

Acute and Recurrent Vesicular Hand Dermatitis

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KEYWORDS

- Pompholyx • Dyshidrosis • Dyshidrotic eczema
- Systemic contact dermatitis • Nomenclature

INTRODUCTION AND NOMENCLATURE

The nomenclature of recurrent, vesicular hand dermatitis, including pompholyx and dyshidrotic eczema, is confusing. In 1873, Tilbury Fox^{1,2} described dyshidrosis as an eruption of deep-seated vesicles on the sides of the fingers and on the palms with little or no clinical sign of inflammation. Three years later, in 1876, Hutchinson described the same features in characterizing cheiopompholyx.³

Initially, when such eruptions were seen in association with hot weather, they were thought to be a manifestation of abnormal sweating, or were associated with “nervousness.” It became clear; however, that the vesicles were in no way connected to the sweat ducts, and the condition has since by most authors been considered to be a morphologic variant of hand eczema.

Kutzner and colleagues⁴ examined 93 biopsies of vesicles from patients with vesicular hand dermatitis and found spongiotic dermatitis and no relationship to the acrosyngia. Simons⁵ and Shelley⁶ had similar findings.

Storrs⁷ has reviewed the nomenclature and stresses that in the strictest sense, the term *pompholyx* refers to a rare, severe eruption of vesicles and bullae on the palms and occasionally also on the soles. Rather than recurrent vesicular hand eczema, she prefers “chronic vesicular hand eczema.” She concludes, however, that this spectrum of dermatitis is probably best described as acute and recurrent vesicular hand dermatitis as suggested in a review by Veien and Menné.⁸

The morphologic diagnosis of recurrent, vesicular hand eczema does not have 1 distinct

etiology. There may be several causes of this morphology, including allergic contact dermatitis, other types of contact dermatitis, dermatophytid, other id reactions, and other endogenous skin diseases such as atopic dermatitis. For a considerable number of patients, it is not possible to establish an etiology.

In this review, the terminology used in the individual papers will be cited. Suggestions for descriptive nomenclature are given in the final section.

CLINICAL APPEARANCE

Among the authors who have dealt with this condition, there is reasonable agreement that vesicular hand eczema is primarily located on the palms, the palmar aspects of the fingers, and the sides of the fingers and that the condition is eruptive. There is less agreement on how common it is, whether or not there may be dermatitis on areas of the body other than the palms and soles, and whether inflammatory lesions should be included.

Fox¹ includes more than just a palmar eruption in his description of dyshidrosis. He includes “more or less dermatitis” in his description and states that “I have seen the back of the hand and the palm with bullae.” He also writes that “the eruption about the hand or hands may be complicated by a rash, more or less general over the body” and that “sometimes awfully painful surface is left behind and becomes chronic.” The condition is described as being of common occurrence. A patient with palmar dyshidrosis as well as lesions on the forearms and upper arms is also described.²

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Hutchinson³ describes less severe forms of the disease cheiropompholyx as “tolerably common, while severe forms are rare.” In his words, “the hands are the first part affected; the feet come next, and in a few instances, a rash appears over the whole body.” Two of the 3 patients had lesions on parts of the body other than the hands.

The author of the current review considers the severe forms of acute vesicular palmar dermatitis to be rare. When they do occur, a cause is seldom found. Morphologically, the condition may present only on the skin of the palms with sharp delineation toward the skin of the forearms and the dorsal aspects of the hands. The palmar skin has an unexplained, curious ability to produce lesions that do not extend to dorsal or forearm skin (**Fig. 1**).

Acute vesicular, palmar dermatitis may present as large, vesicular and/or bullous lesions on non-inflamed skin (**Figs. 2 and 3**), but inflammation is often seen during the course of the eruption. The question of inflammation is, therefore, only of interest in early lesions.

A very pruritic vesicular eruption of limited intensity is a much more common clinical manifestation. It is often seen most clearly on the sides of the fingers, either without inflammation (**Fig. 4**) or with slight inflammation (**Fig. 5**). If frequent vesicular eruptions occur, for example on the palms, the lesions do not have time to heal completely between attacks. Residual scaling may, therefore, be seen and the skin may become visibly inflamed (**Fig. 6**). Careful inspection with a magnifying glass



Fig. 1. Vesicular hand eczema with the involvement of palmar skin but not the skin of the forearms.



Fig. 2. Vesicular and bullous hand dermatitis.

may be necessary to detect the vesicles (**Fig. 7**). At a casual glance, the dermatitis may look like chronic hand eczema. As described by Hutchinson³; a similar eruption may be seen on the soles, although less often than on the palms.

In some patients sensitized to nickel, cobalt, or chromate, the vesicular response can be reproduced experimentally by oral challenge with the hapten in a placebo-controlled fashion (**Figs. 8 and 9**). Time for response is also revealed in such experiments, with vesicular eruptions seen 24 to 48 hours after ingestion of the hapten. A severe, bilateral, vesicular, and bullous eruption was seen in 1 woman with nickel allergy after patch testing with nickel (**Fig. 10**).

Palmar eruptions may be the only manifestation. However, many patients who are contact sensitized to the aforementioned metals will, on contact with the metals, experience a vesicular flare on the hands as well as a flare-up at the sites of recent, previously positive patch tests to the metals. Patients sensitive to nickel may experience flares at sites of contact with nickel.⁹

DIFFERENTIAL DIAGNOSIS

Superficial peeling of the skin—dyshidrosis lamellulosa sicca or recurrent, palmar peeling—may



Fig. 3. Vesicular and bullous hand dermatitis.



Fig. 4. Vesicular hand dermatitis without inflammation on the side of a finger.

mimic recurrent, vesicular hand eczema. This superficial peeling does not have fluid-containing vesicles. It is so superficial that initially small dry scales are seen. The individual scales break and become discrete annular scaling (**Figs. 11 and 12**). If multiple eruptions occur over a short period of time, the stratum corneum thins, resulting in erythema and thin, sensitive skin on the palms.

