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PALMOPLANTAR PUSTULAR PSORIASIS: AN UPDATE ON PATHOPHYSIOLOGY AND REVIEW OF TREATMENT OPTIONS

Introduction

Palmoplantar pustular psoriasis (PPPP) is a localized variant of pustular psoriasis that does not respond predictably to conventional psoriasis treatments and is a notoriously challenging condition to manage even though it shares many clinical and histopathologic features with plaque psoriasis. This review will briefly explore the clinical and pathophysiological features of PPPP and look at the evidence behind treatment of this condition using systemic and advanced therapies.

Clinical Considerations

Palmoplantar pustular psoriasis arguably has three distinct clinical variants: presenting in isolation as palmoplantar pustulosis (PPP), co-existing as palmoplantar pustulosis with plaque psoriasis (PPPP) or occurring as a "paradoxical" reaction to TNF-α inhibitor (TNFi) or other biologics used to treat psoriasis.

Many dermatologists consider PPP to be a distinct entity from pustular psoriasis, suggesting that PPP rarely coexists with plaque psoriasis, and therefore PPP and PPPP should be considered separate conditions.[1] However, studies comparing the transcriptome analysis of lesional skin in patients with PPP and PPPP have shown similar gene expression in both groups, which suggests they may not be distinct conditions. Interestingly, the same study found that transcriptional profiles of PPP/PPPP were distinct from those of plaque psoriasis.[2] Since there is ongoing debate in the area, this review will differentiate between the evidence for PPP vs PPPP where clearly delineated in studies.

Clinically, pustular psoriasis presents as an eruption of superficial sterile pustules, usually on an erythematous base (**Figure 1**). On the palms and soles, the pustules can resolve with hyperkeratotic or exfoliative scale. PPP is predominantly found in female patients, is often worse during the summer months, and is associated with smoking.[3–6] Patients with PPP/PPPP often experience considerable discomfort, and the condition can lead to significant morbidity by impacting activities of daily living, including work and physical exercise.

A modified psoriasis area and severity index (PASI) measure has been developed for PPP/PPPP (PP-PASI) which accounts for palmoplantar surface area involvement as well as erythema, scaling (desquamation) and pustules/vesicles. However, the PP-PASI tool is cumbersome to use in routine clinical practice and is typically only used for clinical research. Therefore, the classification of disease severity and/or

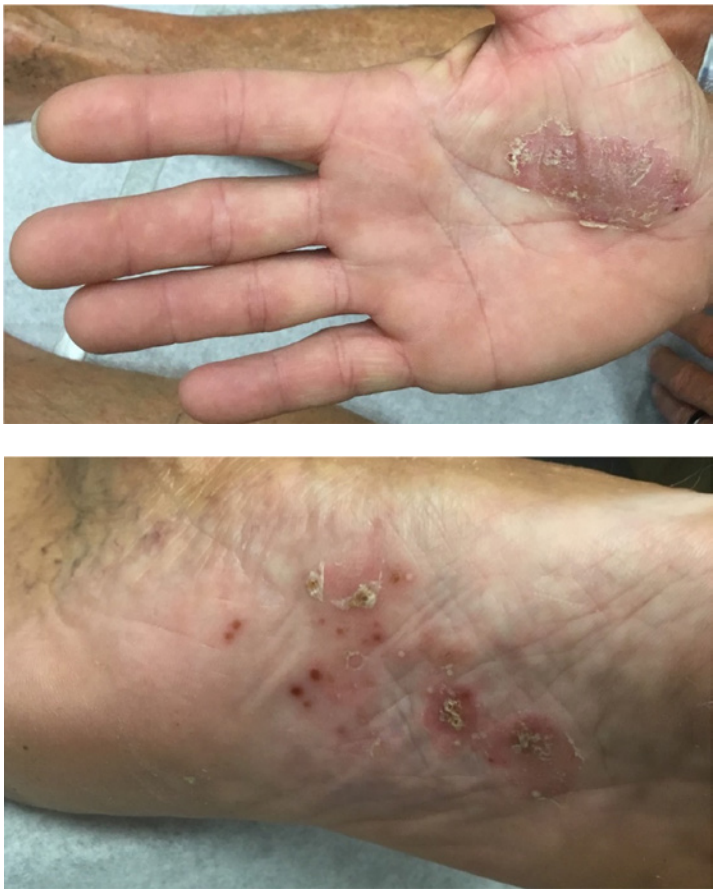

Figure 1 *: Palmoplantar pustular psoriasis on the palmar aspect of the hand and plantar aspect of the foot; courtesy of Fiona Lovegrove, MD*

