Management of palmoplantar pustulosis: do we need to change?

U. Mrowietz and P.C.M. van de Kerkhof*

Psoriasis-Center at the Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Schittenhelmstr. 7, 24105 Kiel, Germany
*Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Correspondence
Ulrich Mrowietz.
E-mail: umrowietz@dermatology.uni-kiel.de

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Summary

Palmoplantar pustulosis (PPP) is difficult to treat. There is little hard evidence for the efficacy of any treatment and no published guidelines for its management. A number of exacerbating factors are well documented and there is some evidence for the importance of others. Smoking is the most recognized environmental trigger and recent research has concentrated on the role of eccrine sweat glands in this regard. Other factors, including tonsillar streptococcal infection and gluten sensitivity, may be important in selected cases. The aim of this review is to challenge dermatologists to consider alternative management strategies for PPP and design clinical trials that will enable the development of useful therapeutic guidelines.

The pathophysiology of palmoplantar pustulosis

Palmoplantar pustulosis (PPP) is a chronic relapsing disease of unknown aetiology confined to the skin of palms and/or soles. Although listed among pustular variants of psoriasis in many textbooks, recent genetic studies have provided evidence that PPP may not be related to psoriasis.1–3 However, one recent survey reported coexistent psoriasis, or a history of it, in 24% of patients diagnosed with PPP.4 An association between PPP, osteitis and hyperostosis mainly of the clavicular and costosternal joints in SAPHO syndrome (synovitis–acne–pustulosis–hyperostosis–osteomyelitis syndrome) is also well documented.5,6 In a study done in the U.S.A., the possibility that there may be morphological subtypes of PPP such as hyperkeratotic, purely pustular and mixed forms of the disease was discussed.7

What is particularly surprising in relation to its differentiation from chronic plaque psoriasis is the development of PPP or a PPP-like rash in patients treated with tumour necrosis factor (TNF)-α antagonists.8,9 Whether this represents true psoriasis and/or PPP or a peculiar form of drug rash is currently unclear.10

Smoking has long been recognized as a culprit in the pathophysiology of PPP. Recently, work from Sweden and Japan has indicated that the palmar eccrine sweat gland may be an important link in the association between tobacco and PPP, as discussed below.

The link between smoking, the palmoplantar sweat apparatus and palmoplantar pustulosis?

The exact impact of smoking and, more importantly, cessation of smoking on the course of PPP is a matter for debate. PPP is predominantly seen in middle-aged women who smoke and there is evidence from a number of studies that most patients presenting with PPP were smokers at the time of disease first onset. Data from an Italian cohort study in psoriasis clearly showed that smoking is particularly associated with pustular lesions, with an odds ratio of 10·5 (95% confidence interval 3·3–33·5).11 Research from Sweden found that current smokers had a 74-fold higher age-adjusted risk for PPP compared with nonsmokers.12 However, there is only sparse evidence that cessation of smoking may lead to an improvement of symptoms and to a decrease of disease activity.13

One possible explanation for the association may be that receptors for nicotine, namely the α-7 nicotinic acetylcholine receptors, are overexpressed in lesional skin associated with sweat glands and ducts of patients with PPP. In addition, the enzyme choline acetyltransferase is upregulated in neutrophils and mast cells in lesional PPP skin. The expression of both can be significantly upregulated by smoking.14,15 Recently, Hagforsen et al.16 proposed that the sweat apparatus is a neuroendocrine organ expressing choline acetyltransferase, acetylcholine esterase, nicotinic receptors, β-adrenergic receptors and the neuroendocrine markers, synaptophysin and chromogranins A and B. Independent data from Japanese
patients substantiate the importance of the acrosyringium as the main site for PPP-specific inflammation.\textsuperscript{17} By using dermoscopy it was found that early vesicles and vesicopustules were only located on the top of the ridges of palmar skin, and not in the furrows. In addition, the pattern of antimicrobial peptide expression was different from that seen in plaque psoriasis. New data describe the involvement of innate immune responses through Langerhans cells and the generation of interleukin (IL)-17 in relation to the acrosyringium and pustule formation.\textsuperscript{18}\n
In the light of the new data on nicotine receptor expression in PPP skin as discussed above, we feel that it would be worth investigating further the relationship between tobacco and PPP with a particular emphasis on the effect of smoking cessation.

