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Letter

Successful treatment of palmoplantar pustulosis with isotretinoin

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Abstract

Importance: Variably considered as a localized subtype of pustular psoriasis, palmoplantar pustulosis (PPP) is commonly treated with topical steroids, acitretin, and local phototherapy with oral or topical psoralen (PUVA). The utility of acitretin for PPP is limited by adverse effects such as myalgias and an extended risk of teratogenicity in female patients. Isotretinoin is a more tolerable retinoid with a shorter teratogenic window, but to date its effectiveness in PPP has not been reported. Herein we present two patients with PPP who responded well to isotretinoin treatment.

Observations: Two patients with PPP refractory to topical therapies were started on acitretin. Both patients developed adverse effects (including headache, myalgias, and mood alterations) leading to acitretin discontinuation. Isotretinoin monotherapy was started in one patient resulting in significant clearing of palmar plaques and scale, and the addition of isotretinoin to UVA therapy resulted in near-complete clearing of recalcitrant plantar plaques in the second patient.

Conclusions and Relevance: Acitretin represents an important treatment for PPP, but is limited by adverse effects and extended teratogenicity. Our experience supports the utility of isotretinoin as a potential therapeutic alternative, which may be particularly beneficial in patients who are poor candidates for or unable to tolerate acitretin therapy.

Keywords: acitretin, isotretinoin, palmoplantar pustulosis, pustular psoriasis, PUVA

Case synopsis

Case 1

A 56-year-old healthy, nonsmoking man presented for evaluation of scaling and fissuring on his hands that had been present for approximately six months. He had been evaluated by an outside dermatologist shortly after symptom onset and was diagnosed with eczema, for which he was treated with topical clobetasol 0.05% ointment and emollients for six months without improvement. On examination, erythematous thin plaques and pustules with overlying white scale were noted on bilateral palms without evidence of nail involvement. In-office scraping of the lesions and potassium hydroxide preparation was negative for fungal organisms. The clinical presentation was felt to be most consistent with palmoplantar pustulosis (PPP) and he was started on twice daily calcipotriene 0.005% ointment in addition to topical clobetasol and an emollient moisturizer (Epiceram ER emulsion). After four months he reported partial improvement and acitretin 10 mg daily was added to the topical regimen without any additional improvement after one month. The acitretin dose was then increased to 50 mg daily and within four weeks, significant (> 50%) improvement in the palmar fissures and scale was observed. However, the patient developed prolonged headaches and debilitating neck stiffness while on 50 mg acitretin daily, and was instructed to discontinue the medication. He was immediately referred for ophthalmologic evaluation. Fundoscopic examination was normal and the headache resolved within 48 hours of acitretin discontinuation. A repeat trial of acitretin 25 mg daily was commenced, but the patient developed recurrent headache and neck pain as well as a depressed mood after two weeks of therapy; acitretin was again discontinued. The patient continued his topical regimen and was counseled regarding isotretinoin as a therapeutic alternative to acitretin. The patient was started on 30 mg isotretinoin daily. After one month of no significant improvement, his dose of isotretinoin was increased to 40 mg (0.5 mg/kg), which resulted in near complete resolution of the palmar plaques within four weeks. The patient developed mild facial dryness and cheilitis, which were managed with topical emollients. He was instructed to attempt a taper of the isotretinoin, but observed that his disease recurred at doses below 30 mg daily. Currently, the patient has been maintained on 30 mg isotretinoin daily for approximately five months with significant improvement of his palmar plaques and scale (Figure 1). Monthly monitoring labs have shown a slight increase in total triglycerides to 168 mg/dL (reference range <150 mg/dL).



Figure 1. Reduction in palmar plaques and scale with isotretinoin monotherapy. A) Pre-treatment left palm with fissures, scale and areas of hyperkeratosis. B) Left palm following four weeks of isotretinoin 40 mg daily and ten weeks of 30 mg daily, demonstrating resolution of fissures and reduction in hyperkeratotic scale.

Case 2

A 64 year old female smoker had presented to the clinic over two years prior for a scaly pruritic rash over her bilateral palms and soles, with more severe involvement of her feet. She was initially treated with twice daily clobetasol 0.05% ointment without improvement. On follow up examination she was noted to have ill-defined erythematous patches with multiple small pustules and overlying scale bilaterally on her palms and soles. A biopsy was performed and was consistent with pustular psoriasis/PPP. Her

topical regimen was augmented with calcitriol ointment and tazarotene 0.05% gel twice daily in addition to the clobetasol ointment with minimal improvement. She was then started on adalimumab 40 mg every other week with moderate improvement in her hand lesions and little to no improvement in the plaques on her feet. Owing to concern over potential adverse effects, the patient discontinued adalimumab after six months and was started on acitretin 25 mg daily. The patient noticed slight clearing of her hand and foot plaques but developed debilitating joint and muscle pains after two weeks on acitretin leading to discontinuation of the medication. She was unable to tolerate restarting acitretin at 10 mg daily owing to recurrent myalgias. The patient was then started on soak PUVA therapy three times weekly in addition to topical clobetasol and tazarotene. After four months of PUVA, she had significant improvement of the scaling on her hands but her feet remained refractory to therapy and she self-discontinued the psoralen soak component of her phototherapy because of concerns of worsening hyperpigmentation in areas of prior pustule location on her soles. The patient was started on isotretinoin 30 mg (0.5 mg/kg) daily in addition to the UVA treatments and after six weeks noted near-complete clearing of the plaques and scale on her feet. Owing to bothersome facial dryness and cheilitis, the isotretinoin dose was decreased to 30 mg every other day, which she has been able to tolerate well for the past four months with good control of her disease (Figure 2).



