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Palmoplantar pustulosis: A distinct entity with a close relationship to psoriasis

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ABSTRACT

Palmoplantar pustulosis (PPP) is characterized by many aseptic small pustules, scales, crusts and erythemas, involving the palms and soles. PPP is frequently seen in Japan, and thus considered as a distinct entity. By contrast, in other countries, PPP is sometimes regarded as an acral variant of pustular psoriasis. Typical clinical features definitely differ between PPP and plaque-type psoriasis, however, in rare cases, PPP presents with features resembling psoriasis vulgaris or pustular psoriasis with palmoplantar pustulation. Although extra-palmoplantar lesions of PPP are not psoriasis, patients with PPP rarely show typical psoriasis during the course. On the other hand, patients with generalized pustular psoriasis (GPP) can exhibit pustular lesions on the palms and soles. Those findings strongly suggest a close relationship between PPP and psoriasis, however, there are a number of differences between PPP and pustular psoriasis. In this review, clinicopathological aspects of PPP are described, and the difference from pustular psoriasis is discussed.

Keywords: Palmoplantar pustulosis; Palmoplantar psoriasis; Pustular psoriasis.

INTRODUCTION

Palmoplantar pustulosis (PPP) is characterized by aseptic small pustules, scales, crusts and erythemas on the palms and soles. The frequency of this disease varies among different countries, and frequently observed in Japan. PPP is sometimes regarded as a localized variant of pustular psoriasis, while others consider PPP to be a distinct nosological entity, different from psoriasis [1-3]. The controversial viewpoints may depend on the different frequency of PPP. Undoubtedly, PPP is closely related to psoriasis, and both disorders share common pathogenesis in a number of aspects. The author has been standing a position that PPP is a distinct entity different from pustular psoriasis. In this review, a close relationship and differences between PPP and pustular psoriasis have been discussed.

SIMILARITIES OF PALMOPLANTAR PUSTULOSIS AND PSORIASIS

PPP has a predilection for females, and involves middle-aged women, usually occurring at the age between 30-40 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. Patients, especially women patients, are either current or previous smokers, and nicotine included in tobacco is suggested to play a role. PPP lesions are typically confined to the palms and soles, while a number of erythematous lesions with scaling sometimes appear on the trunk and/or extremities. Those extra-palmoplantar lesions are seen either chronically or suddenly accompanied by joint pain, following focal infections such as tonsillitis, dental infections, and sinusitis [4]. In the cases of acute onset, solitary pustules may also be seen on the trunk, however, severe cases mimicking pustular psoriasis are also seen. In general, extra-palmoplantar lesions are seen more frequently in patients with severe PPP. Compared with psoriasis, infiltration of the erythema is mild and the lesions are neither well demarcatednor accompanied by thickened scales. Nail lesions are frequently seen in PPP, such as subungual pustule, hyperkeratosis, dystrophy, onycholysis, when inflammation involves the nail matrix.

PATHOPHYSIOLOGY OF PALMOPLANTAR PUSTULOSIS

Histological features of pustular lesion of PPP are the same

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with GPP, showing intraepidermal infiltration of polymorphonuclear neutrophils formingsubcorneal abscess, acanthosis, and cellular infiltrates in the papillary dermis. Although the mechanisms of neutrophil chemotaxis towards the epidermis are unknown, selective accumulation of neutrophils may be caused by the local generation of neutrophil-specific chemoattractants, *i.e.*interleukin-8 (IL-8), growth-related oncogene-α (GRO-α), C5a, platelet-activating factor, and leukotriene B4. Additionally, a number of T-cells are infiltrated below and around the neutrophilic abscess, which is suggested to play an important role by releasing inflammatory cytokines. Among them, tumor necrosis factor-α (TNF-α) induces IL-8 production by peripheral mononuclear cells [5]. IL-8 has been implicated to play an important role in neutrophil recruitment in the lesional skin. In addition, IL-23/IL-17 inflammatory pathway has recently been suggested to be important in PPP. IL-17 promotes neutrophil migration *via* the release of CXC chemokines [6]. IL-17 activates endothelium to lead to neutrophil infiltration in a p38 MAPK-dependent manner [7]. In addition, IL-17 and TNF-α enhance endothelial expression of neutrophil chemokines, *i.e.* CXCL1, CXCL2 and CXCL5, leading to leukocyte migration [8].

Serum levels of IL-17 and IL-22 are increased in patients with PPP [9]. IL-23 expression is upregulated in the lesional skin of PPP [10],and IL-17 is detected close to or in the acrosyringium [11]. Acrosyringium is reported to be the primary target for inflammation in PPP [12, 13]. Acetylcholine is the main inducer of sweating, and many components for cholinergic signaling have been found in the skin. Nicotine acts on nicotinic acetylcholine receptor AChRs (nAChRs) as an agonist, which then leads to the provocation of many functions. In PPP lesional skin, altered nAChR expression was observed, and epidermal α7nAChR expression was abolished compared with normal skin [14]. Patients with PPP may be incapable of activating the endogenous nicotinic anti-inflammatory pathway, due to a decrease of α7nAChR, and show abnormal response to nicotine.

