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REVIEW ARTICLE

Extra-palmoplantar lesions associated with palmoplantar pustulosis

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Abstract

Palmoplantar pustulosis (PPP) is a chronic inflammatory disorder characterized by sterile pustules predominantly involving the palms and soles of middle-aged women. In contrast, regions other than the palms and soles are occasionally affected, manifesting scaly erythemas which resemble psoriasis, and solitary pustules are also seen. Some of these extra-palmoplantar lesions are induced by the Koebner phenomenon or occur after focal infections like tonsillitis. The tenderness and inflammation of the extra-palmoplantar lesions in PPP are milder than in psoriasis. Histological features show mild acanthosis of the epidermis with parakeratosis and mild infiltration of inflammatory cells in the upper dermis. On the other hand, severe pustular lesions are occasionally seen in the palms and soles of the patients with pustular psoriasis. These findings suggest a close relationship between PPP and psoriasis; however, different genetic, environmental, and immunological factors are likely to be involved. Recently, understanding of psoriasis pathophysiology has greatly progressed, and the concept of psoriasis pathogenesis is currently viewed as complicated responses between infiltrating leucocytes and the resident skin, *via* a number of inflammatory cytokines, chemokines, and mediators produced in the skin under regulation of cellular immune systems. By contrast, the pathogenesis of PPP has been poorly investigated. This paper reviews findings of the clinicopathophysiology of PPP, making a focus on the extra-palmoplantar lesions.

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Keywords

Koebner phenomenon, palmoplantar pustulosis, pathogenesis, pustular psoriasis, pustulotic arthro-osteitis

Conflicts of interest

None declared.

Introduction

Palmoplantar pustulosis (PPP) is a chronic disease characterized by sterile pustules occurring at distinct sites on the palms and soles.[1] Additionally, scaly erythemas, vesicles and hyperkeratosis are also found in association. Although the reason for the predominant involvement of the palms and soles is still uncertain, it has been suggested that the source of inflammation in PPP is the acrosyringium.

Clinical features of palmoplantar pustulosis

PPP has a predilection for females, and involves middle-aged women, usually occurring at the age between 30 and 40 years. In the majority of patients, bilateral palmar lesions antecede the plantar involvement with a few months duration. On the other hand, only palmar involvement is occasionally seen, while incidence of only sole involvement is much lower.

Although PPP lesions are typically confined to the palms and soles, clinical manifestations resembling psoriasis, namely, thin, scaly erythemas, occasionally appear on extra-palmoplantar areas such as the forearms, elbows, dorsa of the feet, lower legs, knees, and buttocks (Fig. 1a). Compared with psoriasis, infiltration of the erythema is mild and the lesions are not well demarcated; however, these have been sometimes misdiagnosed as complication with psoriasis. Occasionally, scaly erythemas are recognized on the scalp (Fig. 1b). Additionally, solitary pustules also occur, although less frequently (Fig. 1c). In rare cases, a number of erythematous lesions with scaling may suddenly appear on the trunk accompanied by joint pain, following focal infections such as tonsillitis, dental infections, and sinusitis. More severe cases with pustules have also been reported.[2]

Histological features show mild acanthosis with focal parakeratosis, and exocytosis (Fig. 2a). Infiltration of lymphocytes

