

# PALMO-PLANTAR PUSTULOSIS AND PSORIASIS: The Same But Different?

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## Abstract

Palmo-Plantar Pustulosis (PPP) is a relatively uncommon affliction of the glabrous skin of the hands and feet frequently associated with psoriasis. In recent years there has been much debate around whether the two conditions are the same or distinct clinical entities. PPP is characterised by scaly plaques with an erythemic base studded with sterile pustules and shows subtle but significant differences in its clinical presentation when compared to psoriasis. In addition, the disorder is frequently a chronic condition and is refractory to treatment. This paper reviews the current knowledge of the condition, its known associations and management.

## Introduction

PPP is a relatively uncommon condition which is characterised by symmetrical, erythemic patches of scaly epidermis which is studded with minute 2-4mm pustules (figure 1). It is most commonly located on hands and feet (particularly the thenar and hypothenar eminence on the palms and the central and lateral portions of the plantar surface). The condition begins with a developing area of erythema which then goes on to erupt with minute sterile pustules, coalescing to form larger collections within the epidermis. As the condition progresses pustular lesions may darken and dry out. Flaking of the lesions reveals a thin underlying epidermis with fissures and hyperkeratosis frequently accompanying the condition.

PPP generally exhibits a chronic pattern with relapsing and remitting episodes. The patient may experience pain and discomfort whilst weight bearing. Quality of life (QOL) studies for patients suffering with this disease are sparse and general dermatological QOL measures may not be suitably sensitive for PPP [1]. Despite a small body area percentage being affected, lesions on a dominant hand or on the foot may have significant impact on ambulation and daily activities. In a study of 317 patients with palmoplantar psoriasis and psoriasis, patients with plantar and palmar involvement demonstrated more physical discomfort and disability than those without [2]. This was confirmed in a later study which demonstrated that patients with PPP were more likely to report lower QOL scores in mobility and usual activities compared to those with widespread moderate to severe psoriasis, suggesting it to be more of a problem [3].

## Epidemiology

PPP is a disorder which predominantly affects women much more frequently than men with estimates suggesting a ratio of 5:1 [4]. The condition typically onsets adults in the



Figure 1

30-50 age group and from there may show a relapsing and remitting pattern for many decades afterwards. Studies have shown that around 20% of PPP patients have a family history of psoriasis and evidence of psoriatic lesions elsewhere on the body [5]. Interestingly, reports of PPP progressing into psoriasis have not appeared. Of most interest, is the link between smoking and the development of PPP. The first reports emerged in the 1980's from Japan and the UK [6]. One study from Japan highlighted the elevated incidence in smokers [7] whilst other work confirmed these findings. Rosen found

94% of patients in his cohort to be smokers at the time of onset of their disease [8] whilst similar figures of 92% were discovered in a Brazilian [9] and an African study [10]. A British case-control study demonstrated over 80% of PPP patients were current smokers compared to just 36% of controls, whilst only 10% of persons with the disease had never smoked. Of those 16 patients who had stopped smoking after diagnosis, there had been no improvement in their condition [4]. Other work has suggested only slight improvement of the condition after smoking cessation but small numbers in this study were a limitation [11] suggesting the habit to be a trigger for the condition.

## Aetiology

The link between smoking and the onset of PPP is not entirely clear but may suggest its aetiology. Eriksson and colleagues [12] undertook a unique histological analysis to uncover possible reasons. Using a comparison of control smokers and those with PPP, histological analysis has demonstrated destruction of the sweat duct within the epidermis with a localised pustule formation to be a key feature of the disease. Neutrophil numbers are known to be increased with the disease [13]. Examination of pustule contents has

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shown them to be rich in neutrophils and eosinophils along with accumulations of high numbers of mast cells below the pustule within the dermis along with lymphocytes. Interestingly, IL-8 is a chemoattractant for both eosinophils and neutrophils which has been shown to be present within the sweat duct and within the epidermis of patients with PPP. Moreover, mast cells are known to be able to secrete IL-8 suggesting their role in the pathogenesis of the disorder [12]. More recent research has confirmed the sweat duct to be the main area of inflammation with the disease [14].

