REVIEW ARTICLE

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Pompholyx

A Review of Clinical Features, Differential Diagnosis, and Management

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Abstract

Pompholyx is a vesicobullous disorder of the palms and soles. The condition is hard to treat because of the peculiarities of the affected skin, namely the thick horny layer and richness of the sweat glands. In this article, we review the available therapies, and score the treatments according to the level of evidence.

The cornerstones of topical therapy are corticosteroids, although calcineurin inhibitors also seem to be effective. Topical photochemotherapy with methoxsalen (8-methoxypsoralen) is as effective as systemic photochemotherapy or high-dose UVA-1 irradiation.

Systemic therapy is often necessary in bullous pompholyx. Corticosteroids are commonly used although no controlled study has been published to date. For recalcitrant cases, corticosteroids are combined with immunosuppressants. Alitretinoin has efficacy in chronic hand dermatitis including pompholyx. Another evolving treatment seems to be the intradermal injection of botulinum toxin. Radiotherapy might be an option for selected patients not responding to conventional treatment. In practice, patients benefit most from a combination of treatments.

The aim of this article is to review the clinical features, differential diagnosis, and management of pompholyx. A literature search was conducted using the MEDLINE database and the terms 'pompholyx' and 'dyshidrotic eczema' from January 2000 to April 2010.

1. Clinical Features

Pompholyx or dyshidrotic eczema is a common disease affecting palmoplantar skin.[1] Since palmoplantar skin is rich in eccrine sweat glands, it had been suggested that there was a relationship between the vesicles and these glands.[2] Today, the disease is considered to be a special type of eczema, with a pronounced spongiosis and accumulation of edema fluid in regions with a thick epidermis and an even thicker overlying horny layer. The spongiotic vesicle is intraepidermal. The acrosyringium of the sweat glands is not altered by the disease,[3] which makes the term 'dyshidrosis' a misnomer.

According to Fox,[2] pompholyx is characterized by vesicles and bullae on nonerythematous palmoplantar skin. Based on nonadherence of many authors to the original clinical description of this skin condition, Storrs[4] has recently proposed the use of the term "acute and recurrent vesicular hand dermatitis." I am not sure whether the terminology will change in practice or not.

Happle[5] suggested the term "paraptic eczema" for this condition, when pompholyx is elicited by the hematogenous action of an antigen that has already initiated a T-cell-mediated eczema response on the skin.

There are two clinical types of presentation: bullous (figure 1) and vesicular (figure 2). Vesicular pompholyx is known as dyshidrotic eczema in German-speaking countries, whereas the bullous type is named cheiropodopompholyx.[6]

Pompholyx is associated with itching and burning sensations. Secondary infection with staphylococci is not infrequent. The disease is more common during the warm seasons.[7]

2. Pathogenesis

Pompholyx is seen all over the world, but seems to be less common among Asians.[8] In rare cases, there is a genetic background. In a study from China, a gene locus on chromosome 18q22.1–18q22.3 between markers D18S465 and D18S1362 could be identified in a large family with an autosomal dominant type of pompholyx.[9] However, most cases of pompholyx are sporadic.

Patients with pompholyx show highly significant differences in autonomic vagal modulation under deep respiration (inspiration and expiration), but cardiac autonomic modulation

