

Palmoplantar pustulosis – is there any progress in the treatment?

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Abstract

Despite the fact that palmoplantar pustulosis is still widely known by this name, it is currently regarded as a disease distinct from psoriasis. The real cause is still unknown. Septic foci have been blamed, but their removal may not cure eruptions. A case series of *de novo* occurrence of palmoplantar pustulosis induced by tumor necrosis factor- α antagonist therapy has been reported. It has been shown that stress may be related to exacerbation of palmoplantar pustulosis. Some authors suggest that palmoplantar pustulosis is an autoimmune disease. In sera of patients with palmoplantar pustulosis circulating autoantibodies against nicotinic acetylcholine receptors were detected. The differences between palmoplantar pustulosis and pustular palmoplantar psoriasis are numerous. Genetic studies have failed to find any link between palmoplantar pustulosis and major genetic susceptibility locus for psoriasis vulgaris. Most patients with palmoplantar pustulosis have no evidence of psoriasis elsewhere. Histologically, it closely resembles psoriasis. However, accumulation of neutrophils just beneath the corneal layer, finding known as Munro's microabscess, and dilation of capillaries in the papillary dermis are lacking. Approximately 90% of patients are women. A significantly higher prevalence of smokers was found in the group with palmoplantar pustulosis than in the normal population and a particularly strong association was confirmed between smoking and pustular lesions in patients with psoriasis, OR=5.3 (2.1-13.0). Nevertheless, according to a recent review from the Cochrane Library, there is no evidence that smoking cessation improves the condition once it has developed.

Topical corticosteroids under occlusion are the first-line therapy. Prolonged therapy is needed on a second or third-day basis, in order to sustain the obtained effects. Oral retinoids in combination with oral PUVA are the best second-line therapy. No difference in the efficacy between etretinate and acitretin was found. The disadvantage of systemic retinoid therapy is its teratogenicity. Oral PUVA is effective and the response is enhanced by combination with retinoids. There is an established increased efficacy of a combination of retinoids with PUVA therapy over each treatment modality when used alone. Liarozole may be an effective and well-tolerated therapy, but side effects are like in retinoids. The advantage over acitretin is that raised levels of retinoic acid fall to normal within a few days after cessation of therapy. Significant improvement, but no complete clearance, occurs in most patients treated with low dose cyclosporine. Before starting the treatment, it is necessary to consider: patient's individual factors, since many patients have already received some previous treatment; specific treatment factors such as formulation, way of administration, dose, different drug combinations; regimens and periods of treatment; site of involvement, due to differences between hands and feet in the probability of response to treatment.

Key words

Psoriasis + etiology + therapy; PUVA Therapy; Administration, Topical; Retinoids; Teratogens; Drug Therapy + adverse effects

Palmoplantar pustulosis (PPP) is a chronic inflammatory skin condition characterized by crops of sterile pustules (yellow pus spots) on the palms and soles which erupt unpredictably over months or years. Rapidly, lesions are surrounded by

an erythematous ring and the affected area becomes red and scaly (Figures 1 and 2). Histology reveals intraepidermal vesicles filled with neutrophils. The treatment is often difficult and frustrating. Full remission is rare.



Figure 1. Palmoplantar pustulosis: plantar lesions

Etiology and pathophysiology

Unfortunately, the real cause of PPP is still unknown. Septic foci have been blamed, but their removal may not cure eruptions (1). It has been reported that the disease onset occurred after several months of lithium treatment (2). A case series of *de novo* occurrence of PPP induced by tumor necrosis factor- α (TNF- α) antagonist therapy (biologic therapy for rheumatoid arthritis and psoriasis), has been reported (3). The role of psychological factors in palmoplantar pustulosis has been studied and it has been shown that stress may be related with exacerbation of PPP (4).

Recently, our understanding of psoriasis pathophysiology has greatly progressed, but the pathogenesis of PPP has been poorly investigated. Some authors suggest that PPP is an autoimmune disease. PPP is occasionally associated with thyroid autoimmunity, and the incidence is nearly 16-25% (5,6). Rarely, it is associated with rheumatoid arthritis and Sjogren's syndrome. There are no studies about

coexisting vitiligo and alopecia in patients with PPP. **In sera of patients with palmoplantar pustulosis**, Hagforsen and coauthors detected circulating autoantibodies against nicotinic acetylcholine receptors (7).