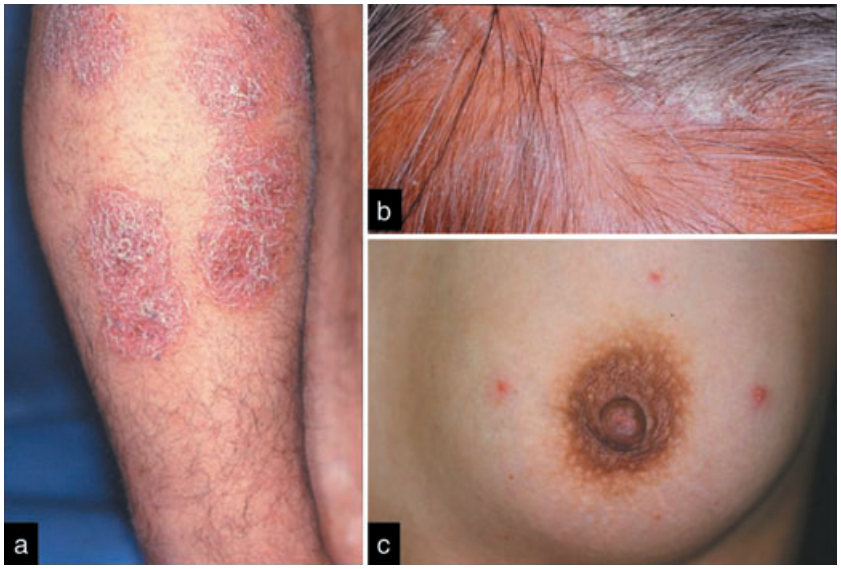

Figure 1 Scaly erythemas on the lower legs (a) and scalp (b). (c) Extra-palmoplantar lesions are sometimes presented as scattered pustules on the body.

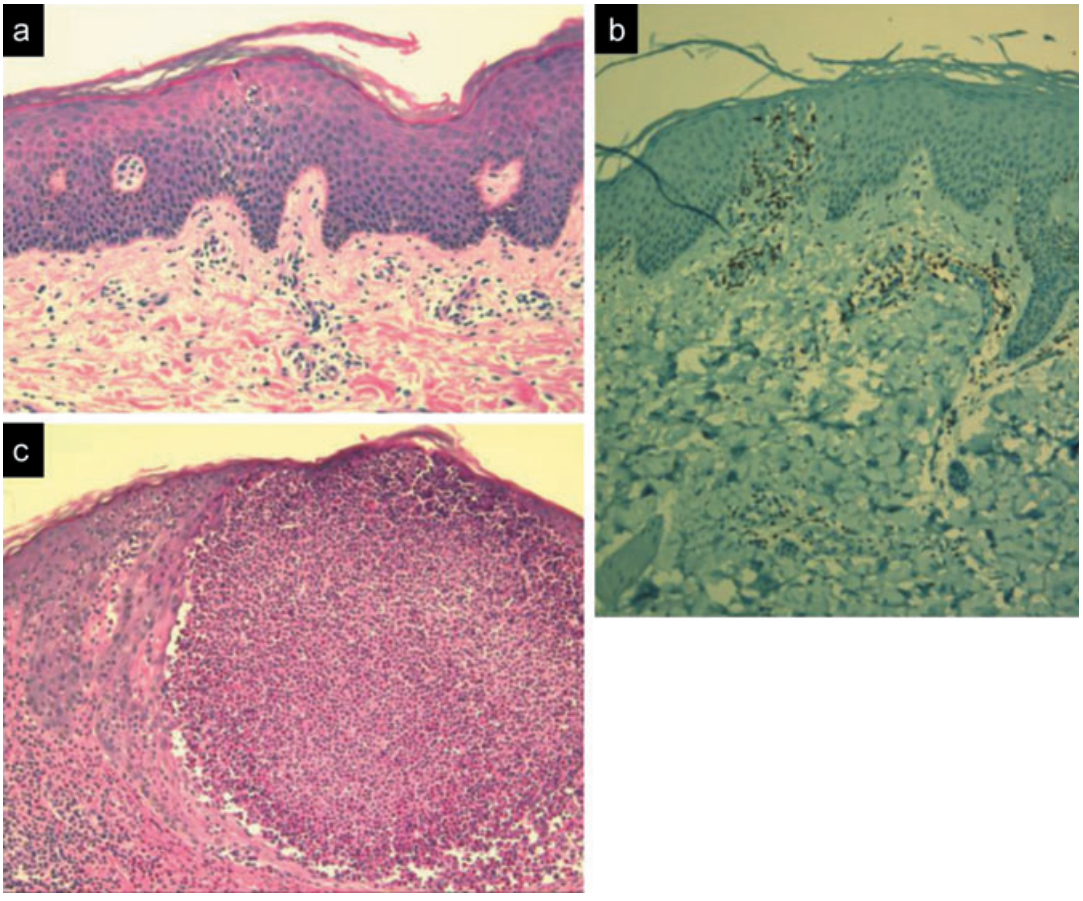

Figure 2 Histological examination. (a) Mild acanthosis of the epidermis with focal parakeratosis, and perivascular infiltrates of mononuclear cells in the upper dermis. (b) The infiltrating cells toward the epidermis are CD3-positive. (c) A biopsy specimen from pustular lesion in a patient with PPP shows spongiform abscess.