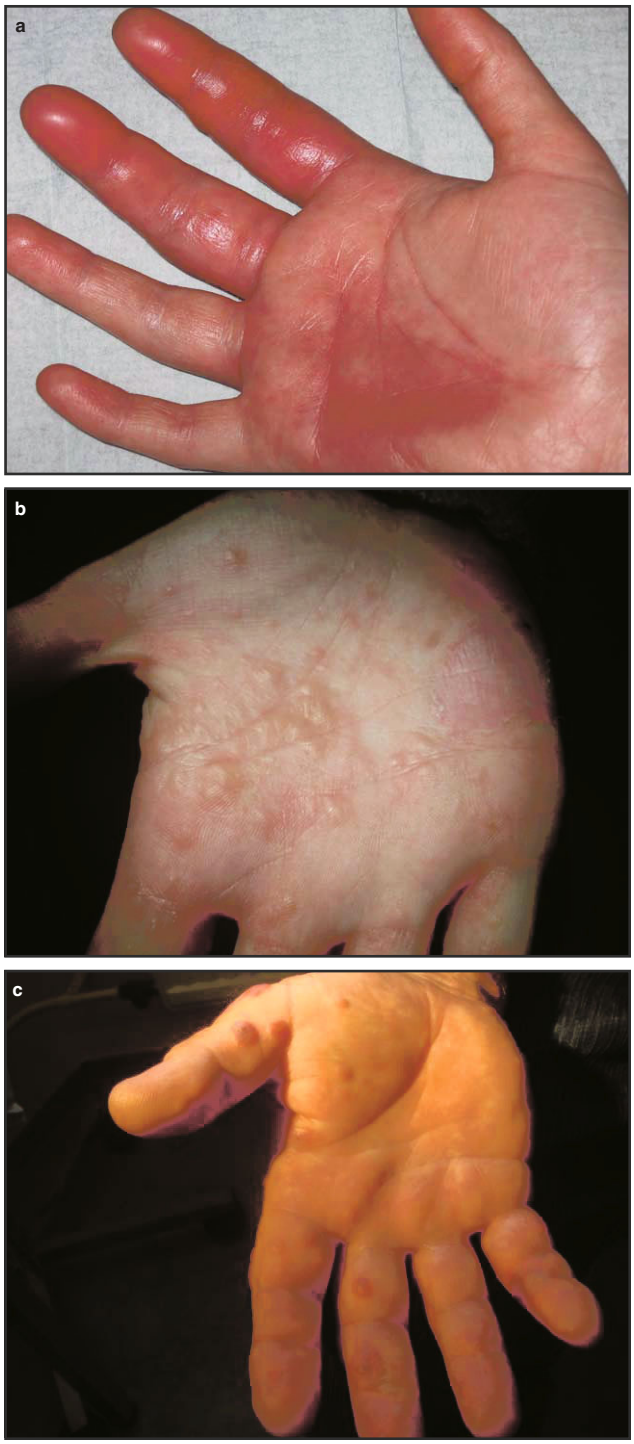

Fig. 1. Bullous cheiropompholyx: (**a**) early presentation; (**b**) later presentation; and (**c**) secondary hemorrhagic bullae in bullous cheiropompholyx in contrast to primary hemorrhagic bullae in autoimmune bullous disease.

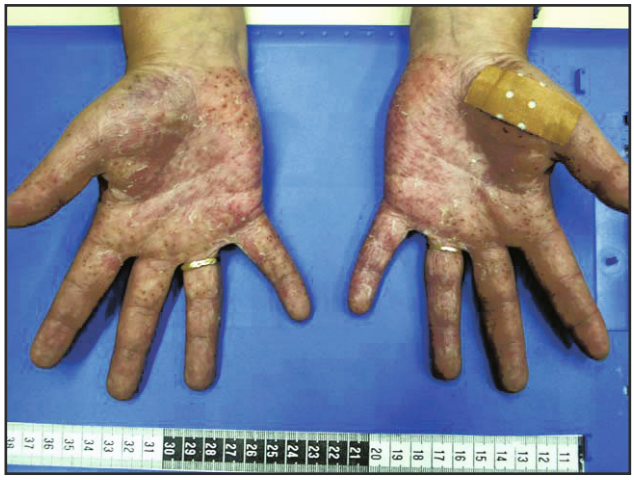

Fig. 2. Vesicular pompholyx.

was hardly altered. It is not known whether these changes are disease inherent or regulatory.[10]

Pompholyx can be associated with atopic dermatitis, contact dermatitis, or adverse drug reactions (table I). In a survey involving 364 patients with pompholyx, contact sensitivity has been observed in about 30%.[14] In the case of nickel sensitivity in pompholyx, patch-test reactions show a great variability over time.[17] On the other hand, relapses are seen no more frequently with oral nickel provocation than with placebo.[24]

In another study involving 120 patients with pompholyx, 67.5% of patients had allergic contact dermatitis, and 10% had mycosis.[1] Other authors have questioned the role of nickel sensitization. In a study of 398 patients, the relative risk for vesiculation in nickel-positive individuals was 0.45 compared with 3.58 for tinea pedis.[25] In a study to identify factors associated with the disease in 100 pompholyx patients in Togo, West Africa, the odds ratios were 15.6 for tinea, 12.6 for atopy, and 4.5 for hyperhidrosis. *Trichophyton rubrum* was the most common etiology of the tinea pedis.[26]