Pustular eruptions like palmoplantar pustulosis may have an early vesicular stage, but pustules usually develop within a few days.⁹ Palmoplantar pustulosis may present with pruritus at onset, but the pruritus is mild and transient, as opposed to the intensely pruritic vesicles associated with recurrent vesicular hand eczema.

Infantile acropustulosis is a vesiculopustular dermatosis that may be seen on the palms, soles, and also on the dorsa of the feet of infants.^{10,11}

As in allergic contact dermatitis caused by direct contact with the hapten, vesicular eruptions seen in protein contact dermatitis are limited to the areas of contact with the offending item.

Bullous pemphigoid may have a vesicular palmar and/or plantar eruption as the presenting symptom.^{12,13} The lesions may be hemorrhagic.^{14,15} Similar findings have been made in linear IgA diseases and in herpes gestationis.^{16,17}



Fig. 5. Vesicular hand dermatitis with moderate inflammation on the side of a finger.



Fig. 6. Vesicular hand dermatitis with inflammation and scaling mimicking chronic hand dermatitis.

THE MECHANISM AND SPECIFICITY OF VESICULAR ERUPTIONS ON THE HANDS AND FINGERS IN RELATION TO SYSTEMIC CONTACT DERMATITIS

The pathomechanism involved in vesicular palmar eruptions is largely unknown. Dermatopathology has shown that the vesicles are part of a spongiotic type of dermatitis, and it is assumed that the vesicles remain intact because of the thick stratum corneum of palmar skin. In other areas of the



Fig. 7. A close-up view of the patient in **Fig. 6**. Note vesicles.



Fig. 8. Sides of the fingers of a chromate-allergic man before placebo-controlled oral challenge with 2.5 mg of chromium given as 7.1 mg potassium dichromate.

skin, spongiotic vesicles would break after minimal trauma.

Deliberate exposure to nickel either by immersion of a finger in a nickel solution or patch testing on the fingers resulted in a vesicular eruption in a limited number of nickel allergic patients.¹⁸

In placebo-controlled trials, oral challenge with nickel in patients sensitive to nickel with recurrent, vesicular hand eczema reproduced the hand eczema on a regular basis.¹⁹ In another study, a flare-up of dermatitis was often seen at the site of a previous, positive patch test to nickel or at the site of current or previous nickel dermatitis.²⁰ De novo vesicular hand eczema has been seen in patients sensitive to nickel or cobalt treated for chronic alcoholism with disulfiram.²¹ Disulfiram is known to mobilize nickel and initially causes a high serum level of nickel.^{22,23} De novo vesicular hand eczema has also been seen in persons with contact sensitivity to neomycin who take oral neomycin in spite of the fact that neomycin is very poorly absorbed.^{24,25}

This evidence leaves little doubt that vesicular eruptions on the hands can be a specific phenomenon and an example of systemic contact dermatitis in contact-sensitized persons. A similar, unknown mechanism may explain vesicular



Fig. 9. The same patient as in Fig. 8, 2 days after the oral challenge.



Fig. 10. A woman with nickel allergy developed a symmetric, bullous eruption on the palms after patch testing with nickel.

dermatophytid of the hands. A positive trichophytin test should be required for making this diagnosis.

To clearly define a vesicular palmar eruption, it is probably necessary to look more specifically at the immune reactions when such an eruption occurs, for example in oral challenge experiments. Which cells are present, and what is the cytokine profile in lesional tissue during an eruption? Comparison of the immune reactions in the palm when a vesicular palmar eruption occurs and events that might be taking place in the neighboring forearm skin could explain why vesicular eruptions seen after oral challenge, for example in patients sensitive to nickel, occur only on palmar skin with no clinical evidence of immune response in the adjacent skin of the forearm or on the dorsum of the hands (see Fig. 1).

DETERMINATION OF SEVERITY

Several instruments have in recent years been developed to assess the severity of hand eczema. Coenraads and colleagues²⁶ have developed a photographic guide with images of the various stages of hand eczema: (1) clear, (2) almost clear, (3) moderate, (4) severe, and (5) very severe.



Fig. 11. Dyshidrosis lamellosa sicca or recurrent palmar peeling.



Fig. 12. Dyshidrosis lamellosa sicca or recurrent palmar peeling. Note annular scaling.

Expert dermatologists evaluated 28 patients with hand eczema in order to validate the guide. There was good interobserver reliability and reproducibility on retesting. A modified photographic guide for use by patients with hand eczema has been developed by Hald and colleagues.²⁷

A point-based score system, the hand eczema severity index (HECSI), includes a score for the number of vesicles.²⁸ The severity of vesicular hand eczema can be evaluated with the HECSI, something that is not possible using the photographic guide.

In the Dyshidrotic Eczema Area and Severity Index (DASI) developed by Vocks and colleagues,²⁹ scores are given for number of vesicles, erythema, desquamation, and itching. The index was found to be useful in 2 clinical trials.

REVIEWS

Menné and Hjorth³⁰ reviewed pompholyx-dyshidrotic eczema defined as an acute or chronic vesicular eruption on the hands and feet. Based on twin studies, no genetic factors were found to be an important cause of the eczema. Allergic contact dermatitis, in particular systemic contact dermatitis, was found to be an important cause.

Lambert³¹ used the term *dysidrose palmo-plan-taire* and distinguished between dermatitis with (1) a known etiology such as an id reaction caused by dermatophytes or other microorganisms, allergic contact dermatitis, or drug reactions and (2) essential dyshidrosis associated with atopy and possibly with sweat retention.

Veien and Menné⁸ introduced the term *acute and recurrent vesicular hand dermatitis*. Patients who had dermatitis in areas other than the hands and feet were also included and it was stressed that the condition is a non-specific reaction pattern that may have many causes.

Lofgren and Warshaw³² distinguished between pompholyx as a rare condition characterized by the explosive onset of large bullae on the hands and dyshidrosis or dyshidrotic eczema as a common, chronic, recurrent condition with 1 mm to 2 mm vesicles on the palms, soles, and/or lateral aspects of the fingers. Treatment options were reviewed extensively.