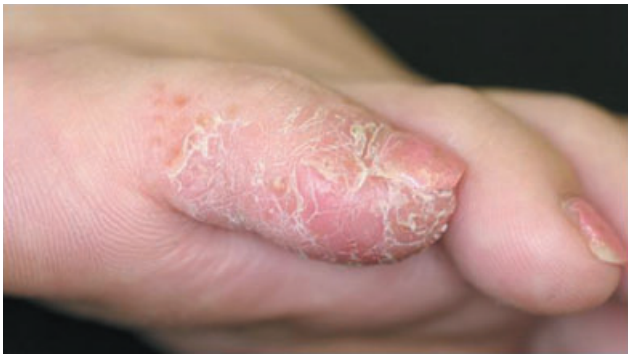

Figure 3 PPP lesions (scaly erythema and small pustules) predominantly seen in the outer aspects of the fifth toe.

positive for CD3 into the epidermis is seen (Fig. 2b). However, the accumulation of neutrophils under the corneal layer, known as Munro's microabscess, is not seen, and dilation of the capillaries in the papillary dermis is absent. Perivascular infiltration of mononuclear cells in the upper dermis is seen. Therefore, there are no specific findings and many features overlap with those of eczematous reaction. Multiple parakeratotic foci alternating with orthohyperkeratosis are the useful.[3] A biopsy specimen taken from a pustular lesion may reveal spongiform abscesses (Fig. 2c).

In general, extra-palmoplantar lesions are seen more frequently in patients with severe PPP. Arthritis frequently accompanies PPP, as will be discussed later. The extra-palmoplantar lesions usually respond to topical corticosteroids or systemic antibiotics; however, oral cyclosporin is sometimes required to achieve an optimal response.[2]

Koebner phenomenon

Koebner phenomenon is marked by the appearance of new skin lesions following mechanical stimuli.[4,5] The Koebner phenomenon occasionally occurs in psoriasis, lichen planus, vitiligo, and certain viral infections. Additionally, though rarely, Koebner phenomenon is associated with PPP. PPP lesions may be induced or exacerbated by mechanical stimuli, such as shoes (Fig. 3) and the local application of disposable chemical pocket warmers to the soles. Additionally, extra-palmoplantar lesions may also be induced by the wearing of a ring on the fingers, and by the friction of the elastic of undergarments on the abdomen.[6] In view of the similarity of PPP to psoriasis, it is not surprising that Koebner phenomenon should occur in PPP. More significantly, these findings suggest a close relationship between PPP and psoriasis.

Precipitating factors

Precipitating factors of PPP are focal infection, smoking, and dental metal allergy. It is well known that focal infection (i.e. tonsillitis, chronic sinusitis, dental infection) triggers or deteriorates PPP. Furthermore, tonsillectomy improves and even completely releases cutaneous as well as skeletal involvement associated with PPP. These facts strongly suggest a key triggering role of focal infection leading to a sequential event inducing PPP. Heat shock proteins (HSPs) are recognized by γδ T-cell receptors and toll-like receptors 2 and 4, and suggested to develop autoimmunity after bacterial infection. Antibodies that react with HSP65 can be found in the sera of patients with PPP,[7] suggesting that HSP-producing chronic infectious bacteria might trigger PPP.

On the other hand, PPP is a representative skin disease showing a close association with smoking, and a high prevalence of tobacco use, including previous use, is recognized especially in women. Cutaneous lesions are improved, though not totally, by giving up smoking habit.

Although the precise role of metal allergy in PPP is still unknown, exacerbation of PPP lesions following metal patch test or dramatic improvement of PPP by metal elimination have been reported.[8]

Recently, it draws attention that pustular lesions are induced during biological therapies targeting the action of tumour necrosis factor-α (TNF-α).[9] These manifestations frequently affect the soles mimicking PPP, and sometimes, extra-palmoplantar areas such as lower legs are also involved. The mechanisms of anti-TNF–induced PPP-like lesions, although pustular psoriasis is an appropriate disorder for anti-TNF-α therapies, are largely unknown.