**The role of tonsils in palmoplantar pustulosis?**

In 1935, when describing PPP as an entity for the first time, as a purulent bacterid of hands and feet, Andrews and Mach-acek\textsuperscript{19} highlighted the usefulness of tonsillectomy. In their report, nine out of 24 caucasian patients with PPP were entirely cured after tonsillectomy. In Japan, it has been known for a long time that tonsillectomy improves PPP to a major extent.\textsuperscript{20}\n
More recent data link immune responses within the tonsillar tissue with PPP. Histopathological examination of specimens derived from tonsillectomy of patients with and without PPP with recurrent tonsillitis elucidated distinct anatomical differences in the follicular structure of tonsillar tissue. Tonsillar crypt epithelial cells were shown to overexpress IL-6 and the p53-related molecules, p63 and p73. In particular, expression of p63 was found to upregulate IL-6 in a nuclear factor KB-dependent manner in PPP-derived tissue.\textsuperscript{21}\n
The expression of cutaneous lymphocyte-associated antigen (CLA) on tonsillar T cells of patients with PPP, which was induced in vitro by streptococcal antigen, has also been demonstrated.\textsuperscript{22} The receptor for CLA on endothelial cells of the microvasculature, E-selectin, was overexpressed in PPP lesional skin. Tonsillar mononuclear cells showed an increased expression of transforming growth factor (TGF)-\beta, which was thought to trigger CLA expression. Interestingly, overexpression of inhibitory SMAD7, a molecule involved in intracellular signalling of TGF-\beta, was found in tonsillar T cells, TGF-\beta levels remained unaltered.\textsuperscript{23}\n
The role of \textalpha;-streptococcal antigen for activation of tonsillar T cells was further substantiated by recent findings that CCR6, the receptor for the chemokine CCL20/macrophage inflammatory protein-3\textalpha;, was highly expressed on T cells found in tonsils and skin of patients with PPP.\textsuperscript{24} After tonsillectomy, the number of CCR6-positive T cells decreased in the peripheral blood. In an animal model in which tonsillar lymphocytes were injected into SCID mice transplanted with skin from patients with PPP and later received an injection with recombinant heat-shock protein (HSP) 60, a correlation between the development of anti-HSP65 antibodies and IL-6 and interferon-\gamma levels was found.\textsuperscript{25} HSP60 is strongly expressed in lesional PPP skin and it is thought that bacterial HSP65 serves as an autoantigen with cross-reactivity for HSP60. The costimulatory molecule, B7h, a ligand for CD28 on T cells, was highly expressed in PPP lesional skin but absent in skin from healthy individuals.\textsuperscript{26}\n
B7h could also serve as receptor for the molecule ‘inducible costimulator’ which is overexpressed in tonsils of patients with PPP. New data describe upregulation of \beta1-integrin on tonsillar T cells in patients with PPP and its induction by streptococcal antigen. After tonsillectomy, \beta1-integrin/CD4-positive T-cell numbers decreased in the peripheral blood.\textsuperscript{27}\n
These data provide evidence for a ‘tonsil–palmoplantar–skin axis’ which may be present in patients with PPP on the basis of a hereto undefined genetic susceptibility. Proper prospective studies are needed to confirm these findings in Japanese and other populations and to determine which patients with PPP may benefit from tonsillectomy.

**The role of gluten sensitivity in palmoplantar pustulosis?**

Almost 20 years ago, a study from Sweden reported that in a subgroup of patients with PPP anti-IgA antibodies against gliadin were present.\textsuperscript{28} In another subgroup of these antibody-positive patients, celiac disease was diagnosed by commonly accepted criteria including duodenal biopsy. When these patients were managed with a gluten-free diet, a major improvement of PPP was observed.\textsuperscript{29} In a subsequent study in 123 patients with PPP, antigliadin antibodies were present in 18% of patients and antibodies against tissue transglutaminase in 10% of patients.\textsuperscript{4} Celiac disease could be diagnosed in 6% of the patients with PPP. When patients who tested positive for antibodies adhered to a gluten-free diet complete or nearly complete clearance of disease was achieved, paralleled by a decrease of antibody levels. Improvement was also seen in those antibody-positive patients adhering to a gluten-free diet but who were still smoking.

Outside Sweden, however, these results have not been confirmed as yet and one small study from Germany found no antigliadin antibodies in 32 patients and no antitissue transglutaminase antibodies in 18 patients tested.\textsuperscript{30} Further studies of patients with PPP are needed to determine the validity of the Swedish reports. Meanwhile it may be worth recommending testing for these antibodies as part of their routine work-up.