EPIDEMIOLOGY

Thelin and Agrup³³ examined a 1-year series of 68 patients with pompholyx in the outpatient clinic of the dermatology department at the University Hospital in Lund, Sweden. The 68 cases were an estimated 1 percent of all patients referred to the department. Unfortunately, no clear inclusion or exclusion criteria were provided.

As a part of a population-based investigation in Sweden, Agrup found that acrovesiculatio recidivans was present in 6% of the hand dermatoses examined.³⁴

In a population-based study by Meding,³⁵ 5% of 1457 patients were diagnosed with pompholyx. Patients with allergic contact dermatitis, irritant contact dermatitis, and atopic dermatitis were excluded from the study.

Among 522 consecutive patients with hand eczema seen in a private dermatology clinic that serves as a secondary referral center, recurrent vesicular hand eczema was the most common morphologic diagnosis, irrespective of etiology in 54 men (31%) and 173 women (50%).³⁶

It is obvious that the variation in frequency of vesicular hand eczema in the aforementioned studies is at least in part because of differences in the definition of the condition.

Other studies of patients with acute or recurrent vesicular hand eczema have typically dealt with series of patients seen in the outpatient clinics of hospital departments of dermatology.

CAUSES

Young³⁷ described 75 patients and compared them to 55 controls. He used the term *dysidrotic (endogen) eczema* and listed the synonyms *dysidrosis*, *dysidrosiform eruption*, *pompholyx*, and *cheiro-pompholyx* for describing a symmetric eruption, primarily of vesicles (or bullae) on the palms and soles.

Forty-five percent of Young's patients had 1 or more positive intracutaneous tests to inhalant or food allergens compared with 5.5% of the controls. Twenty-eight percent of the patients and 3.5 percent of the controls had a positive intracutaneous test and a family history of atopy. Similar findings among 68 patients with dyshidrosis were made by Shuppli.³⁸

Twenty five of the patients (33%) in Young's study experienced seasonal variation in the frequency of eruptions. Nineteen of the patients had eruptions of vesicular hand eczema in the spring and summer months. Five of the 19, compared with 3 of 56 who did not experience flares during the spring and summer had a positive intracutaneous test to pollen. Vesicular hand eczema was provoked by the injection of a pollen extract in 2 patients.

Menighini and Angelini³⁹ examined 364 consecutive patients with pompholyx of the palms and/or soles. Pompholyx was defined as a recurrent or chronic eruption of deep-seated vesicles on non-erythematous skin of the palms and/or soles but a small proportion of patients had inflammatory skin changes. All 364 patients were patch tested, and for 213, intradermal tests with among other substances such as candidin, epidermophytin, or trichophytin were performed. Thirty percent had 1 or more positive patch tests, mostly to topical drugs. Only 7 patients reacted to nickel. Two hundred eighteen of the patients were men, and 146 were women. Skin testing with microbial antigens contributed little to a final etiologic diagnosis.

Lodi and coworkers⁴⁰ examined 104 patients with a clinical diagnosis of pompholyx defined as crops of clear, deeply seated, sago-like, often very itchy vesicles and/or bullae with no erythema. These patients were compared with 208 controls matched for age and sex who had no eczema. Fifty percent of the patients, compared with 11.5% of the controls, had a personal or family history of atopy. Forty-eight percent of the patients and 16% of the controls had 1 or more positive patch tests, most commonly to nickel (20%), whereas 6% of the controls had positive patch tests to nickel. Six of 83 patients with negative patch tests to nickel reacted to oral challenge with 5.6 mg nickel but not to a placebo. Biopsies obtained from all 104 patients showed spongiotic dermatitis with lymphocytes scattered throughout the epidermis.

Castelain⁴¹ compared the results of his investigation of 145 patients with "Les Dysidroses" with the results of other similar studies. Twenty-six percent of the patients had what he described as atopic "dysidroses." Ten of Castelain's patients experienced flares of their dermatitis after oral challenge with nickel, cobalt, and/or chromate.

One patient reacted to oral challenge with balsam of Peru.

A likely etiologic diagnosis was made for 99 of the 145 patients included in Castelain's study, whereas for 46 patients, no specific diagnosis could be made.

Shelley⁶ conducted experimental studies to determine the role of the sweat glands in dyshidrosis (pompholyx) and found no relationship. The condition defined as acute, recurrent, non-inflammatory vesicular eruption was strictly limited to the palms and/or soles and followed a non-specific reaction pattern that could be induced by drugs or id reactions or be psychosomatic.

Guillet and colleagues⁴² examined 120 patients referred for pompholyx. There were no clear inclusion criteria, and the term *allergic contact pompholyx* was introduced as the most common cause of the eczema seen in 81 of the 120 patients. It is of concern that the most common, relevant positive patch test was to shower gel and the second most common was to shampoo.

Pitché and colleagues⁴³ performed a case-control study of 100 patients with pompholyx and 200 controls. In a multivariate analysis, atopy and tinea pedis were found to be the only factors statistically associated with pompholyx.

In a Chinese family, a gene associated with pompholyx was found on chromosome 18.⁴⁴

RELATIONSHIP TO ATOPY

Schwanitz⁴⁵ performed a detailed study of 58 patients with dyshidrosis and coined the term "Das atopische Palmoplantarekzem." An association to smoking was found and considered the entity to be a variant of atopic dermatitis.

Lodi and colleagues⁴⁰ found personal and familial atopy in 50% of their patients with pompholyx compared with 11.5% in controls.

Norris and colleagues⁴⁶ observed pompholyx in 8 of 50 adult patients admitted to hospital for the treatment of atopic dermatitis. No explanation was found for the eruptions but speculated that the high temperature of the ward could have caused the condition.

Bryld found no statistical association between atopy and vesicular hand eczema in his study of twins⁴⁷ nor did Edman⁴⁸ among 153 patients with palmar eczema.