Palmoplantar pustulosis and psoriasis

The relationship between PPP and psoriasis vulgaris is unclear. No consensus has been reached regarding the question whether palmoplantar pustulosis represents a variant of palmoplantar pustular psoriasis (PPPP). Despite the fact that palmoplantar pustulosis is still widely known by this name, the condition is currently regarded as a disease distinct from psoriasis. Social stigma is common. Though the discomfort in PPP is common (itching, burning, fissures, poor mobility), it is also known that patients with palmoplantar psoriasis suffer more physical disability and discomfort than patients with other forms of psoriasis (8).

The differences between PPP and PPPP are numerous. Genetic studies have failed to find any link between PPP and major genetic susceptibility locus for psoriasis vulgaris (9). Most patients with PPP have no evidence of psoriasis elsewhere. Enfors and Molin found that this proportion varies from 2%-24%, depending on the studied groups (10). Some authors found 84% of patients with psoriatic lesions on extra-palmoplantar areas, e.g., forearms, elbows, dorsa of the feet, knees, lower legs, buttocks (11). There is milder tenderness and inflammation of extra-palmoplantar lesions in PPP than in patients with psoriasis (Figure 3). Psoriatic arthritis is only exceptionally associated



Figure 2. Palmoplantar pustulosis: lesions on the feet



Figure 3. Patient with pustular palmoplantar psoriasis showing extra-palmoplantar lesions

with PPP. Sternocostoclavicular, manubriosternal and sternocostal joints are most frequently affected.

Approximately 90% of PPP patients are women.

Histologically, PPP closely resembles the histology of psoriasis. However, accumulation of neutrophils just beneath the corneal layer, finding known as Munro's microabscess, and dilation of capillaries in the papillary dermis are lacking. There are no specific findings and many features overlap with those seen in eczematous reactions (12,13).

A significantly higher prevalence of smokers was found in the group with palmoplantar pustulosis than in the normal population and a particularly strong association was confirmed between smoking and pustular lesions in patients with psoriasis, $OR=5.3$ (2.1-13.0). Nevertheless, according to a recent review from the Cochrane Library, there is no evidence that smoking cessation improves the condition once it has developed (14).

Therapy

The therapy for PPP/PPPP is unsatisfactory. There is no specific agent which induces long lasting remission. Many different systemic and topical therapeutic agents

have been used. None of them can reliably suppress or cure the condition. Many of them are toxic, and there is little information regarding their relative efficacy. Differences regarding the cost to benefit ratio between various therapeutic modalities are significant.

Chalmers and colleagues (14) have searched the *Cochrane Group Specialized Register* (January 2003), the *Cochrane Central Register of Controlled Trials* (the Cochrane Library issue 1, 2003), the *Medline* (1996 to February 2003), and the *EMBASE* (1988 – 2003). They also cross-checked the Salford Database of Psoriasis Trials, the reference list of articles and also contacted authors included in trials, members of *The Cochrane Skin Group* and dermatologists interested in psoriasis. The selection criteria were randomized controlled trials on patients with chronic PPP who received one or more interventions (14). Twenty-three trials including 724 persons were studied.

Systemic retinoides

According to the Cochrane Collaboration Guidelines, out of eight trials that have been conducted, six compared etretinate with placebo, one acitretin with etretinate, and one liarozole versus placebo. The duration of trials was 8-16 weeks. Good or

excellent response was obtained in 39% of patients who received retinoids as compared with 17% who received placebo; 62% of patients who received retinoids maintained chronic remission of three months duration as compared with 21% who received placebo (14). Lassus (15) found no difference in the efficacy between etretinate and acitretin. The main disadvantage of systemic retinoid therapy is its teratogenicity.

Psoralen with ultraviolet A (PUVA) photochemotherapy

Eight trials were conducted to assess the efficacy of psoralen with ultraviolet A (PUVA) photochemotherapy for palmoplantar pustulosis: four studies comparing PUVA with placebo, one topical PUVA with systemic PUVA, and three PUVA with etretinate (Cochrane Collaboration) (14).

Oral PUVA

Oral PUVA therapy for palmoplantar pustulosis produces variable results. In two different studies, oral PUVA produced improvement in 100% and 64% of patients, respectively, and placebo in 59% and 14% of patients, respectively (16,17). When using complete clearance as the outcome measure, in two previously mentioned studies, oral PUVA produced complete clearance in 55% and 21% of involved areas respectively, while with placebo, there was no complete clearance in any of involved areas in both studies (16,17).

Topical PUVA

When using clearance of involved areas as the outcome measure, with topical PUVA, Layton (18) found 0% and Matsunami (19) 10% of cleared areas, while both the authors found no complete clearance in any of involved areas when treated with placebo.