Figure 2. Reduction of plantar pustules and scale following UVA therapy with adjuvant isotretinoin. A) Pre-treatment right foot with significant hyperkeratosis and multiple ruptured pustules. B) Right foot following six weeks of isotretinoin 30 mg daily and eight weeks of isotretinoin 30 mg every other day in addition to UVA treatments three times weekly showing near-complete resolution of plantar scale and plaques with residual erythroderma.

Discussion

Palmoplantar pustulosis (PPP) is a chronic inflammatory dermatosis of the palms and soles that most commonly presents in the fifth or sixth decades of life [1]. PPP is characterized by recurrent outbreaks of sterile pustules on the palms and soles of the feet

as well as background erythema, scaling and fissuring of the skin. Women are three times more likely to develop PPP than men [2]. Although the involvement is limited with respect to body surface area (BSA), PPP carries a high patient morbidity owing to the location. In addition, PPP tends to be recalcitrant to therapy. Variably referred to as palmoplantar pustular psoriasis, pustulosis palmoplantaris, and pustulosis palmaris et plantaris, PPP was first described clinically by Barber in 1930 and considered to be a localized variant of pustular psoriasis [3]. Although in 2007 the International Psoriasis Council proposed that PPP should be considered a separate condition from psoriasis, the classification of PPP is controversial and it has been variably considered to be a localized pustular subtype of psoriasis as well as a clinically distinct entity [2, 4]. The disease has been associated with the presence of psoriatic lesions elsewhere on the body in approximately 18% of cases and with concomitant psoriatic arthritis (PsA) in 26% of patients [2]. A number of environmental factors have also been associated with exacerbations of PPP including stress, local infections (such as sinusitis or tonsillitis), metal allergies, and treatment with TNF inhibitors [2]. Whereas the etiology of PPP has not been completely elucidated, it appears that the palmoplantar eccrine sweat glands (acrosyringia) are the main targets of inflammation resulting in pustule formation localized to these structures [5]. Although there may be significant overlap in the clinical disease presentations, the genetic profile of PPP is distinct from that of psoriasis vulgaris and the development of PPP has been strongly associated with tobacco use [6]. Increased cutaneous expression of nicotinic acetylcholine receptors has been observed in PPP and may play a role in disease pathogenesis and its association with tobacco smoking [7]. Multiple other comorbid conditions have been found to occur at a higher frequency in patients with PPP as compared to the general population, including gluten intolerance (celiac disease), autoimmune thyroiditis, and disturbances in calcium homeostasis [1].

The recommended first-line therapy for localized PPP in the absence of arthritis is a high-potency topical corticosteroid such as clobetasol, augmented with occlusion for refractory cases. Second line treatments include acitretin and local phototherapy with oral or topical psoralen (PUVA). Cyclosporine and methotrexate (off-label) are considered third-line agents for resistant cases of PPP [8]. In addition to other effects, by modulating keratinocyte proliferation, retinoids exert an anti-proliferative effect on the epidermis and are thus of therapeutic utility in psoriasis [9]. Acitretin is the only systemic retinoid that is currently FDA-approved for the treatment of psoriasis and is an active metabolite of etretinate, which was the first systemic oral retinoid to be approved for psoriasis in 1986. Etretinate was withdrawn from the market in 1998 owing to its long half-life (two years) and resultant prolonged teratogenic potential [9]. The half-life of acitretin is 3-4 weeks, but because of esterification to etretinate in the liver (which is promoted by alcohol consumption) the compound is detectable in the body for up to two years. Thus, women of childbearing potential must use contraception for three years after cessation of acitretin, limiting its utility in this patient population [9]. The efficacy of acitretin is dose-dependent, and doses between 25-50 mg daily have been shown to be most effective while still limiting the potential for adverse effects [10]. In addition to prolonged teratogenicity, other major adverse effects of acitretin include cheilitis, alopecia, hepatotoxicity, hypertriglyceridemia, myalgias, and pseudotumor cerebri [9].

Isotretinoin (13-cis-retinoic acid) is currently approved for severe nodular-cystic acne, but the potent anti-inflammatory properties of this retinoid combined with inhibitory effects on cutaneous blood flow and sebaceous gland proliferation have led to its off-label use in a variety of non-acne conditions including rosacea, cutaneous lupus erythematosus (CLE), psoriasis, Darier's disease, and sebaceous hyperplasia [11]. As with acitretin, the teratogenic effects of isotretinoin require monthly pregnancy tests and two forms of contraception in reproductive age females while on the medication. However, the half-life of isotretinoin is significantly shorter than that of acitretin and patients are advised to wait at least one month following cessation of long-term isotretinoin therapy before cessation of strict birth control methods [11]. Isotretinoin has been used successfully to treat generalized pustular psoriasis in both adults (1.5-2.0 mg/kg daily) and children (40 mg/daily) [12, 13]. Although isotretinoin is inferior to etretinate as monotherapy for plaque psoriasis, in combination with PUVA the agents have been shown to have comparable efficacy [14, 15].

Herein we have described two cases of PPP successfully treated with isotretinoin. Both patients had previously improved on acitretin but were forced to discontinue the medication owing to acitretin-associated adverse effects. Isotretinoin administration in both patients was well tolerated and the minor adverse effects noted included facial xerosis and cheilitis (managed by slight decreases in the isotretinoin dose and topical emollients) as well as elevation of total triglycerides above the normal range in one patient. Although isotretinoin has been described for generalized pustular psoriasis and as an adjunct to PUVA for treatment of plaque psoriasis, to date no prior reports of isotretinoin for PPP have been identified in the literature [13, 15]. Isotretinoin may represent a potential therapeutic alternative for patients with PPP who are unable to tolerate the adverse side effects of acitretin or in reproductive age women for whom the extended teratogenic potential of acitretin represents a therapeutic challenge.

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