monitoring of treatment outcomes has not been standardized, making it challenging to set expectations for treatment outcomes in the clinic.

Histopathology

PPP/PPPP is typically a clinical diagnosis and is not routinely biopsied, as biopsy on the palms or soles can be uncomfortable for the patient. If biopsied, pustular psoriasis has histopathological features which are similar to those seen with plaque psoriasis and include hyperkeratosis, acanthosis, parakeratosis, dermal mononuclear and neutrophilic infiltrates, and intraepidermal neutrophil collections (Munro's microabscesses).[7]

Pathophysiology

The pathophysiology of PPPP is not well understood, however, the acrosyringium of the eccrine sweat gland (the most intraepidermal portion, consisting of the terminal spiral duct) is thought to be the primary source of inflammation and pustule formation.[8,9] The inflammatory process in PPPP is initiated by the innate immune system at the level of the acrosyringium. The antimicrobial peptide cathelicidin (LL-37) is found in the acrosyringium in patients with PPPP, in early-stage vesicles, prior to the formation of pustules.[10] Langerhans cells, which are skin-resident macrophages that serve as antigen-presenting cells, are increased around or in the acrosyringium in the lesional and non-lesional skin of patients with PPPP.[11] These findings suggest that patients with PPPP are predisposed to an antigen-driven inflammatory process.

A recent transcriptional analysis of lesional skin taken from generalized pustular psoriasis (GPP) and PPP/PPPP found that both conditions show similar dysregulation of IL-36, Th17, and neutrophilic and keratinocyte-driven inflammatory pathways as compared to healthy volunteers.[12] The role of the IL-36 pathway in PPP/PPPP is less well understood as compared to GPP. Mutations in the gene IL36RN, encoding IL-36 receptor antagonist (IL-36Ra) are associated with GPP; however, these pathogenic variants occur at a much lower rate in patients with PPP/PPPP compared with GPP.[13]

The pro-inflammatory IL-17 cytokine family likely also contributes to the inflammatory process in PPPP. Expression of the pro-inflammatory cytokine IL-17A is seen in lesional skin from patients with PPP/PPPP,[9] while IL-12 and IL-23 were not found to be as prominently expressed. Smoking has been shown to increase IL-17 levels[9,14] and impair the nicotinic anti-inflammatory pathway;[15] smoking cessation can lead to improvement of PPP/PPPP.[16]

Lastly, pustular psoriasis can occur as a "paradoxical reaction" to TNFi therapy, typically when used in the treatment of other immune-mediated inflammatory diseases (IMIDs).[17] Paradoxical PPP likely results from an overactive innate immune response driven by type-I interferon.[18]

Treatment Options

While topical therapies are considered for first-line use in the management of PPP/PPPP,[19] they rarely induce remission or long-term control.

<u>Standard Systemic Agents</u>

Acitretin has been widely considered a first-line systemic therapy for the treatment of PPP/PPPP,[19,20] however, its use is constrained by teratogenicity and is therefore contraindicated in women of childbearing potential. Interestingly, another oral retinoid, alitretinoin, showed no benefit versus placebo in treatment of adult patients with PPP/PPPP in a phase 2, randomized, double-blind, multicentre study.[21] Cyclosporine is typically considered a second-line systemic therapy (as are biologic medications, covered below); however, cyclosporine is typically

used as a short-term "rescue" medication and is not a practical therapy for the ongoing and chronic nature of a condition such as PPP/PPPP.