The blisters and vesicles on the palms do not contain infectious material. Their formation is thought to be mediated by an allergic reaction to the pathogen, called the id reaction.[27]

Pompholyx has been observed as a manifestation of infection with HIV. In this case, antiretroviral therapy was beneficial for the skin disease as well.[28]

There is a variety of other aggravating factors, such as irritants, prolonged use of protective gloves, smoking, stress, and even endoscopic thoracic sympathectomy for palmar hyperhidrosis.[29] Among 120 pompholyx patients from France, one-third had hyperhidrosis.[1] Smoking also has a negative influence on the efficacy of phototherapy, such as bath-psoralen plus UVA irradiation (bath-PUVA).[1,30] However, diseases with disturbed sweating such as Parkinson disease are not associated with an increased risk of pompholyx.[31] In rare cases, pompholyx can be photoinduced.[32]

The course is often chronic or chronic-cyclic, even in patients in whom the aggravating factors can be avoided. There might be longer periods of remission in these patients, but when pompholyx relapses there is no quick response to treatment.

Table I. Contact allergens and drugs associated with pompholyx

Substance/drug	Allergen	Frequency	References
Anti-wart drugs	Resorcinol	Rare	11
	Diphencyprone	Rare	12
Cosmetics and hygiene products	Balsam of Peru, fragrances	≤32%	13,14
HAART	Unknown	Rare	15
IV immunoglobulins	Unknown	Occasional	16
Metals	Nickel	≤30%	17
	Cobalt	4%	13
Mother's milk	Chromium from food	Rare	18
Mycophenolate mofetil		Rare	19
Plants	Ragweed	Not uncommon	20
Photosensitivity	Piroxicam	Rare	21
Rubber	p-phenylenediamine	8%	13
Shoes	Rubber vulcanizer	Occasional	22
Tobacco powder	Sorbic acid	Rare	23

HAART = highly active antiretroviral therapy; **IV** = intravenous.

Table II. Differential diagnoses of pompholyx

Disease	Reference
Acropustulosis of infancy	33
Adult T-cell leukemia/lymphoma	34
Bullous impetigo	35
Bullous T-cell lymphoma	36
Dyshidrosiform pemphigoid	37
Linear IgA disease with (hemorrhagic) pompholyx	38
Epidermolysis bullosa	39
Erythema multiforme	40
Hand-foot-and-mouth disease	41
Herpes infection	42
HTLV-1 infection (adult cutaneous T-cell lymphoma)	43
Fixed drug eruption	44
Friction blisters	45
Pemphigus vulgaris	46
Polymorphic dermatitis in pregnancy	47
Psoriasis pustulosa	48
SAPHO syndrome	49
Scabies	33
Subcorneal pustular dermatosis	50
Vasculitis allergica (cutaneous small vessel vasculitis)	6

HTLV-1 = human T-lymphotrophic virus (human T-cell leukemia virus)-1; **SAPHO** = synovitis, acne, pustulosis, hyperostosis, and osteitis.

3. Differential Diagnosis

There are several important differential diagnoses that have to be excluded by careful history, clinical evaluation, histopathology, patch testing, microbiologic, and mycologic investigations (table II; figure 3).

Hemorrhagic blisters are suspicious for autoimmune bullous disease and lymphoma[51,52] but may occur in pompholyx as well (figure 1c).

4. Management

Management is not simple and relapses occur frequently. Aggravating factors, such as smoking, should be avoided. Medical treatment ranges from topical to systemic therapies. The targets for treatment are 3-fold: (i) suppression of blister formation and inflammation; (ii) relief from itch; and (iii) prevention or treatment of infection.[9]

As a standardized assessment method for the severity of pompholyx, the Dyshidrotic Eczema Area and Severity Index (DASI) has been developed. It is based on the number of vesicles per square centimeter, erythema, desquamation, itch, and the extension of the affected area.[53] The DASI can also be used to monitor treatment effects.

Management needs to be adapted to etiopathogenesis. In patients with tinea pedis, antifungal therapy is necessary. Patients with contact allergies should avoid identified allergens.