Topical PUVA versus systemic PUVA

Lassus et al. assessed effects of etretinate compared with different regimens of PUVA in the treatment of persistent palmoplantar pustulosis: 8% of patients cleared with topical PUVA, as compared to 0% of patients who were treated with systemic PUVA (20).

PUVA versus retinoids

The obtained results were so different, that the data were not pooled. Thus, no definite benefits of retinoids over PUVA or vice versa were established (14).

Retinoids and PUVA combination (Re-PUVA)

Oral PUVA is effective (16,17) and the response is enhanced by combining it with retinoids (Re-PUVA) (21).

Re-PUVA versus PUVA and RePUVA versus retinoids

Comparing PUVA combined with etretinate and PUVA combined with placebo therapy for palmoplantar pustular psoriasis, Re-PUVA cleared all 100% versus 55.5% of areas treated with PUVA alone (21). However, three studies showed discrepancies in conclusions (17,19,21). Nevertheless, Chalmers and coauthors concluded that there is an established increased efficacy of combination of retinoids with PUVA therapy over each treatment modality when used alone (14).

Liarozole

An imidazole derivative, liarozole is a member of a new class of drugs that inhibits the metabolism of all-*trans*-retinoic acid by inhibition of retinoic acid 4-hydroxylase. It gives a retinoid-like effect by increasing endogenous levels of naturally occurring all-*trans*retinoic acid and other retinoids upstream of retinoic acid 4-hydroxylase. The advantage of liarozole over acitretin is that the raised levels of retinoic acid fall to normal within a few days after cessation of therapy. A randomized, double-blind, placebo controlled study indicated that 75 mg liarozole, twice daily, may be an effective and well-tolerated therapy for palmoplantar pustulosis (22). Side effects are retinoid-like: teratogenicity, hyperlipidemia and mucocutaneous dryness.

Cyclosporine

Two double-blind placebo-controlled trials of cyclosporine in the treatment of palmoplantar pustulosis were performed in 1998 and 1993, by Erkko and Reitamo, respectively (23,24). Significant improvement, but no complete clearance occurred in most patients with palmoplantar pustulosis treated with low dose cyclosporine of 2.5 mg/kgBW/day.

Methotrexate

Some studies of methotrexate used in the treatment of palmoplantar pustulosis have shown marked improvement, but there are no controlled studies in the literature.

Tetracycline

Only modest improvement was achieved in 38% of patients with palmoplantar pustulosis treated with tetracycline for one and three months versus 13% treated with placebo (25).

Hydroxycarbamide

Regarding treatment of palmoplantar pustulosis with hydroxyurea, Hattel and Sondergaard found no significant difference in disease severity scores between placebo and intervention periods (26).

Colchicine

Known to inhibit neutrophil function, colchicine has been claimed to be effective in palmoplantar pustulosis. However, this has not been confirmed by randomized controlled trials [27,28]. In 1984 and 1982, two cross-over studies by Thestrup-Pedersen and Mann have been reported, respectively (27,28). In the study by Thestrup-Pedersen, colchicine and placebo produced an improvement in 37% and 11.1% of patients, respectively (27). Failure of colchicine for palmoplantar pustulosis was reported by Mann (28).

Colchicine induces moderate improvement of palmoplantar pustulosis, but it also has a high rate of side effects. Thus, Chalmers et al. concluded that some evidence suggested possible modest benefits from colchicine at the expense of high rate side effects (14). Some authors would, however, still try colchicine as the first line medication in the treatment of palmoplantar pustulosis (29).

Grenz ray therapy

There is some evidence of improvement of palmoplantar pustulosis from Grenz ray therapy (very low voltage X ray therapy) (14). Opposite to this, Lindelof reported that none of the patients achieved clearance (30). Since Grenz ray therapy only improves the condition, it may be a useful adjunct in the treatment of palmoplantar pustulosis (14).

Topical corticosteroids and other topical therapy

Potent or superpotent steroids are drugs of choice and may be used under plastic film of hydrocolloid occlusion, particularly at the very beginning of therapy (31).

Superpotent topical corticosteroids may be beneficial for short term treatment. Hydrocolloid gel occlusion can enhance the efficacy of moderate corticosteroid creams, when applied every third day up to a maximum of 4 weeks. In a right-left comparative study, Kragballe found that sides treated with a medium strength corticosteroid cream under hydrocolloid occlusion cleared completely in 12 of 19 patients (63%) compared to sides treated with a highly potent

corticosteroid cream, that cleared in 3 of 19 patients (16%) (32). Therefore Mrowietz suggests prolonged topical steroid therapy, on a second- or third-day basis, in order to sustain the obtained effects (31).