TRIGGERING FACTORS

PPP is frequently associated with foci of chronic bacterial infection [15]. Bacterial products stimulate enhanced production of IL-23, which triggers T-cells to produce IL-17. Tonsillitis is the most closely associated focal infection with PPP, and tonsillectomy improves and even completely releases cutaneous as well as skeletal lesions [16]. In addition, odontogenic infection, sinusitis, cholecystitis, and appendicitis also sometimes precede the onset of PPP. These facts strongly suggest a key triggering role of bacterial infection leading to a sequential event inducing PPP. *In vitro*, bacterial infection activates tonsillar T-cells to enhance cutaneous lymphocyte-associated antigen (CLA) expression [17] and enhances cytokine production such as IL-6, TNF-α, and interferon-γ (IFN-γ) [18]. Toll-like receptors (TLRs) play important roles in the innate immune responses following bacterial infection. Heat shock proteins (HSPs) are recognized by γδ T-cell receptors and TLR-2 and -4 [19], and may act as an endogenous and/or exogenous signal to trigger immune responses. TLRs signal the presence of an infection and direct the adaptive immune response against microbial antigens by inducing proinflammatory cytokines and upregulating costimulatory molecules of antigen presenting cells.

On the other hand, the exacerbation of GPP is triggered by infection, pregnancy and various drugs such as corticosteroids, terbinafine, ciprofloxacin, amoxicillin, isoniazid, and so on. Occasionally, it is difficult to differentiate acute generalized exanthematouspustulosis (AGEP). Many of those agents or factors induce TNF-α, which plays a crucial role in the induction of GPP. By contrast, PPP-like lesions, and rarely GPP, are induced by anti-TNF drugs, as a paradoxical reaction.