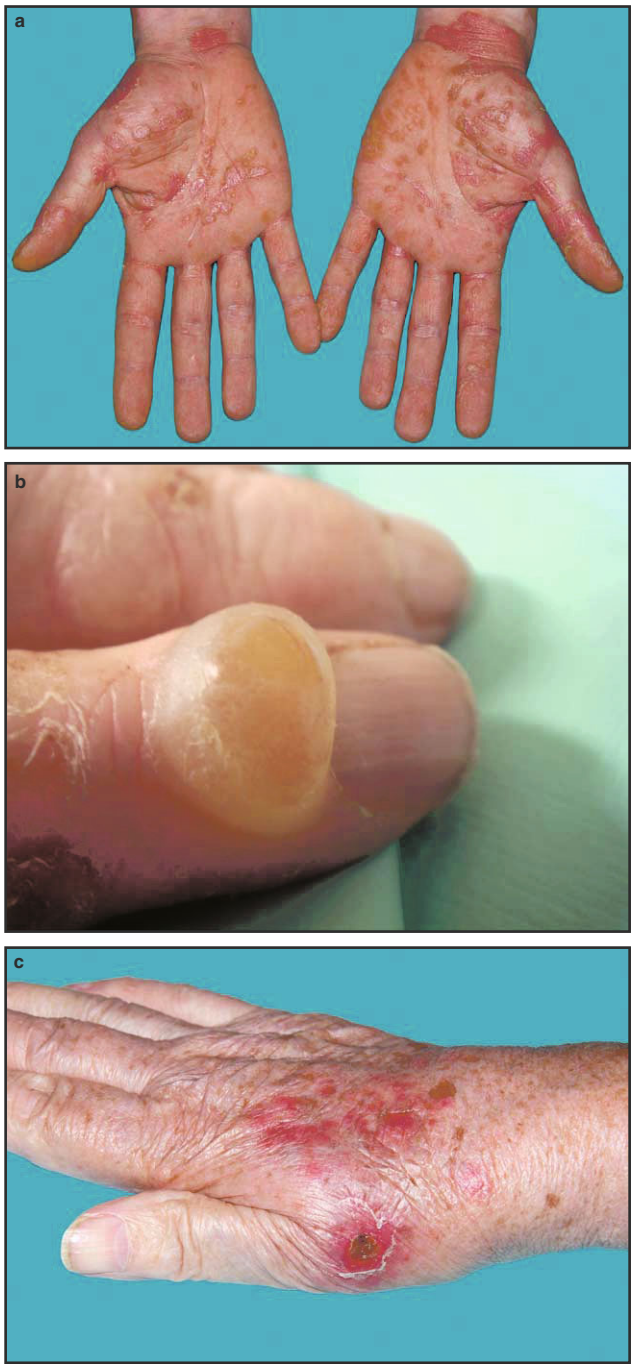

Fig. 3. Differential diagnoses of pompholyx: (**a**) pustular psoriasis; (**b**) bullous pemphigoid; and (**c**) vasculitis allergica (cutaneous small vessel vasculitis).

4.1 Topical Therapy

4.1.1 Corticosteroids

Topical corticosteroids are the cornerstone of treatment. However, published evidence is limited. Veien et al.[54] reported on 120 patients with chronic hand eczema, including 13 with recurrent 'vesicular hand dermatitis' who were using mometasone furoate fatty cream in a randomized, open-label, prospective trial. They noted that dorsal hand eczema was controlled more rapidly than palmar or dorsal and palmar. Vesiculation at the beginning had no significant effect on the time it took to control the dermatitis.[54] Improvement has been achieved with clobetasol propionate in combination with a hydrocolloid dressing for a limited time.[55,56]

4.1.2 Calcineurin Inhibitors

Topical tacrolimus was as effective as mometasone furoate 0.1% ointment in a randomized, observer-blind trial in 16 patients with vesicular pompholyx of the palms. After 2 weeks of treatment, the DASI was reduced by more than 50% with both treatments.[57]

Pimecrolimus 1% cream has been used in combination with occlusion to improve drug delivery in pompholyx.[58] In a larger, randomized, double-blind, vehicle-controlled trial, 294 patients with chronic hand dermatitis, including pompholyx, were treated with topical pimecrolimus 1% cream under occlusion. The improvement was better in the pimecrolimus-treated patients without involvement of the palms. Overall, the difference between vehicle and pimecrolimus did not reach statistical significance in this study ($p = 0.068$).[59]