CONTACT DERMATITIS, DRUG REACTIONS, AND RECURRENT VESICULAR HAND ECZEMA

Allergic and irritant contact dermatitis caused by external contact with the offending items has also been described as the cause of vesicular

hand eczema. An irritant reaction to soluble oil was the suspected cause in 1 series of patients.⁴⁹ In 1 patient an irritant reaction following contact with *Dieffenbachia* presented as a vesicular eruption on the palms.⁵⁰

Meneghini and Angelini³⁹ found a number of cases of allergic contact dermatitis to topical drugs among their group of 364 patients with pompholyx.

Of 50 patients clinically suspected of having pompholyx, 20 had 1 or more positive patch tests, most commonly to nickel, potassium dichromate, phenylenediamine, nitrofurazone, and fragrance mix.^{51,52}

De novo eruptions of vesicular hand eczema have been seen in contact-sensitized patients who have ingested the contact allergen. Ekelund and Möller⁵³ gave oral neomycin to 12 patients known to be sensitive to neomycin and saw pompholyx in 3 patients.

A patient sensitive to pyrazinobutazone had a vesicular palmar flare-up reaction when 300 mg of pyrazinobutazone was given orally twice daily for 3 days.⁵³ Oral piroxicam induced vesicular hand eczema in a contact-sensitized patient.⁵⁴

In 1 study, 4 patients sensitive to preservatives in moistened toilet tissue had symmetric vesicular hand dermatitis.⁵⁵ Fungicides used on flowers caused erythematous vesicular palmar dermatitis in a florist.⁵⁶

Eighteen of 20 patients with positive patch tests to sesquiterpene lactone mix had 1 or more positive patch tests to herbal teas. Seventeen of the patients were patch tested because they had long-standing hand eczema of pompholyx type.⁵⁷

In another study of sesquiterpene lactone-sensitive patients, Möller and colleagues⁵⁸ patch tested 17 patients with ragweed, recently discovered in Sweden. Sixteen of the patients had chronic hand eczema of pompholyx type. Fifteen of the 17 reacted to ragweed. Fifteen of the 16 with pompholyx had a flare of the pompholyx after patch testing with ragweed.

An id-like vesicular eruption on the palms was seen in a patient with allergic contact dermatitis on the ankle as a result of a neoprene ankle support.⁵⁹

Thyssen and Maibach⁶⁰ reviewed drug-elicited systemic contact dermatitis and noted that pompholyx, baboon syndrome, and a macular-papular rash occurred in the same patients, suggesting related pathomechanisms.

IMPLANTED METALS

Metals used for prostheses, wires, screws, and plates used to repair fractures or for orthodontic

purposes have been suspected to have cutaneous side effects. The alloys used in these appliances have varied over time. Current usage does not seem to constitute a significant problem with regard to vesicular hand eczema.

In the older literature there are, however, rather convincing case reports of such side effects. For example, widespread dermatitis, including a vesicular palmar and plantar eruption, was seen in a chromate-sensitive patient after insertion of a metal dental plate. The dermatitis disappeared after the plate was removed and recurred when the plate was reinserted.⁶¹

A 14-year-old boy developed palmar and plantar eczema after orthodontic treatment with bands of stainless steel containing chromium and nickel. He had positive patch tests to nickel and cobalt. The dermatitis faded after discontinuation of the orthodontic treatment.⁶²

Three girls who were seen by a dermatologist because of vesicular hand dermatitis wore steel wires as part of their orthodontic treatment. The wires contained nickel and chromium. One had a positive patch test to chromate and reacted to placebo-controlled oral challenge with 2.5 mg chromium given as potassium dichromate. Two were patch test negative. One of the 2 had a positive reaction to oral challenge with 2.5 mg nickel, the other to oral challenge with chromate. The dermatitis of 2 of the 3 girls faded after discontinuation of orthodontic treatment.⁶³

Two patients sensitive to nickel developed vesicular palmar dermatitis after the use of infusion needles shown to release nickel.⁶⁴

Three of 4 patients, sensitive to nickel developed pompholyx-like hand eczema when metal clips were used for closure after an operation. All 3 patients had positive reactions to patch tests with the clips.⁶⁵

A man whose ankle fracture was repaired with a nickel-chromium steel plate developed vesicular hand eczema 1 month after the operation. Patch testing showed a +++ reaction to nickel and a +reaction to chromate. The hand eczema improved upon removal of the steel plate.⁶⁶

A patient who developed vesicular hand eczema after a titanium plate and screws were used to repair a fractured hand had negative patch tests to titanium but a lymphocyte transformation test to titanium was positive.⁶⁷

ORAL INGESTION OF METALS

After Christensen and Möller in 1975⁶⁸ found that 9 of 12 women sensitive to nickel had flares of vesicular hand eczema after an oral dose of nickel, numerous studies have confirmed their results.²⁰

The flare-up of vesicular hand eczema in patients sensitive to nickel appears to be a specific clinical expression of their disease. This view is supported by a study of 202 patients with vesicular hand eczema and negative patch tests who were challenged orally with nickel, cobalt, and chromate. Flares of vesicular hand eczema after oral challenge with nickel were seen primarily in young women, whereas men reacted more often to chromate.⁶⁹ Some of the women who reacted to nickel had a history of nickel sensitivity, indicating that some of the patch tests may have been false negative. In contrast to this study, a similar study among patients who had dermatoses other than vesicular hand eczema had no vesicular flares after oral challenge with the metals nickel, cobalt, and chromium.⁷⁰

After intoxication with nickel from a dialysis system, none of 23 patients developed vesicular hand eczema. The nickel concentration in plasma was approximately 3 mg/L.⁷¹ None of 20 workers who accidentally ingested up to 2.5 g of nickel in drinking water developed vesicular hand eczema.⁷² Symptoms of intoxication were nausea, abdominal pain, vomiting, diarrhea, coughing, and shortness of breath.

