alone. A classical dose has been applied to the patients who had at least 10 recurrent and hyperkeratotic lesions 2 wk after cryotherapy and cleaning at a rate between 50% and 100% has been reported[47].

Photodynamic therapy: Photodynamic therapy (PDT) is an effective treatment option for AKs, field cancerization and non-melanoma skin tumors. The most frequently used photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester methyl aminolevulinate (MAL), which are the precursors of protoporphyrin IX (Pp IX)[1,2,41]. Pp IX increases mostly in hyperproliferative cells. It absorbs light and causes formation of cytotoxic free oxygen radicals as a result of a photochemical reaction. These radicals lead to cellular necrosis and apoptosis[48]. Cleaning the sloughs and scales with curettage or keratolitic creams before the treatment increases the effect. The photosensitizing cream is applied with occlusion at least 3 h before the procedure. The incubation times, treatment protocols and light sources vary to a large extent. There are efforts to establish the optimal standards for treatment.

The treatment is administered once to thin AKs and AKs of medium thickness. If the effect is not satisfactory 3 mo later, the procedure is repeated once more. The

procedure is performed in 2 sessions with a 1-wk interval in hyperkeratotic AKs if severe atypia is present histopathologically, and in immunosuppressive patients. The most frequent side effects are local reactions in the application site and pain in the irradiation site. Rare side effects include nausea, weakness, paresthesia and headache. ALA-PDT is more effective in severe scalp lesions. MAL-PDT's disadvantage is that it is more expensive than ALA-PDT[48].

PDT produces better cosmetic outcomes than cryosurgery and enables treatment of broader areas with a single session procedure, but cryotherapy has been found superior to PDT in the face and scalp, and in thicker lesions. Local side effects are also milder in cryotherapy[1].

The effect of PDT applied in 3 sessions with monthly intervals was investigated in a study. The lesion biopsy values taken at baseline and at the end of the 3rd month were assessed and the rate of cleaning in AKs was found as 89.5%. The effect at the end of the 2nd treatment was found similar to that of the 3rd session. A significant decrease was found histologically in keratinocyte atypia and the extent of atypia, as well as significant improvements in collagen storage and healing of solar elastosis[49]. Recently, a new nanoformulation of 5-ALA (nano-ALA) PDT was compared with MALT PDT in a pilot study. Passos *et al*[50] found that the efficacy of nano-ALA is 10% higher than of MAL in treating skin field cancerization.

In a meta-analysis involving 25 studies on AK and field cancerization and including 5562 patients, all active treatment methods were found superior to placebo, and the most effective treatment method in terms of total cleaning obtained was found to be ALA-PDT (SUCRA score 90.8%), followed by 4-wk 5% imiquimod (71.7%) and 0.5% 5-FU cream (64.1%)[51].

Piroxicam: Piroxicam (PXM), is a nonsteroidal anti-inflammatory drug which is nonspecific COX-1 and COX-2 inhibitor. Campione *et al*[52] reported that local use of piroxicam was eligible, safe, effective, and well tolerated option for the treatment of AKs and field cancerization (PXM). It was used its 1% gel formation applied twice daily for 12 wk. But its use in AKs is still off-label.

COMBINATION TREATMENTS

Combination treatments are required in patients who have treatment-resistant, multiple lesions at different stages. Although there is no standard guideline on treatment combinations, lesion-targeted and field-targeted treatments may be combined to increase efficacy. Three point seven five percent imiquimod therapy following cryotherapy has been found useful and safe. The complete cleaning rates obtained from a 90-d diclofenac gel therapy following cryotherapy have been found twice as much compared to cryotherapy alone (64% *vs* 32%). Significant increases in the effect have also been achieved in post-cryotherapy 5-FU and post-cryotherapy ingenol mebutate therapies. It has also been shown that more success can be achieved with PDT applied after 5% imiquimod cream, 5% 5-FU or diclofenac gel therapies compared to the success achieved in each therapy alone[1,53].

AK TREATMENT IN ORGAN TRANSPLANT RECIPIENTS

Organ transplant recipients (OTR) are at high risk for NMSTs. Lesion-targeted treatments, cryotherapies, electrocautery, curettages and CO_2 lasers can be safely used in these patients. Diclofenac gel has been compared to placebo in 32 OTR patients in a 16-wk treatment. While the complete cleaning of AKs was 41% in the diclofenac group, it was found to be 0% in the placebo group. No patients were reported to develop invasive SCCs at the end of a 24-mo follow-up period[54].

Ingham *et al*[55] have been applied 5% 5-FU cream to AK lesions on eight renal transplant recipients face twice daily for 3 wk. They reported that 5-FU effective and safe treatment in renal transplant recipients. Imiquimod 5% cream has been found safe in heart, liver and kidney transplant patients if used 3 times a week not more than 2 sachets at a time on areas not exceeding 100 cm^2[56]. It was shown that PDT prevent new AKs formation in renal transplant recipients[57]. But PDT is less effective in immunosuppressed patients compared to the immunocompetent people in the AKs treatment[58].

PROTECTION

Childhood and adolescence are the really important periods for sun protection. The protection from the sun behavior acquired in these periods plays a key role in both prevention of excessive sun exposure and sunburns in childhood and acquisition of protection from the sun protection habit that will continue lifelong[1]. Sunscreens may be useful in high-risk groups. Ulrich *et al*[59] have investigated the effect of sunscreens on protection from NMST in OTR. They reported at the end of the 24-mo study that there was a decrease in the number of basal lesions in the group using sunscreens and they had fewer lesions than the control group. Therefore, protection from the sun is advisable for all patients with field cancerization. Patients should also be trained on the correct use of sunscreens.

It was shown that daily use of 30 mg acitretin for a period of 6 mo in renal transplant patients with multiple AKs resulted in a decrease in the number of AKs and it was effective in preventing the development of SCCs[60].

The chemopreventive effect of nonsteroidal anti-inflammatory drugs such as diclofenac gel on nonmelanoma skin cancers has been demonstrated[52].

FOLLOW-UP

If there are no special risk factors, patients are recommended to examine themselves every 3 mo. New

lesions are recorded, if any, and in the presence of suspicious lesions examination by a clinician is required[1]. Through professional examinations and follow-up, formation of new lesions and occurrence of any changes can be detected at an early stage, other cancers such as melanoma can be identified and patients can be educated and informed about their diseases.

The oral mucosa, palmar regions, scalp and genital regions should also be assessed during examinations and in the presence of an invasive ca risk lymphatic glands should also be examined. Self-examination by the patients themself is as important as clinical assessments and the patient should be trained for self-examination. Patients who have been subject to long-term immune suppression as in OTR require special monitoring for invasive NMSTs. Such patients should undergo annual dermatologic examinations and monthly self-examinations. OTR patients should be examined for NMSTs before the transplantation.

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