Pathophysiology

The characteristic histopathological features of PPP exhibit intraepidermal infiltration of polymorphonuclear neutrophils forming pustules. Although the mechanisms of neutrophil chemotaxis towards the epidermis are unknown, selective accumulation of neutrophils could be supposed to be caused by the local generation of neutrophil-specific chemoattractants [i.e. interleukin-8 (IL-8), C5a, platelet-activating factor, and leukotriene B4], and lesional keratinocytes may play an important role in eliciting neutrophilic inflammatory response mechanisms. IL-8 is a potent chemoattractant and activator for neutrophils, and shown to be immunostained in the keratinocytes of lesional skin of PPP.[10] One of other possible candidates for neutrophil attraction is growth-related oncogene-α (GRO-α).

Additionally, more or less numbers of CD4-positive T cells are infiltrated below and around the pustules in the skin, which are suggested to play an important role by releasing inflammatory cytokines. Tonsillar T cells express cutaneous lymphocyte-associated antigen (CLA) in patients with PPP, which may migrate into the skin. CLA is a homing receptor, and CLA-positive T cells identify a population of memory effector T cells. *In vitro*, bacterial infection activates tonsillar T cells to enhance CLA expression[11] and cytokine production such as IL-6, TNF-α, and interferon-γ (IFN-γ).[12] Tonsillar cript epithelial cells of PPP tonsils secret high amounts of IL-6.[13] Inducible co-stimulator

(ICOS) is induced on T cells, and its ligand B7 h is expressed in lymphoid and non-lymphoid tissues. The interaction between ICOS and B7 h is supposed to play one of important pathways in inflammatory and immunological process. Recent studies show that expression of ICOS is higher in the tonsil tissues as well as skin lesions in PPP.[14] These data suggest that activated tonsillar T cells by infection migrate into the skin, forming cutaneous lesions, via a number of inflammatory cytoknes, in PPP.

Bacterial products stimulate enhanced production of IL-23, which triggers T cells to produce IL-17. IL-17 promotes neutrophil migration via the release of CXC chemokines.[15] IL-23/IL-17 inflammatory pathway is recently suggested to be central to the inflammatory and pustular types of psoriasis,[16] and may be important also in PPP.

Smoking may induce vasoconstriction, or functional and morphological alterations in the polymorphonuclear leucocytes. Nicotine acts as an agonist on nicotine acetylcholine receptors, and can influence cellular functions. Nicotine acetylcholine receptor expressions are expressed in the eccrine glands, ducts and endothelium in the skin, which pattern is altered by smoking.[17] Forty-two per cent of the patients with PPP had antibody against nicotinic acetylcholine receptors in the sera.[18]

Coexistence of autoimmune disorders

PPP has been suggested to be an autoimmune disease, and thus sometimes complicated with other local and/or systemic autoimmune disorders. Autoimmune thyroid diseases show an immune response against the thyroid gland. PPP is occasionally associated with thyroid autoimmunity, and the incidence is nearly 16–25% with a high prevalence.[19] No large survey aiming at a number of PPP patients coexisting either vitiligo or alopecia has been performed as yet, except for single case reports. In addition, PPP is sometimes seen in patients with Sjögren's syndrome and rheumatoid arthritis.

Is PPP a subtype of pustular psoriasis?

Some regard PPP as a variant of pustular psoriasis, whereas others consider PPP to be a distinct nosological entity. PPP was previously known as 'pustular psoriasis of the extremities.' Baker and Ryan[20] classified generalized pustular psoriasis (GPP) into several subgroups including the 'palm-sole' type, which can be regarded as PPP. Sometimes, severe palmoplantar pustular lesions are noted in patients with acute GPP. The pustular lesions present not as solitary pustules, but as coalescent sheet-like pustular formations (Fig. 4). These cases may suggest that PPP is the palm-sole type of GPP.

Nail changes are often seen in patients with PPP, with nail dystrophy being the most common form.[21] In addition, subungual pustules are also seen. In the initial stage, subungual pustule may be solitary and transient, without affecting any nail changes (Fig. 5). These changes, following numerous recurrences, often eventuate in destructive nail dystrophy.

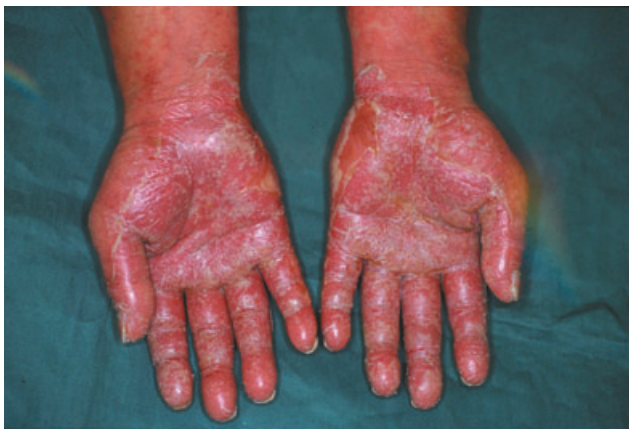

Figure 4 Sheet-like, coalescent pustular lesions on the palms in a patient with acute GPP.