4.1.3 Bexarotene Gel

Bexarotene is a retinoid X receptor agonist that has been approved by the US FDA for use in cutaneous T-cell lymphoma. The compound is contraindicated in premenopausal women without sufficient contraception because of the teratogenic potential of retinoids. In a phase I–II, randomized, open-label study of bexarotene 1% gel alone and in combination with a hydrocortisone 1% ointment or a mometasone furoate 0.1% ointment, 55 patients with severe chronic hand dermatitis were treated.[60] Bexarotene gel was applied at least twice daily. The response rate of patients achieving at least 50% improvement in the hand eczema area and severity index (HEASI) was 79% for bexarotene gel alone, 85% for the combination with mometasone furoate, and 64% for the combination with hydrocortisone. An improvement of the HEASI score of >90% was achieved in 36% of patients treated with bexarotene alone, in 38% of patients treated with bexarotene and mometasone furoate, and in 14% of patients with the combination of bexarotene and hydrocortisone. In a subgroup of 'other types of eczema/dyshidrotic eczema,' the clearance rate with bexarotene gel monotherapy was 50%. Adverse effects related to bexarotene gel included burning, stinging, irritation, and flare of dermatitis.[60] This study reveals that the combination of bexarotene gel with a topical mid-potency corticosteroid such as mometasone furoate is beneficial, whereas weaker corticosteroids do not add any benefit in such a combination. It has not been evaluated systematically whether more potent corticosteroids in combination with bexarotene gel would further improve the outcome in pompholyx.

4.2 Systemic Therapy

4.2.1 Corticosteroids

The basic systemic therapy in bullous pompholyx consists of systemic corticosteroids. Depending on the severity and the area affected, initial dosages between 40 and 100 mg/day are employed.[6] The dosage is gradually tapered after blister formation ceases. Other authors recommend the use of intramuscular triamcinolone acetonide 40–80 mg.[10] However, this treatment has never been investigated by randomized, prospective trials. Systemic corticosteroids are rarely advisable for long-term use because of undesirable adverse effects.

4.2.2 Immunosuppressants

In the case of recalcitrant pompholyx, other immunosuppressive drugs have occasionally been used, such as azathioprine 100–150 mg/day,[61] low-dose methotrexate (initially 15–25 mg once a week),[62] and mycophenolate mofetil 2 g/day.[63]

Cyclosporine (ciclosporin) was used in four patients with vesicular pompholyx. A starting dosage of at least 2.5 mg/kg/day was necessary to induce a response. Relapse is common after withdrawal of the treatment.[64] These data are not sufficient to recommend any of the systemic therapies ahead of any of the others based on their efficacy and safety profile.

4.2.3 Retinoids

Alitretinoin (9-cis-retinoic acid) is a retinoid for systemic use. It has been described as a panagonist since the compound activates retinoid X receptors as well as all retinoic acid receptors. Headache and mucocutaneous adverse effects are seen, as with other oral retinoids. Because of teratogenicity, all oral

retinoids are strictly contraindicated in premenopausal women who are not using sufficient contraception.[65]

In a European, randomized, double-blind, placebo-controlled, multicenter trial, 319 patients with chronic hand dermatitis refractory to standard therapy were evaluated.[66] In a four-armed study design, patients received either placebo or alitretinoin at dosages of 10 mg, 20 mg, or 40 mg once daily for 12 weeks. Responders were followed up for another 3 months. Alitretinoin led to a significant, dose-dependent improvement of the disease status in up to 53% of patients, with an up to 70% reduction in disease symptoms and signs. In this trial, a group of 70 patients with pompholyx was included; the response rate in this subgroup was not statistically different between placebo and alitretinoin.[66]

A recent paper reported the results of a randomized, double-blind, placebo-controlled, multicenter trial in ten European countries and in Canada.[67] A total of 1032 patients with refractory chronic hand dermatitis (eczema) were included. The treatment was organized in three arms, i.e. alitretinoin 10 mg or 30 mg or placebo once a day for 24 weeks. Clear or almost clear hands were achieved in 48% of alitretinoin-treated patients versus 17% of placebo recipients. There were more responses in the 30 mg group compared with the 10 mg group. The study included a group of 377 patients with pompholyx. In this group, the response rate was 16% in the placebo recipients, 23% in the patients receiving alitretinoin 10 mg/day, and 33% in the group receiving alitretinoin 30 mg/day.[67]

In conclusion, although oral alitretinoin is effective in recalcitrant hand eczema in general, it is of limited efficacy in pompholyx. A combination therapy with topical corticosteroids could achieve higher response rates; however, this has yet not been evaluated in a controlled clinical trial.