Whether or not patients sensitive to nickel react to oral challenge with nickel is probably a question of dose. Few patients react to 0.5 mg nickel, about half react to 2.5 mg nickel, whereas most patients react to 5 mg or more of nickel.⁷³

A flare-up of vesicular hand eczema has also been seen after deliberate ingestion of food with high nickel content.⁷⁴

The amount of nickel in serum in the general population is less than 0.3 mg/L, and the upper limit is 1.1 mg/L.⁷⁵ In sweat from the arms, Omokhodion⁷⁶ found a concentration of 69.9 mg/L of nickel.

Among a group of 25 patients with pompholyx, the perspiration volume was found to be 2.5 times higher than age-matched controls without pompholyx. Among the patients sensitive to metal in this group, most had vesicular flare-ups on the hands after oral challenge with the metal.⁷⁷

The studies mentioned earlier indicate that nickel excreted in sweat may reactivate vesicular hand eczema and that this response can be reliably reproduced by oral challenge with nickel.

NICKEL AND COBALT

Thirty-one of 49 patients with nickel allergy (63%) reacted to oral challenge with 2.24 mg of nickel in a controlled study. Fifteen of the patients who reacted to nickel had vesicular hand eczema.⁷⁸

One patient developed a *de novo* pompholyx reaction after oral challenge with 3 mg of nickel.

This patient was 1 of 30 patients who took part in a study of recall reactions of positive nickel patch tests after oral challenge with a placebo, 1 mg of nickel, and 3 mg of nickel. The study showed a correlation between the intensity of a previously positive patch test and the flare-up reaction.⁷⁹

Veien and colleagues⁸⁰ performed a placebo-controlled study of oral challenge with 2.5 mg nickel and 1 mg cobalt in 144 patients with positive patch tests to nickel and/or cobalt and morphology of dermatitis for which a systemic cause of the dermatitis was suspected. Seventy-five of the 144 patients had flares of their dermatitis after challenge with nickel and/or cobalt.

Of 97 patients with positive patch tests only to nickel, 31 reacted only to oral challenge with nickel, 8 reacted to both nickel and cobalt and 8 reacted to cobalt.

Four of 34 patients with positive patch tests to both nickel and cobalt reacted to oral challenge with nickel, 5 reacted to nickel and cobalt and 10 to cobalt alone. Seven of 13 with positive patch tests to cobalt alone reacted only to oral challenge with cobalt, 1 reacted to nickel and cobalt and 1 reacted only to nickel.

This study indicates that cobalt may be of significance in maintaining the dermatitis of patients who have positive patch tests to both nickel and cobalt. These results are supported by animal experiments that showed increased reactivity following oral challenge with the hapten in guinea pigs that were sensitized to both nickel and cobalt than in non-sensitized animals.⁸¹

Fifty-three of the 144 patients in the aforementioned study⁸⁰ had recurrent vesicular hand eczema. Of the 13 patients who had positive patch tests to cobalt alone, 6 had recurrent vesicular hand eczema. Three of the 6 reacted to oral challenge with cobalt.

The results prompted a study of patients who were sensitive only to cobalt. Four of 6 patients sensitive to cobalt with vesicular hand eczema had flares of their hand dermatitis after placebo-controlled oral challenge with 1 mg cobalt. Three of the 4 who reacted to cobalt experienced improvement of their dermatitis after following a low-cobalt diet.⁸²

In a recent review of the literature on cobalt and dyshidrotic eczema and cobalt in food, Stuckert and Nedorost⁸³ provide a detailed low-cobalt diet.

A cobalt-sensitive patient who was treated with disulfiram for chronic alcoholism developed vesicular hand eczema 1 to 2 days after initiation of this therapy.⁸⁴

Several case reports have supported the observation of flare-ups of nickel dermatitis after the initiation of disulfiram treatment of alcoholism in

patients sensitive to nickel.⁸⁵ Such flare-ups have included vesicular hand dermatitis.²²

The fact that disulfiram chelates nickel has been used therapeutically. Groups of patients sensitive to nickel with vesicular hand eczema have been treated with a daily dose from 50 mg to 300 mg of disulfiram. Most of the patients initially experienced flares of their dermatitis, but in several series of patients, the treatment proved effective.

Fowler found disulfiram to be effective in the treatment of 9 patients with hand eczema and nickel allergy in a double-blind, placebo-controlled, crossover study.⁸⁶ Kaaber and colleagues⁸⁷ found disulfiram to be marginally more effective than placebo in a placebo-controlled trial of 24 patients with nickel allergy and vesicular hand eczema.

Sharma treated 11 patients sensitive to nickel with vesicular hand eczema for 4 weeks with disulfiram as well as a low-nickel diet.⁸⁸ The hand eczema of 10 of the 11 patients cleared completely compared with 1 of 10 patients who received a placebo tablet and no dietary instructions.

Hepatic side effects have limited the use of disulfiram as a routine treatment. In a retrospective study, Kaaber and colleagues⁸⁹ studied 61 patients sensitive to nickel with hand eczema who had been treated in 63 treatment series with 50 mg to 400 mg disulfiram for 4 to 56 weeks. Eleven patients developed biochemical evidence of hepatotoxicity. Five had clinical evidence of hepatitis. For 4 of the patients this was verified by liver biopsy. In 29 treatment series, the dermatitis cleared, in 19 series it improved, and in 15 series no change was seen.

Pigatto⁹⁰ found that 1500 mg to 2000 mg of disodium cromoglycate given 3 times a day reduced vesicular palmar dermatitis in patients sensitive to nickel. He suggested that these patients be treated with a combination of diet treatment and disodium cromoglycate.

Nickel is one of the most common metals in the earth's crust, and it is present to a varying degree in foodstuffs derived from plants and also as a contaminant from the processing of some foods. In a modified meta-analysis of the data on experimental oral exposure to nickel in patients sensitive to nickel, Jensen⁷³ reviewed 17 studies of oral challenge with nickel in such patients. Nine of the studies were included in a dose-response model. Patients sensitive to nickel reacted to oral nickel in a dose-dependent manner, and a minority of these patients reacted to the amounts of nickel realistically present in food and in drinking water.