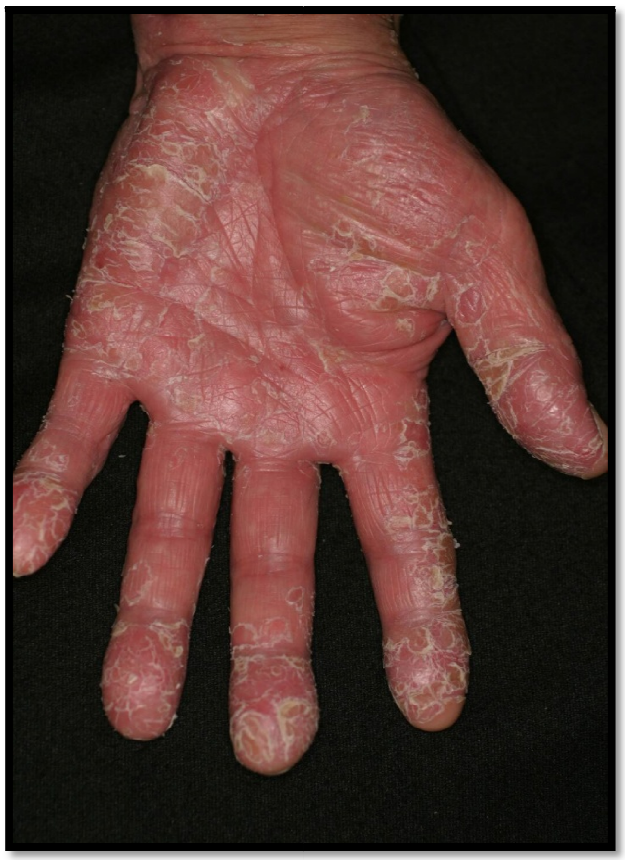


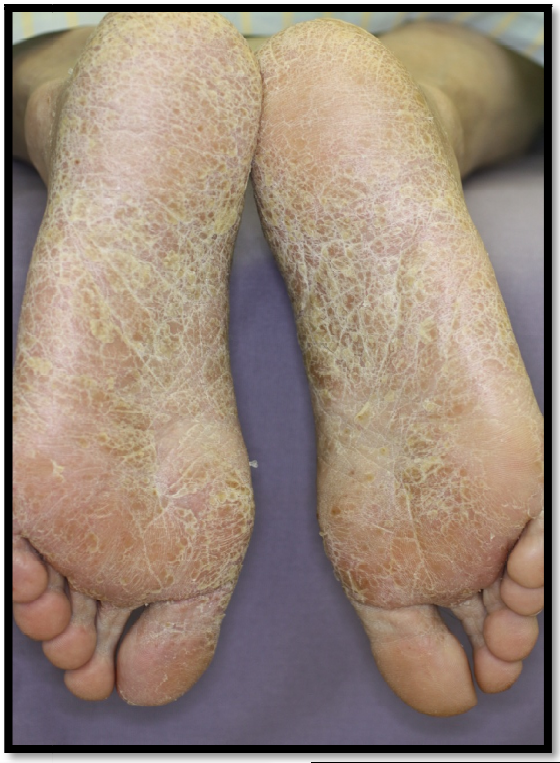
Figure 1. Palmoplantar psoriasis

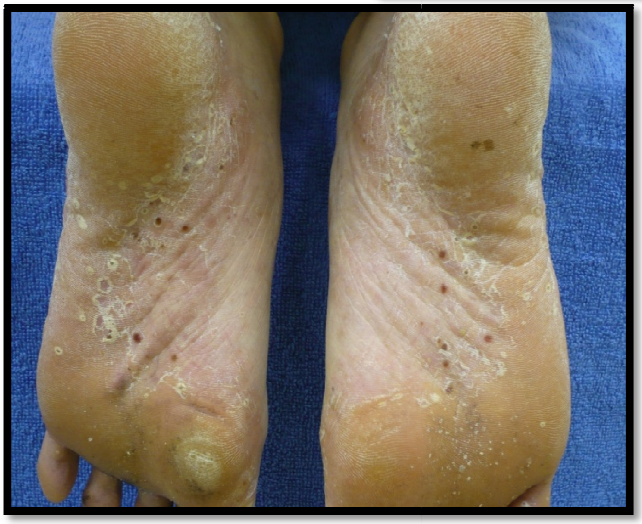
CO-EXISTENCE OF PALMOPLANTAR PUSTULOSIS AND PSORIASIS

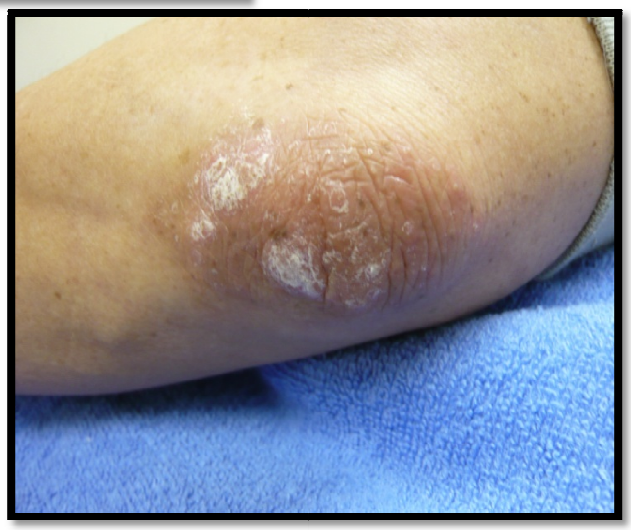
Patients with psoriasis vulgaris occasionally develop predominantly on the palms and/or soles, which is called palmoplantar psoriasis (Figure1). Infiltrative keratotic erythemas are seen, but absent from pustular lesions.

Patients develop typical psoriatic plaques on other sites than palmoplantar areas. On the other hand, patients with PPP develop hyperkeratotic lesions especially on the soles (Figure 2). Those cases indicate clinical similarities of both diseases, and extra-palmoplantar lesions associated with PPP sometimes present with features resembling psoriasis. Co-existence of typical features of PPP on acral sites and typical psoriasis on the elbow or knees is rarely seen (Figure 3a, 3b). In Japan, PPP is frequently seen, however, true collision of PPP and psoriasis is extremely rare. Ammoury et al. [20] also reported that plaque psoriasis at distant sites from PPP is exceptional, and concluded that PPP should not be considered as a variant of psoriasis.

Figure 2. Hyperkeratotic type PPP on the soles







(a) **(b)**

Figure 3. (a) Plantar lesions of PPP, showing a number of pustules, crusts, and scales. (b) Well-circumscribed keratotic erythema on the elbow in the same individual

GENERALIZED PUSTULAR PSORIASIS

Generalized pustular psoriasis (GPP) is a rare systemic disease characterized by widespread, superficial sterile pustules over the trunk, which often rapidly develop into

erythroderma. Pustular psoriasis is divided into generalized and localized, and the former type includes Zumbusch type, impetigo herpetiformis (acute GPP of pregnancy), annular and circinate form, juvenile and infantile pustular psoriasis, and generalized form of acrodermatitis continua (Hallopeau). PPP was previously known as 'pustular psoriasis of the extremities'. Baker and Ryan [21] formerly classified GPP into several subgroups including the "palm-sole" type. Both PPP and GPP are characterized by aseptic pustular formation, which reflect enhanced activity of neutrophil recruitment to the skin. The pustular lesions present not as solitary pustules, but as coalescent sheet-like pustular formations. These facts may suggest that PPP is the palm-sole type of GPP. Clinical appearances between both diseases are different, however, patients with GPP sometimes present with severe pustular lesions on the palms and/or soles [4]. Infantile GPP is seen, although rare, whereas there are no pediatric cases of PPP.