**Other disease associations in palmoplantar pustulosis?**

Autoimmune thyroid disease is more frequently found in patients with PPP.\textsuperscript{31} Interestingly, in a study from Spain, it was demonstrated that all patients with PPP showing thyroid dysfunction were also smokers which may relate this possible association to smoking rather than to the presence of PPP.\textsuperscript{32} There is also evidence that diabetes type 2 is more frequently found in women with PPP.\textsuperscript{33}
Finally, two studies have linked metals to PPP. One article found an interesting association between PPP and positive patch test reactions to metals including nickel and cobalt, and a high leucotriene 
B₄ concentration in pustules and serum was described in a small group of seven Japanese patients with PPP. In another report, the aggravating effect of zinc dental fillings in PPP was described.

Drug treatment of palmoplantar pustulosis

The treatment of PPP has always been difficult. Resistance to therapy and frequent relapse makes it a frustrating condition to treat. No therapeutic standard has yet been defined and no guidelines have been published on the treatment of PPP. Virtually all therapeutic options known from psoriasis or autoimmune diseases have been tried in PPP. Therapeutic recommendations given in textbooks mainly rely on case reports and the authors’ own experience. Only a few placebo-controlled data are available, which are insufficient to provide the basis of a practical treatment algorithm. A recent Cochrane review found that only topical corticosteroids under occlusion, acitretin (and the formerly used etretinate), psoralen plus ultraviolet A (PUVA) and the combination of both (Re-PUVA) were of proven benefit. Many agents are used although without any firm evidence of efficacy. In a retrospective study from Turkey, 83% of patients markedly improved after treatment with retinoids, 60% with colchicum, 57% with methotrexate and 50% with ciclosporin. No controlled data exist for PPP in many countries. Besides acitretin, methotrexate and PUVA, ciclosporin is used to treat PPP with success; however, a long-term treatment with this drug is not supported by existing guidelines. In North America and Switzerland, where alefacept is registered, there is limited evidence for a favourable response at least in a subgroup of patients. Two observations provide evidence that the antifungal drugitraconazole may be useful to treat PPP.

In an interesting contrast to psoriasis, TNF-α antagonists are of very limited value for PPP therapy. In some case reports, an improvement was reported whereas in others there was no effect on PPP. In a small trial with 15 patients with PPP, etanercept was only effective in a small subgroup. Regarding the PPP variant induced by treatment with TNF-α antagonists, recent work showed that PPP improved or even cleared while anti-TNF-α therapy was continued. Therefore, discontinuation of the TNF-α antagonist is not indicated in all patients presenting with such forms of PPP.

Our own experience shows that therapy of PPP with the new IL12/23 p40 antagonist ustekinumab was of limited value, with only two out of four treated patients responding even on a weight-adjusted dose regimen.

Numerous case reports describe successful or unsuccessful therapeutic strategies with various drugs, procedures and measures none of them leading to a substantial change of the current treatment recommendations.

Proposed management algorithm for palmoplantar pustulosis

We propose, based on the evidence presented above and subject to the recommended studies below, the following algorithm for the management of PPP:

1. Patients should be informed about the impact of smoking on the disease, and help should be provided to enter these patients into smoking cessation programmes. Patients should also be informed that improvement of PPP may take several months to occur after smoking is stopped.
2. Patients should be referred to otolaryngology to consider tonsillectomy.
3. Screening for the presence of thyroid dysfunction and/or for antigliadin/antitissue transglutaminase antibodies may be initiated when appropriate. In particular, this should be considered in patients with the signs and symptoms, or a previous history, of celiac disease. These measures should be considered in addition to conventional drug treatment recommended for PPP.

Future research

Clinical research is needed to address the following issues:

1. Are conventional antipsoriatic agents such as methotrexate, ciclosporin, fumaric acid esters, and the new biologic agents effective in the treatment of PPP? Properly designed double-blind placebo-controlled studies are needed to address this.
2. What is the effect of smoking cessation in patients with PPP who smoke?
3. What is the prevalence of gluten sensitivity and other endocrine disease in PPP?
4. What is the role of tonsillectomy and which patients are likely to benefit?

What’s already known about this topic?

- Palmoplantar pustulosis is a difficult to treat condition.
- There is no standard treatment or guidelines.
- Aggravation factors including smoking are known.
- Palmoplantar pustulosis may be associated with celiac disease or positive antigliadin/antitissue transglutaminase antibodies.
- In Asian patients, tonsillectomy is a common measure for treatment of palmoplantar pustulosis.

What does this study add?

- Awareness that besides drug treatment other factors are important for the outcome of any intervention.
- An algorithm for management of palmoplantar pustulosis is proposed.
- By following the recommendations patient care will be improved.