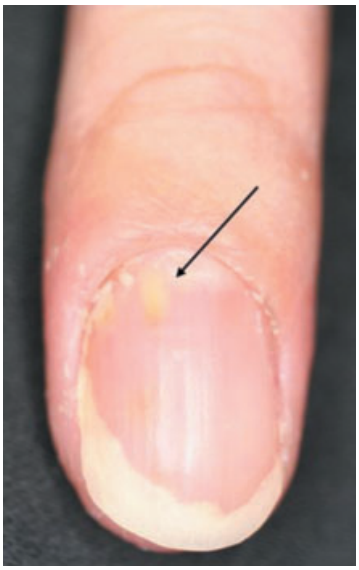

Figure 5 Subungual solitary pustule without destruction of the nail.

Genetics

No common genetic background of psoriasis and PPP has been confirmed. *PSORS1* is the major susceptibility locus that includes the *HLA-C* gene on chromosome 6p21. By contrast, PPP is not directly associated with PSORS1.[22] IL-19 subfamily of genes located on chromosome 1q31–32 is recently suggested to be potentially susceptible to PPP.[23] IL20 haplotype GAA is associated with an increased, while GGG with a decreased susceptibility for PPP. The genetic variations within the *IL-19* gene cluster may affect both psoriasis and PPP, but these two disorders may still be independent.

Pustulotic arthro-osteitis

Although there are no definite data, patients presenting with extra-palmoplantar lesions show severe cutaneous as well as joint manifestations. Sternocostoclavicular hyperostosis is frequently associated with PPP, and characterized by periosteal and endosteal hyperossification of the sternum, clavics, sacroiliac joint, and upper ribs.[24] Patients complain of severe pain and swelling in these areas. This condition is worsened by focal infections (e.g. streptococcal throat infection), and the pain associated with sternocostoclavicular hyperostosis is mitigated by systemic administration of antibiotics or the surgical removal of focal infections, as with a tonsillectomy. Inflammatory and chemotactic cytokines in the sera dramatically decrease following a tonsillectomy.[25] In rare cases, severe pain persists even after surgery, and pain management sometimes requires oral cyclosporin.[26] The clinical symptoms of sternocostoclavicular hyperostosis and the cutaneous manifestations parallel each other, and biopsy specimens of the joint reveal nonspecific inflammation.[24] Migration of streptococcal-specific T cells from the tonsil into skin and joints may occur, although further studies will be necessary.

The SAPHO syndrome is defined by the association of synovitis, acne, pustulosis, hyperostosis, and osteitis. The prototypical skin lesion associated with SAPHO syndrome is PPP. Another skin lesion is severe acne, but not all those clinical manifestations need to be present. The main characteristic features of skeletal manifestations are hyperostosis intermingled with areas of osteolysis and arthritis. The most frequently involved sites are the anterior chest wall, but the hyperostotic lesions involve the pelvic girdle, and spine.

Differential diagnosis

Because patients are usually treated with topical corticosteroids, folliculitis should be differentiated from the primary symptoms, especially when it manifests as pustular lesions on the lower limbs.

Acute generalized pustular bacterid (AGPB; pustulosis acuta generalisata) is characterized by scattered, systemic, scaly erythemas including sterile pustules affecting the hands, feet, extremities, and trunk.[27,28] AGPB is most frequently induced by streptococcal infection, and is accompanied by general symptoms such as fever, arthralgia, increased levels of erythrocyte sedimentation rate and C-reactive protein. In rare cases, PPP has a sudden onset involving numerous pustules on the palms and dorsa of the hands and fewer pustules on the trunk and arms mimicking AGPB.[29] PPP and AGPB can be regarded as closely related entities. AGPB is generalized, but transient; while PPP is localized and chronic. AGPB is thought to be an immune complex-mediated pustular vasculitis,[30] and enhanced neutrophil chemotaxis due to vascular injury may lead to pustular formation.

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