Nielsen and colleagues⁷⁴ asked 14 patients sensitive to nickel with vesicular hand eczema to ingest foods rich in nickel. Eleven of them

experienced flares of their vesicular hand eczema. The patients were asked to follow a very special diet and consume large amounts of foods that would not normally be eaten, and the study showed the principle that it is possible for these patients to ingest sufficient amounts of nickel to reproduce their vesicular hand eczema.

It would, therefore, be tempting to try to reduce the nickel intake of such patients, in particular, those whose dermatitis does not clear when external contact with nickel is avoided and whose clinical picture is not easily explained by external contact with nickel.

The first of such diet trials was performed in the 1970s when limited knowledge of the nickel content in food was available. Of 28 patients with vesicular hand eczema and nickel allergy, 17 experienced flares of hand eczema after a single-blind, oral challenge with nickel.⁹¹ Aggravation was determined clinically and by blinded evaluation of close-up photographs taken before and after the challenge. The dermatitis of 9 of the 17 patients improved after 6 weeks on a low-nickel diet. For 11 of the 14 patients for whom information on the level of nickel in urine was available after the 6 week period, urine excretion was reduced.

The diet phase of this study was open. It is extremely difficult to carry out long-term diet trials in a well controlled fashion. The determination of the urinary excretion of nickel compensates to some extent for the lack of controls.

A subsequent study by Veien and colleagues⁹² included 216 patients sensitive to nickel whose dermatitis was suspected to be of endogenous origin. The patients were selected over a 5-year period from among 770 consecutive patients sensitive to nickel diagnosed after patch testing in a private practice of dermatology. The 216 patients were challenged orally with 2.5 mg of nickel given as nickel sulfate in a placebo-controlled, double-blind design. Of the 96 patients who reacted to nickel but not to the placebo, 90 agreed to follow a low-nickel diet for 1 to 2 months. After that period, the patients were seen again. Seventy-three of the 90 patients had obvious or some benefit from the diet. They were asked to continue the diet in a moderate form, to make it more socially acceptable and in order to avoid some of the less healthy effects of the diet.

A questionnaire was mailed to the patients 1 to 2 years after initiation of the diet to enquire about long-term results. Fifty-five of the 64 questionnaires returned could be evaluated. Forty of the 55 patients stated that they had long-term benefit of the diet. Thirty-one of the 55 patients had recurrent vesicular hand eczema. Twenty-one of the 31 had long-term benefit of the diet.

CHROMATE

In relation to hand eczema, chromate has attracted much less attention than nickel. Of 50 patients with pompholyx, Jain and colleagues⁵¹ found that 8% had positive patch tests to potassium dichromate. Yokozeki⁷⁷ found that 25% of 25 patients with pompholyx had positive patch tests to chromate, 16% reacted to cobalt, and 28% to nickel. Oral challenge with 2.5 mg nickel, 1 mg cobalt, or 2.5 mg chromium resulted in flares of hand dermatitis in 4 of 6 patients.

Kaaber and Veien⁹³ challenged 31 patients who had positive patch tests to potassium dichromate with an oral dose of 2.5 mg chromium given as potassium dichromate in a double-blind, placebo-controlled trial. Close-up photographs taken before and 2 days after the challenge were evaluated blindly. Eleven of the 31 patients reacted to dichromate but not to the placebo. Nine of 14 of the patients who had vesicular hand dermatitis reacted to chromate, compared with 2 of 11 who did not have vesicular hand eczema.

A man and a woman challenged with 2.5 mg of chromium in a placebo-controlled study reacted to the challenge with flares of vesicular hand eczema as well as flares of scaly, keratotic eruptions on the elbows.⁹⁴

After oral challenge with 2.5 mg of chromium, a man with vesicular hand eczema developed pruritus on the hands.⁹⁵ When 5 mg of chromium was given, a vesicular eruption was seen after 12 hours.

Thirty patients with positive patch tests to potassium dichromate were challenged orally with 2.5 mg of chromium in a double-blind, placebo-controlled study. Eight of 12 of the patients in the study who had vesicular hand eczema reacted to the oral challenge with chromate but not to the placebo.⁹⁶

RECURRENT VESICULAR HAND ECZEMA AND FOOD INTAKE

Flood and Perry⁹⁷ found that the eczema of 30 patients with recurrent vesicular hand eczema improved after they had followed a strict diet, avoiding foods that were suspected of causing the eczema. The foods they avoided were tuna, tomato, pineapple, American cheese, milk, egg, wheat, lamb, chocolate, and chicken. The results of a trial with another 13 patients with eczematoid dermatitis were published in which they concluded that cutaneous testing was not dependable, and that the only reliable diagnostic test was to watch the reaction after the patients ingest the suspected food.⁹⁸

Rowe⁹⁹ found that food played a role in the dermatitis of 82 of 182 patients with hand dermatitis. Recurrent, vesicular dermatitis in some of the patients was described, but exact number was not given. The dermatitis was referred to as atopic food allergy and cases caused by pollen were also seen.

Livingood and Pillsbury¹⁰⁰ described 26 patients in whom they were convinced food items played an important role in the eczema. Most of the patients had hand eczema, and judging from some of the illustrations accompanying the paper, some patients obviously had recurrent vesicular hand dermatitis.

The eczema of 21 coffee drinkers (>10 cups a day), 9 of whom had recurrent vesicular hand eczema, improved after coffee consumption was reduced. Five of the patients were challenged orally with caffeine without reaction.¹⁰¹

A man who had a positive patch test to garlic experienced vesicular hand eczema after the ingestion of garlic tablets. He also reacted with a flare of the eczema after placebo-controlled oral challenge with garlic.¹⁰²

One of 4 patients with contact allergy to lettuce had a flare of vesicular hand eczema after oral challenge with lettuce.¹⁰³ Paulsen¹⁰⁴ described a similar situation in her thesis. One of 4 patients with contact allergy to lettuce developed vesicular hand eczema within 12 hours of oral challenge with lettuce. An oral challenge was performed with feverfew among 10 patients with contact allergy to feverfew. One of 7 with hand eczema had a positive reaction. No details were given of the type of hand eczema seen.