Sweat glands in the palms and soles are part of the sympathetic nervous system – sweating being activated by Acetylcholine (ACh). Levels of the neuro-transmitter are balanced by local enzymes – choline acetyltransferase (ChAT) acetylcholinesterase (AChE) regulate the ACh level by synthesizing and degrading ACh respectively. However, more recently it has been shown that keratinocytes are able to produce these enzymes themselves. There are two known types of ACh receptor – nicotinic and muscarinic. Receptor sites in different parts of the body are uniquely constructed of particular sub-units which governs their individual functions. When nicotinic receptors are exposed to nicotine, it has an ACh agonist effect but does not get degraded by AChE thus potentially having a prolonged stimulatory effect. Hagforsen [15, 16] focused attention on the sweat duct itself and discovered that the distribution of nicotinic receptors was altered in smokers hypothesizing that nicotine exposure was responsible for triggering inflammation of the sweat duct in PPP patients. His experiments indicated that inflammation and pustule formation was brought about by immune cross-reactivity against specific sub-units within the sweat duct receptors, which was up regulated in smokers, leading to the conclusion that the disorder is an auto-immune process.

Other causes of the condition have been discussed. Since the 1960's a condition has been recognised which characteristically shows osteo-articular manifestations accompanied by a pustulosis. Termed SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis), it is a rare condition occurring in children and adults [17]. Clinically, since the introduction of biological agents, a number of cases of PPP have been documented as being triggered by patients taking medicines [18] such as adalimumab, etanercept, rituximab and infliximab [19-22] which most likely represents an adverse reaction to the drug which based on current case reports appears to be a rare finding.

### **PPP & other comorbidities**

The hypothesis that PPP is an autoimmune (AI) disease can be strengthened when looking at patients with the disease. One feature of AI disease is that sufferers generally are at risk of having more than one AI condition [23]. Previous surveys of patients with PPP have uncovered a range of co-existing conditions. Firstly, thyroid disease has been shown to be a

common co-morbidity. One study highlighted abnormalities in TSH, Thyroxine and Thyroperoxidase levels in patients with PPP (even at a sub-clinical level) [12]. In another study of 12 patients, 25% were demonstrated to have co-existing thyroid pathology [24]. Other studies have confirmed these findings [8, 25, 26]. The reasons for this association are unclear but it has been suggested that similarities in the homology of these hormones and cell function of the thyroid bears close resemblance to the keratinocyte [12] leading to cross over in its effects. Other AI disease which has been reported to co-exist includes gluten intolerance (coeliac disease) [12, 27] and disturbances in calcium homeostasis [28].

Beyond AI disease other potential co-morbidities have been proposed. In a Scottish study of 73 patients diagnosed with PPP, a survey was undertaken looking at coincidental diseases. In their data they discovered 27% had active plaque psoriasis, 2% had a family history of PPP whilst there were 24% with Ischaemic heart disease, 38% with hypertension and 49% dyslipidaemia which was higher than expected leading the authors to suggest that lipid profiles be measured in PPP patients as it is a strong risk factor for IHD. Interestingly, 29% of this group were diagnosed with depression suggesting the effect of the chronic skin disease has on patients [27]. The higher rate of depression in PPP patients had also reported in an earlier study along with a slight increase in the risk of diabetes [28].

A number of researchers have examined allergies amongst PPP sufferers as a possible aggravating pathology [29-31]. In a paper reviewing 21 patients with diagnosed PPP, patch tests were positive in 60% of patients. Typical allergens identified included nickel, formaldehyde, mercury, neomycin and balsam of Peru with the authors suggesting co-existing allergy may prolong the symptoms of PPP [32]. Other case reports have highlighted spontaneous regression of PPP following removal of metal implants suggesting a high probability of allergy behind the pustulosis [33-35].