Other topical agents, such as vitamin D3 analogues (calcipotriol/calcipotriene), tazarotene or anthralin, may prevent early relapses that occur in some patients. Topical retinoids can be used to avoid adverse effects or to strengthen the effects of steroids.

TNF- α antagonists

In regard to the therapy of palmoplantar pustulosis with tumor necrosis factor-alpha (TNF- α) antagonists, such as infliximab, no agreement has been reached (14). Though biologic, TNF antagonists are more likely to exacerbate than improve palmoplantar pustulosis. The lack of head-to-head studies makes recommendations concerning their individual use difficult. However, efalizumab, a monoclonal recombinant humanized IgG1 antibody, that binds specifically to the CD11, a subunit of lymphocyte function-associated antigen-1 (LFA-1), specifically developed for psoriasis, has been reported as beneficial for palmoplantar pustulosis. This finding awaits confirmation. Moreover, the drug has recently been withdrawn, due to the development of at least three confirmed cases of progressive, multifocal leukoencephalopathy in patients on prolonged (>3 years) monotherapy (33).

Further randomized clinical trials are needed to confirm therapeutic efficacy of biologic agents for palmoplantar pustulosis.

5-aminolevulinic acid photodynamic therapy

A small number of patients have been reported to be treated with photodynamic therapy using 5-aminolevulinic acid (5-ALA) for palmoplantar pustulosis and we have some evidence to suggest a possible modest benefit.

Implications for practice

Many therapeutic modalities have been used to treat palmoplantar pustulosis, but only few high quality studies were identified in the review of Chalmers R, et al. (14). The treatment is often difficult and frustrating.

Topical corticosteroids under occlusion are the first-line therapy. Prolonged therapy is necessary.

Systemic photochemotherapy and systemic retinoids are both of value for palmoplantar pustulosis.

Systemic PUVA can induce clearance in up to 40% of patients with PPP.

Systemic retinoids (0.5 mg/kg/bw/day) may induce improvement in 2/3 of patients with PPP. A good or excellent response may occur in 2/5 of patients with PPP.

Re-PUVA has the best clearance rate in about 2/3 PPP patients and is more favourable in comparison with PUVA or retinoid therapy alone. Oral retinoids in combination with oral PUVA are the best of second-line therapies.

Other therapeutic modalities for PPP have modest effects. Chalmers and coauthors found no eligible studies examining other topical therapies such as tar, anthralin, calcipotriol or tazarotene (14).

Conclusion

Before starting the treatment of patients with PPP, it is necessary to consider the following: patient individual factors - since many patients have already received some previous treatment; specific treatment factors - such as formulation, way of administration (parenteral, oral, topical, physical), dose, concentration, combination of different drugs, different regimens and periods of treatment; site of involvement - due to differences between hands and feet in the probability of response to treatment.

Abbreviations

- PPP - Palmoplantar pustulosis
- PPPP - Palmoplantar pustular psoriasis
- PUVA - Psoralen with ultraviolet A
- Re-PUVA - Retinoids and PUVA combination
- TNF- α - Tumor necrosis factor- α
- LFA-1 - Lymphocyte function-associated antigen-1
- 5-ALA - 5-aminolevulinic acid

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Palmoplantarna pustuloza – ima li pomaka u lečenju?

Sažetak

Definicija: Palmoplantarna pustuloza je hronična upalna bolest koju odlikuju eruptivne pustule na dlanovima i tabanima sa periodima egzacerbacije i parcijalne, retko potpune regresije.

Ne postoji opšta saglasnost da su palmoplantarna pustuloza i lokalizovana, palmoplantarna pustulozna psorijaza ista bolest. Iako je oboljenje poznato pod tim nazivom, palmoplantarna pustuloza se tek trenutno smatra posebnim, od psorijaze odvojenim entitetom.

Etiopatogeneza: Stvarni uzrok nastanka oboljenja nije utvrđen. Fokalne infekcije mogu biti prisutne ali se njihovom sanacijom ne postiže u svim slučajevima izlječenje. Opisani su *de novo* slučajevi u kojima je bolest nastupila u toku terapije antagonistima faktora nekroze tumora alfa. Pojedini slučajevi se mogu povezati sa stresom. Pojedini autori smatraju da je palmoplantarna pustuloza autoimuna bolest. U serumu obolelih otkrivena su antitela usmerena protiv nikotinskih acetilholinskih receptora. Ispitivanja su pokazala da je prevalencija pušača kod pacijenata sa palmoplantarnom pustulozom signifikantno viša od prevalencije u opštoj populaciji i da postoji visoko signifikantna povezanost

između pušenja i pustulozne psorijaze OR=5,3 (2,1–13). Ipak, ne postoje dokazi da prestanak pušenja dovodi do poboljšanja postojećih promena.