Biologics

Biologics, which are consistently highly effective in the treatment of plaque psoriasis, have less consistent treatment outcomes with PPP/PPPP.[22–24]

TNFi have shown efficacy in the treatment of PPP/PPPP in multiple case reports.[22,25] An open-label study using adalimumab at 40mg subcutaneously every two weeks, showed improvement in 6/11 (54.5%) patients of at least one point in Physician's Global Assessment (PGA) after 12 weeks of treatment.[26] The treatment of 10 subjects with etanercept showed a statistically significant decrease in median PP-PASI at week 24 compared to placebo, however, some patients showed overall worsening of disease despite etanercept treatment.[27]

Despite evidence that IL-12 and IL-23 may play a less important role than IL-17 in the pathophysiology of PPP/PPPP, some evidence supports IL-12/-23 inhibitor treatment. A case series demonstrated successful treatment of PPP/PPPP using ustekinumab,[28] but a randomized placebo-controlled trial showed no statistically significant difference in PPPASI-50 response (a 50% reduction in PP-PASI score) between PPP/PPPP patients treated with ustekinumab versus placebo.[9] In a Japanese study of patients with moderate-to-severe PPP, patients receiving guselkumab demonstrated significantly higher PPPASI-50 response at week 16 compared to placebo.[29] Two case reports describe the successful use of risankizumab in PPP[30] and in "paradoxical" PPP developed as a result of adalimumab therapy.[31]

Since the IL-17 pathway appears to contribute to the development of PPP/PPPP, IL-17 inhibitors are an obvious treatment consideration. The 2PRECISE trial was a phase 3b multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating secukinumab treatment for PPP/PPPP. While the primary endpoint of PPPASI-75 response at week 16 was not met, 26.6% of subjects treated with secukinumab at the 300mg subcutaneous dose achieved PPPASI-75 vs 14.4% in the placebo arm (P= 0.0411).[32] In a longer-term follow up, this increased to 41.8% of patients achieving PPPASI-75 at week 52. Higher rates of Dermatology Life Quality Index (DLQI) 0 or 1 were achieved by patients in the treatment arm. A small case series showed that brodalumab was not successful in 4 patients with PPP/PPPP.[33] Evidence regarding ixekizumab or bimekizumab treatment for PPP/PPPP is not currently available.

Treatment of GPP via IL-36 pathway inhibition appears to be highly effective,[34,35] but unfortunately, IL-36 may not be as central to PPP/PPPP as it is to GPP disease pathogenesis. Spesolimab, an IL-36Ra, did not meet the primary endpoint of PPPASI-50 at week 16 in a phase 2a study of PPP.[36] In a post-hoc sub-group analysis, spesolimab was shown to be more effective in patients with severe disease versus placebo. Data from a larger phase IIb study of spesolimab with 152 PPP patients also did not meet its primary endpoint of PP-PASI change at week 16 (Burden et al AAD Poster # 32923), but sub-group analyses are pending.

Small Molecule Inhibitors

Limited clinical trial data support the use of small-molecule inhibitors in the treatment of PPPP. A phase 2 open-label single arm study of apremilast in 21 patients with moderate-to-severe PPP showed a median PP-PASI improvement of 57.1% ($p < 0.001$) at week 20 compared to baseline.[37] No published data currently exist for the JAK inhibitors deucravacitinib, or upadacitinib[38], however there are 2 published case reports on the use of tofacitinib in the treatment of PPPP.[39,40]

Summary

PPP/PPPP remains a challenging condition to treat. Gene expression data and an improved understanding of the pathophysiology suggest that the inflammation differs from that of plaque psoriasis and is driven by IL-17, IL-36, and innate immune pathways localized to the acrosyringium of the eccrine gland. Clinically, there is currently a deficit of safe, effective and long-term therapies for PPP/PPPP. Biologic therapies, while promising, still do not achieve the clinical response we have come to expect for our patients with plaque psoriasis. Hopefully, with an improved understanding of the condition and an increase in the available treatment options for inflammatory skin disorders, patients with PPP/PPPP will soon have improved choices.

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