Dooms-Goossens and colleagues¹⁰⁵ described 3 patients with contact allergy to spices whose vesicular hand eczema flared after ingestion of various spices.

Hjorth¹⁰⁶ described a male physician whose vesicular hand eczema flared after ingestion of a large amount of orange marmalade. The patient had wanted to test the Hjorth's advice to avoid foods that might contain balsams after patch testing had resulted in a positive reaction to balsam of Peru.

In a placebo-controlled, double-blind study, 17 patients were challenged orally with balsam of Peru. Four of 4 patients who had recurrent vesicular hand eczema experienced flares of their hand eczema after challenge with balsam of Peru but not after the placebo.¹⁰⁷

Niinimäki saw a reaction after oral challenge with 1 g balsam of Peru in 8 of 22 patients. A reaction was defined as an increase in the number of vesicles in the palms 1 day after the challenge. All the patients had positive patch tests to balsam of Peru.¹⁰⁸ In

another study, pompholyx reaction was seen in 3 of 7 patients with hand eczema after 71 patients with positive patch tests to balsam of Peru participated in an oral challenge with spices.¹⁰⁹

Pfützner and colleagues¹¹⁰ described 3 patients with systemic contact dermatitis to balsam of Peru. One had dyshidrotic dermatitis on her hands as well as eczema in the armpits and groin.

Twenty-eight of 46 patients treated with long-term dietary restriction of balsams in food, selected from among 834 patients with positive patch tests to balsam of Peru, indicated in a questionnaire that diet treatment was helpful in the long-term control of their dermatitis. Diet treatment was effective for 10 of 16 with vesicular hand eczema.¹¹¹

OTHER CAUSES OF VESICULAR HAND ECZEMA

Hansen and colleagues¹¹² considered the psychosomatic aspects of pompholyx in a study of 20 patients—most of who were women—and concluded that the pathogenesis might be a complication of (pregenital) conversion, with the hands as the affected body part. Ten of the 20 patients had positive patch tests, 6 of them to nickel.

In a speculative paper, Kellum¹¹³ describes the “dyshidrotic personality” as serious-minded, conscientious, dependable, and with an almost compulsive approach to life. Means with which to handle daily tension are suggested.

Biofeedback training was successfully used in treating 5 patients with pompholyx. Three of the patients experienced flares of their dermatitis as a result of stress.¹¹⁴

Skin conductance conditioning by means of biofeedback was used in treating 33 patients with dyshidrotic eczema. Twenty-two of the patients were trained to decrease skin conductance and 11 to increase it. It appeared that training to decrease skin conductance improved the dermatitis.¹¹⁵

A patient with hyperhidrosis and long-standing palmar eczema who was treated with unilateral cervical sympathectomy experienced clearing of hyperhidrosis and eczema on the treated but not on the untreated side. No mention was made of whether the patient had vesicular eczema.¹¹⁶

In spite of the apparent success of biofeedback training, there is no recent literature dealing with the method in relation to patients with vesicular hand eczema.

Photo-induced pompholyx was seen in 5 patients after intense exposure to sunlight.¹¹⁷ In 4 patients, all smokers, dyshidrotic eczema of the feet was followed by painful ulcerations at

the sites of the eczema. Three of the patients also had dyshidrotic eczema on the hands.¹¹⁸

DERMATOPHYTID

A classical cause of vesicular hand eczema is a dermatophytid following tinea of the feet. There is a paucity of literature on this reaction.

Peck¹¹⁹ described in great detail 23 cases of epidermophytid on the hands. Two types of id reactions were noticed; one that was indistinguishable from dyshidrosis or cheiopompholyx and a squamous form which appeared as dyshidrosis lamellosa sicca. The latter form was generally considered to be a sequela of the first.

Histologically, the 2 conditions were similar and had the appearance of dyshidrosis.

Kaaman and Tossander¹²⁰ described 9 patients with dermatophytid on the hands. Examination showed that 7 of the patients had vesicular hand dermatitis, and 2 had erythema and scaling.

Veien and colleagues¹²¹ found 37 cases of dermatophytid. Twenty-seven of 78 patients (35%) with inflammatory *Trichophyton (T.) mentagrophytes* of the feet had a dermatophytid compared with 9 of 128 (7%) of those infected with *T. rubrum*.

A study of 398 individual twins who had fungal cultures made from material from the fourth interdigital space on the right foot showed that patients with tinea pedis had a statistically significant increased relative risk for vesicular hand eczema.⁴⁷

TREATMENT

Current treatment options for dyshidrosis have been expertly reviewed by Lofgren and Warshaw³² and details will, therefore, not be given here. The authors stress that pompholyx on the hands with explosive eruptions of large bullae is a different entity from dyshidrosis. The latter is described as a common eruption of symmetric vesicular eruptions on the palms, soles, and/or lateral aspects of the fingers with no eruptions elsewhere on the body. The vesicles are 1 mm to 2 mm in size and are deep-seated on a non-erythematous base.

One difficulty with this definition appears in the next sentence where it is stated that the course is frequently chronic. The author of the current review has seen these eruptions with no obvious inflammation and has seen them clear within a month. However, pompholyx, as it is defined by Lofgren and Warshaw, and the vesicular eruption for which they use the term *dyshidrosis* are not common conditions. The most common eruption is the repeated eruption at irregular intervals of vesicles that eventually causes inflammation and scaling.

Recurrent vesicular hand eczema is characterized by symmetric, very pruritic vesicular eruptions in the palms, on the palmar aspects and sides of the fingers, and occasionally on the plantar aspects of the feet.

Theoretically, a single, endogenous, vesicular eruption on the hands and fingers would clear spontaneously if the patients sat still and did not use their hands! In the real world, patients do use their hands, and contact with irritants or allergens will aggravate the dermatitis. Recurrent vesicular hand dermatitis is, therefore, most commonly an eczematous eruption and should be treated accordingly.