### **PPP & its association with psoriasis**

Psoriasis is a common disorder characterised by erythematous plaques arising on the skin with detachable silvery scales. Within its clinical spectrum exists a number of variants such as guttate, inverse or flexural psoriasis and less commonly acrodermatitis continua of Hallopeau, for example. PPP in many texts is also traditionally referred to as a localised form or “variant” of psoriasis but recently this has been challenged, and remains unresolved, although evidence of it being a separate entity is increasing.

Following on from earlier work [36], a study examining the presence of the PSORS1 gene in patients with psoriasis vulgaris, guttate psoriasis and PPP was undertaken in 2003. The results demonstrated that although the psoriasis vulgaris and guttate psoriasis showed strong associations with the gene, no such link was demonstrated with PPP [37] casting

doubt on its origins as a true psoriatic variant suggesting it to be a separate disease. Other authors have also argued it to be a co-morbidity [38] citing the lack of genetic susceptibilities but also observing how the two conditions may arise together. Additionally, PPP may arise without psoriatic lesions elsewhere and that studies have shown that psoriatic arthritis is not associated with PPP [39]. Other clinical differences with psoriasis that have been reported include the higher female preponderance, the later age of onset [40], the strong association with smoking [9]. Differences in nail symptoms have also been examined. Patients with psoriasis tend to have more pitting and a faster nail growth whilst growth rates in patients with PPP have been shown to be normal [41]. Abnormalities also seen in the nails of patients with PPP include indentations and transverse ridging [42]. Finally, it is also commonly observed that treatments normally used to treat psoriasis, fail to work on those with PPP. For example, systemic drugs, exposure to sunlight and topical treatments seldom improves the condition, which are generally effective for psoriasis. Although pustular psoriasis is reported as variant of disease affecting any part of the skin, PPP by definition is limited to the hands and feet and exhibits unique properties again demonstrating it as a separate condition.

## Management of PPP

Consensus on the treatment for PPP to date has been disappointing and clinically for podiatrists there is little that may be offered to the patient in clinic using standard podiatric therapies. Urea based emollients may be of benefit with symptomatic treatment of dryness and skin fissures. There is much written on the difficulties of treating the disease as it is often refractory with frequent relapses even when it shows success. Topical treatments have generally been disappointing as affected skin is hyperkeratotic and therefore difficult for agents to penetrate. A Cochrane review in 2006 [43] concluded that the ideal treatment for PPP remained elusive and that robust studies were required to make any informed decisions on potentially effective treatments. In 2014, a further systematic review was undertaken to re-examine the evidence for therapeutic options [44] and despite a few more studies being published in the interim period, uncovered a similar lack of evidence to support formation of standard guidelines. In the absence of these, they reviewed the limited evidence and developed consensus-based recommendations for patients with PPP:

- First line – potent or very potent topical corticosteroids under occlusion (to enhance penetration).
- Second line – oral retinoid (acetrein) and phototherapy [PUVA]
- Third line – ciclosporin or methotrexate (with the latter having less evidence of effectiveness)

Although biological drugs have been known to rarely provoke PPP eruptions in patients, their therapeutic use for PPP is only emerging. Rapso & Torres [45] in looking at future therapies undertook a review of progress to date using these agents. In their paper they highlighted how many studies of the drugs in psoriasis have excluded patients with PPP but some reports of improvements in patients with PPP are emerging.

## Conclusion

Palmoplantar pustulosis is an uncommon autoimmune disease characterised by sterile pustules and hyperkeratosis of the palms and soles. The condition is most likely to be a distinct entity from psoriasis, based on the clinical comparisons in published case control studies. Current work suggests the disease is an immune mediated destruction of the acrosyringium in the palmar and plantar skin. Studies to date have suggested smoking to be a significant risk factor for the development of the condition. Management to date of the condition is extremely challenging with few effective therapies being recommended based on evidence. New biological agents may offer hope to patients with the disorder but further work is required to fully establish this.

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