Odnos prema psorijazi: Razlike između palmoplantarne pustuloze i plamoplantarne pustulozne psorijaze su brojne. Nedavna genetska ispitivanja nisu utvrdila povezanost između palmoplantarne pustuloze i glavnog lokusa koji se dovodi u vezu sa povišenom genetskom predispozicijom za obolevanje od psorijaze. Većina pacijenata sa palmoplantarnom pustulozom nema psorijazu na drugom delu tela. Prevalencija psorijatičnih promena na udaljenim mestima varira počev od 2% preko 24% do 84%, od studije do studije. Žene obolevaju češće od muškaraca i čine 90% svih obolelih. Palmoplantarna pustuloza pokazuje visok stepen histološke podudarnosti sa psorijazom. Za razliku od psorijaze, kod palmoplantarne pustuloze ne dolazi do vazodilatacije kapilara u papilarnom dermisu, niti akumulacije neutrofilnih granulocita neposredno ispod kornealnog sloja (*Munro* mikroapscesi).

Terapija: Lečenje palmoplantarne pustuloze

je nezadovoljavajuće. Mnogi medikamenti su primenjivani, a nijedan pouzdano ne suprimira bolest niti dovodi do izlečenja (katrani, topijski kortikosteriodi, ditranol, fotohemoterapija, oralni tetraciklini, metotreksat, retinoidi, lokalni ili sistemski, ciklosporin, kolhicin, biološka sredstva).

Lokalna primena kortikosteroida pod okluzijom, jedina je od lokalnih terapijskih procedura, koja se pokazala efikasnom za lečenje palmoplantarne pustuloze. Terapiju održavanja potrebno je sprovesti alternativnim nanošenjem leka svakog drugog/trećeg dana. Potrebne su dalje studije o efikasnosti ostalih preparata za lokalnu primenu.

Najbolji metod za lečenje palmoplantarne pustuloze u drugom terapijskom redu, predstavlja kombinacija sistemskih retinoida i sistemske (oralne) PUVA fotohemoterapije (Re-PUVA). Razlika u efikasnosti između etretinata i acitretina nije utvrđena. Manjkavost sistemske primene retinoida predstavlja opasnost od teratogenog efekta. Sistemskom PUVA terapijom postiže se dobar efekat ali se terapijska efikasnost signifikatno povećava u kombinaciji sa sistemskom primenom retinoida. Ova kombinacija se pokazala suverenom nad monoterapijom, kako u odnosu na PUVA tako i na retinoide.

Liarozole je imidazolski derivat a pripada novoj kategoriji lekova koji blokiraju metabolizam *all-trans* retinoične kiseline putem inhibicije enzima 4-hidroksilaze retinoične kiseline. Pokazao je efikasnost koja s jedne strane obećava ali istovremeno zahteva ozbiljnu proveru. Dobro se podnosi. Neželjena dejstva su kao i kod terapije sistemskim retinoidima, ali je njegova prednost u odnosu na acitretin to što se po prestanku primene lirozola, povišen nivo retinoične kiseline u serumu vraća na fiziološku vrednost u toku samo nekoliko dana.

Ciklosporin primenjen u niskim dozama (2 mg/kgTT dnevno) izaziva signifikantno poboljšanje ali ne i potpuno povlačenje promena.

Zaključak: Terapija treba da bude prilagođena svakom pojedincu, a to znači da je pre započinjanja lečenja potrebno razmotriti činioce kao što su: individualne osobine svakog pojedinog pacijenta, s obzirom da su mnogi pacijenti već prethodno lečeni; faktori specifični za odgovarajući metod lečenja, npr. način primene leka, koncentracija aktivne supstancije, doza, kombinovana primena dva ili više različitih leka, različiti režimi u terapijskom pristupu, dužina lečenja; lokalizacija promena, s obzirom na razlike u terapijskom odgovoru između kože dlanova i tabana koje se mogu očekivati.

Ključne reči

Psorijaza + etiologija + terapija; PUVA terapija; Spoljašnja primena; Retinoidi; Teratogeni; Farmakoterapija + neželjena dejstva