Topical steroids can suppress the symptoms of recurrent vesicular hand dermatitis and remain the cornerstone of the topical treatment of eczematous hand dermatoses.¹²² There have been reports of the usefulness of calcineurin inhibitors, but their effect is generally limited.¹²³ A review by Wollina¹²⁴ identifies phototherapy as a cornerstone in the treatment of pompholyx.

Glucocorticoids can be a useful systemic treatment, but no studies of the treatment of vesicular hand dermatitis with glucocorticoids have been made. It has been suggested that patients with rare eruptions take 30 mg prednisolone daily for a few days and then stop treatment. This will frequently abort an eruption that it would otherwise take weeks to control with topical treatment.

In an open study of 5 patients with pompholyx, methotrexate was useful in doses from 12.5 mg to 20 mg per week.¹²⁵

Azathioprine was found to be useful in doses from 50 mg to 150 mg per day in 6 patients with pompholyx.¹²⁶

Alitretinoin is a new retinoid with anti-inflammatory properties. In a large controlled study of 1032 patients, it was shown to be effective in the treatment of chronic hand eczema. A group of the patients had pompholyx, and although the cure rate among these patients was not as high as for patients with keratotic hand eczema, the pompholyx of 37 of 111 patients cleared or had almost cleared after 12 weeks.¹²⁷

Oral Psoralen Ultra-Violet A (PUVA) treatments have been shown to be effective in the treatment of vesicular hand dermatitis as have topical PUVA treatments.¹²⁸ Radiation therapy has been effective in small series of patients with vesicular hand eczema.¹²⁹

Iontophoresis is an old treatment for hyperhidrosis. Although it has been shown that pompholyx is a vesicular dermatitis with no direct relationship to the sweat glands, patients with pompholyx often experience excessive sweating.⁷⁷ In a randomized, single-blind,

right-left study, iontophoresis was shown to improve vesicular hand eczema.¹³⁰

Botulinum toxin has been used successfully to treat palmar hyperhidrosis as shown in promising studies involving patients with dyshidrotic eczema.¹³¹ Treatment of the palms is painful and requires a nerve block.

Other treatment modalities like biofeedback techniques, diet treatment, and hyposensitization are discussed throughout the issue. Details are presented in Lofgren and Warshaw's review.³²

SUMMARY

It is difficult to extract meaningful conclusions about the incidence and prevalence of acute and recurrent hand eczema from the literature. This is largely because of the lack of a common definition.

Some authors use the terms *pompholyx* and *dyshidrosis* for the rare, explosive, vesicular, bullous eruptions and include only patients with this condition among those they consider to have vesicular hand dermatitis. Others include moderate types of eruptive vesicular hand dermatitis in their studies. This means that the latter have a much larger percentage of vesicular hand dermatitis in their cohorts of hand eczema patients than the former.

If the morphologic terms *vesicular* and/or *bullous* are used, and the dynamic term *eruptive* is added, it should be possible to define this intriguing eruptive condition on the palms and/or the sides of the fingers. There seems to be no reason to exclude patients who have dermatitis on parts of the body other than the palms and soles. Many of the patients included in the original description of dyshidrosis/cheiropompholyx had dermatitis at sites other than the palms and soles.

The author is of the opinion that the terms *dys-hidrosis* and *dyshidrotic eczema* are best abandoned because all evidence points toward an eczematous reaction that is unrelated to the sweat ducts.

The term *pompholyx* has been used to describe the rare, severe, noninflamed, symmetric vesicular or bullous eruption on the palms and/or soles as well as other types of vesicular eczematous eruptions. *Pompholyx* is best used to describe only the rare, severe, eruptive variant of vesicular hand dermatitis.

Vesicular eczematous eruptions on the palms and sides of the fingers represent a spectrum ranging from

1. the rare, symmetric, acute, severely pruritic, and painful eruption of vesicles and bullae (see **Figs. 2 and 3**)

2. recurrent, usually symmetric eruptions of severely pruritic, non-inflamed vesicles seen on the palms with a distinct demarcation where palmar skin joins the skin of the forearm (see **Fig. 1**) and/or on the sides of 1 or several fingers of both hands (see **Fig. 4**) with recurrences so infrequent that the skin heals between attacks without the development of inflammation
3. an eczematous eruption similar to 2 but with recurrences so frequent that inflammation and scaling are seen. Unless studied through a magnifying glass, this eruption could easily appear to be chronic hand eczema (see **Figs. 6** and **7**). However, tiny clusters of vesicles may be seen, and the patient gives a history of bouts of severely pruritic vesicles. As a result of scratching, the vesicles on thin skin or the sides of the fingers are often broken and look like tiny erosions.

All 3 of the above entities can be described as acute and recurrent vesicular hand dermatitis. Since 1 is rare, the term *recurrent vesicular hand dermatitis* will encompass 2 and 3 and, thereby, most cases of this entity. Since there may be overlap between 2 and 3, there seems little reason to separate them. To make a diagnosis of acute and recurrent vesicular dermatitis, the dynamics in terms of an eruptive dermatosis should be added to the morphology.

Some patients, atopics for example, have dermatitis on parts of the body other than the palms, fingers and/or soles at the same time as recurrent, vesicular hand dermatitis. It seems unwarranted to exclude such patients from the workup used for patients with recurrent, vesicular hand dermatitis.

As Shelley has pointed out,⁶ this morphology of hand dermatitis most likely represents a non-specific reaction pattern that may have many different causes. The background may be atopic dermatitis, a drug reaction, allergic contact dermatitis following external or internal challenge, protein contact dermatitis, a dermatophytid, a psychosomatic reaction, or may have some other as yet unknown source.

In the workup of the individual patient, it can be useful to keep in mind the experience gained in the numerous oral challenge experiments in patients with allergic contact dermatitis who have been challenged with the hapten to which they are allergic. These experiments have shown that vesicular eruptions on the hands develop approximately 24 hours after the challenge. Patients with vesicular eruptions should, therefore, be instructed to search for eliciting causes 1 to 2 days before the eruption of pruritic vesicles.

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