GPP is recently implicated as one of autoinflammatory diseases [22]. IL-36-α, -β, -γ are novel members of IL-1 family, which bind to the IL-36 receptor and lead to the activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. IL-36 receptor antagonist (IL-36RN) antagonizes the activity of IL-36. Recent studies have shown a significant role of IL-36 in psoriasis [23],and in particular, genetic analysis has revealed the mutations of IL-36RN in familial and also sporadic occurrence of GPP [24-28]. A deficiency of IL-36RN leads to the excessive IL-1 production and overproduction of IL-8 in keratinocytes in response to IL-36. By contrast, although there are few findings indicating the possibility that PPP is also regarded as an autoinflammatory condition, mutations of the IL-36RN gene has recently been reported to rarely underlie in some cases with PPP as well asacrodermatitis continua (Hallopeau) [29], suggesting that there may be a certain genetic backgrounds in common among GPP, PPP and acrodermatitis continua, or rather suggesting that the cases manifesting symptoms of PPP with such gene mutations may not be truly PPP. Acquired factors, such as environmental or life-style issues, need to be elucidated to distinguish between localized and generalized diseases, if they are on the same spectrum of pustular neutrophilic disorders.

The IL-19 subfamily of genes located on chromosome 1q31-32 has been suggested to be potentially susceptible to PPP [30]. IL-20 haplotype GAA is associated with an increased susceptibility, while GGG is associated with a decreased susceptibility, to PPP. In addition, PPP showed no association with PSORS1 [31], and TNF-238 and -308 promoter polymorphism are associated with psoriasis but not with PPP [32].

Table 1. Comparison of PPP and GPP

	PPP	GPP
Smoking	＋＋＋	＋
Focal infection	＋＋＋	±
Joint manifestation	PAO	PsA
Itching	Prior to onset of pustules	±
Exacerbating factor	Infection	Infection, pregnancy, drug
Nail involvement	＋～＋＋	＋～＋＋
Pediatric involvement	－	＋
Thyroid disease	＋～＋＋	±
Systemic inflammation	±	＋＋
Koebner phenomenon	＋	＋＋

PPP: palmoplantar pustulosis, GPP: generalized pustular psoriasis, PAO: pustuloticarthro-osteitis,

PsA: psoriatic arthritis

CO-MORBIDITIES OF PALMOPLANTAR PUSTULOSIS AND GENERALIZED PUSTULAR PSORIASIS

Recently, the co-morbidities associated with PPP have been surveyed [33]. However, in this report, the representative co-morbidities with psoriasis, such as cardiovascular diseases including ischaemic heart disease, hypertention, and dyslipidaemia, were presented in a high ratio. Furthermore, they described that psoriatic artyhropathy was present in 12%. It is highly suspected that they enrolled many patients with either palmoplantar psoriasis or palmoplantar pustular psoriasis in their study. Whether the examined patients are truly PPP, not psoriasis, may be doubtful.

On the other hand, because GPP is a severe form of psoriasis, many conditions such as arthralgia, metabolic syndrome, cardiovascular event, ophthalmological involvement, and inflammatory bowel diseases are accompanied. In addition, cholestasis frequently occurs in patients with GPP, and liver biopsy revealed neutrophilic cholangitis [34], which suggest a pathogenic role of activated neutrophils for liver damages. So far, pulmonary involvement in the course of psoriasis was estimated to be extremely rare, and only a few cases of acute respiratory distress syndrome were reported in association with GPP and/or psoriatic erythroderma [35, 36]. Possible aetiologies such as microbial infection, drug-induced reaction and capillary leak syndrome, via proinflammatory cytokines such as TNF-α, IL-6, and IL-8, have been proposed.

CONCLUSION

The comparison of PPP and GPP is shown in Table 1. Although there are many features of clinical symptoms including nail abnormality and joint involvement in common, several different aspects should also be recognized. Recently, psoriasis is regarded as a systemic inflammatory disorder, and various organ involvements are seen in patients with severe psoriasis, especially with GPP, i.e. cardiovascular disease, inflammatory bowel disease, joint manifestations, uveitis, acute respiratory distress syndrome, and chronic kidney disease. By contrast, organ involvement in association with PPP still needs further investigations. Although PPP sometimes shows features overlapping with either psoriasis or GPP, and both PPP and GPP are included in autoinflammatory pustular neutrophilic diseases [37], PPP nevertheless should be regarded as a distinct entity, different from acral variant of GPP.

CONFLICT OF INTERESTS

The author states no conflict of interests.

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