4.2.4 Biologics

A 40-year-old woman with a 6-year history of recalcitrant atopic cheiropompholyx was treated with subcutaneous injections of the tumor necrosis factor-α inhibitor etanercept 25 mg twice weekly.[68] At a 6-week follow-up, the pompholyx had cleared. Remission was sustained for 4 months, after which time the patient experienced a flare-up. The dosage of etanercept was doubled, but was ineffective and was, therefore, eventually discontinued.[68] Further investigations are needed with the use of biologics for pompholyx.

4.2.5 Antihistamines

Antihistamines have been used to control accompanying pruritus, although there is no proof of their efficacy in pompholyx. Sodium cromoglicate (disodium cromoglycate) was found to be more effective in the treatment and prevention of nickel-sensitive pompholyx than a low-nickel diet by diminishing the intestinal nickel uptake.[69] The use of sodium cromoglicate raises several questions. First, since only a proportion of pompholyx patients are nickel sensitized, would this drug be ineffective in the other patients? Second, how long should sodium cromoglicate be used for secondary prevention in nickel-sensitized patients? Probably as a life-long treatment, but there are no scientific data to support long-term prevention.

4.3 Botulinum Toxin

Botulinum toxin A (BTXA) shows potent anhidrotic activity, and sweating is an aggravating factor in pompholyx. In a pilot study with left-right comparison, intracutaneous injection of BTXA (100 U of Botox® [Allergan, Inc., Irvine, CA, USA] in one palm on day 1) was used in addition to topical corticosteroids. Among the six patients who completed the 8-week trial, the DASI was significantly lower, and itching and vesiculation disappeared earlier in the hand treated with BTXA.[70]

Another study involving ten patients compared the effect of BTXA alone (mean dose of 162 U of Botox® per palm on one hand) with the untreated side as control. Seven of ten patients experienced a good to very good effect on vesicular pompholyx and a decrease in itching.[71] Other reports also mentioned the ability of BTXA to improve itch, vesiculation, and erythema.[72,73] Pain on injection is a common adverse effect that limits the use of BTXA in general.

4.4 Phototherapy and Photochemotherapy

Selective UVB phototherapy (300–320 nm) combined with balneotherapy was found to be more effective in palmoplantar dermatoses, including pompholyx, than broad-spectrum UVB (280–320 nm).[74] Narrow-band UVB (311 nm) and UVA-1 (340–400 nm) irradiation have been proven to be superior to broad-band UVB for certain indications.[75]

Systemic photochemotherapy with PUVA (320–400 nm) is effective in vesicular pompholyx, although it has the disadvantage of generalized photosensitivity and adverse effects on the gastrointestinal tract by the photosensitizer methoxsalen (8-methoxypsoralen; 8-MOP). To reduce the risk of unwanted adverse effects, there have been modifications to the classical systemic PUVA therapy, such as bath-PUVA and cream-PUVA. For bath-PUVA, 8-MOP is used in a water bath prior to irradiation. Cream-PUVA employs a cream containing the photosensitizer applied 20 minutes prior to UV exposure.

Bath-PUVA is an effective treatment modality for palmoplantar eczema. However, smokers with vesicular pompholyx are less sensitive to bath-PUVA than non-smokers, and a complete remission is less realistic as long as the patient continues to smoke.[30]

Cream-PUVA is as effective as bath-PUVA in the treatment of palmoplantar dermatoses.[76]

Topical PUVA with 8-MOP has been compared with UVA in a randomized, double-blind, within-patient trial. Twelve patients with vesicular pompholyx completed 8 weeks of treatment. There was no statistical difference in the improvement between topical PUVA and UVA alone.[77]

UVA-1 irradiation was found to be effective in vesicular pompholyx of the palms in an uncontrolled trial.[78] UVA-1 irradiation (40 J/cm^2) given five times a week was compared with placebo in a double-blind, controlled trial of vesicular pompholyx. UVA was more effective than the placebo.[79] High-dose UVA-1 irradiation (maximum single dose of 130 J/cm^2; cumulative dose of 1720 J/cm^2) was as effective as cream-PUVA in a left-right study of 27 patients with vesicular pompholyx as measured by the DASI.[80]

Table III. Evidence-based medicine in pompholyx

Treatments	Evidence level[a]
Botulinum toxin A	3[b]
Immunosuppressants (azathioprine, methotrexate, cyclosporine [ciclosporin], mycophenolate mofetil, corticosteroids, etc.)	4a[b]
Retinoids (alitretinoin)	2
PUVA	2
Radiotherapy	4a
Selective UVB phototherapy	3
Tap water iontophoresis	3[b]
Topical corticosteroids	2
Topical calcineurin inhibitors	2
Topical bexarotene plus mid-potency corticosteroid	2
UVA-1	2

a Levels of evidence-based medicine in clinical studies. Level 1: evidence is available for meta-analysis from several randomized controlled studies; level 2: evidence is available from at least one randomized controlled trial; level 3: evidence is available from good methodologic studies without randomization; level 4a: evidence is available from clinical case reports; level 4b: this represents a consensus of respected experts or expert committees.

b Mostly with topical corticosteroids.

PUVA = psoralen plus UVA.

Table IV. General advice for hand and foot care for patients with pompholyx

Wash hands and feet as infrequently as possible
Avoid soaps, and direct contact with household cleansers, fresh fruits, and fresh meat
Dry hands and feet carefully
Use protective gloves for hair care, including shampooing
Use protective plastic gloves only with white cotton gloves beneath
Use cotton socks and change them regularly
Stop smoking

4.5 Radiotherapy

Grenz rays and conventional superficial x-rays have been used either alone or in combination with topical corticosteroids for refractory hand dermatitis (eczema). In a double-blind study, conventional x-rays (300 rad) were superior to Grenz rays.[81] Complete remission of pompholyx is also possible with low-dose external beam megavoltage radiation.[82]

4.6 Tap Water Ionotophoresis

Tap water iontophoresis is an effective measure to control excessive sweating of palms and soles. In a study of 20 patients with pompholyx, it was more effective than corticosteroid-free topical treatment alone.[83]

In a study with 20 pompholyx patients, tap water iontophoresis resulted in faster relief of symptoms, particularly itch, than topical corticosteroids alone. There was a statistically significant difference in the relapse-free interval, i.e. 6 versus 2 months.[84]

5. Conclusion

It is surprising that although pompholyx is a common disease, relatively few randomized controlled trials of its treatment have been performed and published. For an overview on evidence-based medicine for pompholyx see table III. The current best treatment for pompholyx is a combination of topical and systemic therapy. In practice, the most common combination used is topical and short-term systemic corticosteroids. However, no randomized study has been published in the international medical literature for such a treatment. Good proof of evidence is available for topical drugs such as corticosteroids, calcineurin inhibitors, and bexarotene.

Among phototherapies, PUVA and high-dose UVA-1 seem to be equal in efficacy, with probably a more balanced risk-

benefit ratio for UVA-1. However, the long-term risks are not well known, and the equipment is more expensive, for high-dose UVA-1. Systemic PUVA does not offer any benefit compared with topical PUVA and UVA-1.

If there is aggravation of the disease by focal hyperhidrosis, tap water iontophoresis and BTXA have been proven to not only improve abnormal sweating but also to have beneficial effects on pompholyx. A better understanding of the mechanisms of action of botulinum toxin may be helpful in developing a new class of anti-inflammatory drugs.

In systemic therapy, corticosteroids remain the cornerstone of treatment, although alitretinoin has recently shown efficacy. In recalcitrant cases, a combination of corticosteroids with immunosuppressants or a complete switch to immunosuppressants may be useful but none of the systemic pharmacotherapies (including biologics) has been evaluated in controlled trials.

Pharmacologic treatment (and other treatments as well) should be accompanied by general advice for patients with pompholyx (table IV).

The current situation in pompholyx demonstrates the urgent need for controlled trials, in particular for systemic treatment options.

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