

A 3-Year Causative Study of Pompholyx in 120 Patients

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Objective: To assess the relative frequency of the different causes of pompholyx evoked in the literature.

Design: Prospective survey.

Setting: Clinical outpatient setting.

Patients: A total of 120 consecutive patients with pompholyx referred to our department from 2000 through 2003.

Main Outcome Measures: Systematic investigation of different causes of pompholyx: fungal intertrigo, hyperhidrosis, atopy, contact eczema, and internal reactions with systematic provocation tests to metals, balsam of Peru, and food allergen when suspected.

Results: The present study found the following causes of pompholyx in the 120 patients: mycosis (10.0%); allergic contact pompholyx (67.5%), with cosmetic and hy-

giene products as the main factor (31.7%), followed by metals (16.7%); and internal reactivation from drug, food, or haptenic (nickel) origin (6.7%). The remaining 15.0% of patients were classified as idiopathic patients, but all were atopic. (Percentages do not total 100 because of rounding.)

Conclusions: Our data confirm the existence of reactional pompholyx to interdigital-plantar intertrigos and endogenous reactions to metals or other allergens, but they mainly point at the unexpected importance of a so-called contact pompholyx in which cosmetic and hygiene products play a preponderant role compared with metals. The great frequency of atopic conditions, even if idiopathic pompholyx is not inferred as an equivalent of atopy, should lead to further causative investigations before undertaking more expensive or extensive treatments of refractory pompholyx.

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POMPHOLYX OR PALMOPLANTAR dyshidrosis is a common disorder characterized by recurrent crops of vesicles or bullae on the lateral aspects of the fingers and the palms and soles with nonerythematous skin.¹ Various causative factors have been proposed, including mycoses, hyperhidrosis, nickel allergy, and internal reactivation of contact allergy. To better understand the causative profile of this multifactorial disease,

mittee. Lesions were palmar (70.0%), plantar (10.0%), or palmoplantar (20.0%). The mean age of patients was 35 years (range, 7-72 years). Of the patients, 80.0% were between the ages of 30 and 40 years. There were more females (n=65) than males (n=55); the female-male ratio was 1.18. Selection criteria excluded patients who had erythema associated with vesicles, thus eliminating contact eczemas. A

*For editorial comment
see page 1578*



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we prospectively studied 120 patients in search of atopy, hyperhidrosis, mycosis, contact eczema, and reaction to tobacco, food, and drugs.

METHODS

A total of 120 consecutive patients were referred for pompholyx over 3 years, from 2000 to 2003. All 120 patients and control subjects gave oral consent to participate in this study, which was approved by the local ethics com-

second important selection criterion was the cyclic pattern of recurrent short-term attacks. A detailed history was obtained from each patient and from a series of 100 controls matched by age and sex to determine if some of them were aware of an atopic condition, contact sensitization, possible food or drug allergy, or interdigital dermatitis. All of them were questioned about smoking habits and perspiration, and patients with pompholyx were specifically interviewed and asked about the likelihood of potential trigger factors, such as perspiration, smoking, drugs, foods, and emotional stress.

Patients and controls were examined for clinical signs of interdigital-plantar fungal in-

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tertrigo. Patients with pompholyx underwent systematic skin scraping of the fourth interdigital space of the right foot (Sabouraud culture) and of the interdigital dermatitis site, if any. To look for possible internal reactivation, all patients were orally challenged in a double-blinded intake with a single dose of 2.5 mg of nickel given as nickel sulfate and 1 mg of cobalt given as cobalt sulfate in accordance with the model initially proposed by Veien et al.² All patients were tested for contact allergy to their personal hygiene products diluted to 0.1% (soap, shower gel, shampoo, and shaving cream), to a battery of ingredients that we commonly use for investigating cosmetic allergy (lanolin alcohol, cocamidopropyl betaine, lauryl sulfate, thimerosal, propylene glycol, and octyl gallate), and to the allergen standard European panel (Experimental Contact Dermatitis Research Group panel). All allergens were placed in aluminum patch test chambers (Finn chambers) taped to the skin of the back, removed after 48 hours, and read at 72 and 96 hours in the event of a positive reaction to differentiate allergic and irritant reactions. If erythema decreased at 96 hours, a positive test result was considered to be due to irritation phenomena. The skin reactions were scored on a scale from 0 to 3 (0 indicates no reaction; +, erythema; ++, erythema and papule; and + + +, erythema and vesicle or bullae).

The presence of atopy was assessed in accordance with the criteria of Hannifin and Rajka, and total IgE levels were measured. Skin tests with immediate reading and determination of specific IgE were performed whenever the responsibility of food was suspected. Smokers were systematically tested with patch tests for smoked tobacco, and fresh tobacco was placed on aluminum chambers covered with petroleum jelly and taped to the skin of the back, with removal after 48 hours and reading at 72 hours. Moreover, all smoking patients were asked to stop smoking for 15 days, and then to resume smoking to evaluate the occurrence of disease during a period of smoking and a period of nonsmoking, to assess if pompholyx was triggered or exacerbated by tobacco.

In case of confirmed mycosis, patients were prescribed bifonazole for 3 weeks; they were examined 1, 2, and 6 months later to assess the effect of this antifungal treatment on pompholyx. In case of a positive patch reaction, the clinical relevance of the test was confirmed by an elimination program and open external provocation, patients being thus evaluated on the results of both outcome of the elimination program and challenge with later checkups at 1 and 2 months. The external challenge involved commercial products or devices containing substances giving a positive skin reaction. If some foods or drugs were suspected in triggering or exacerbating pathological symptoms, 2 open elimination blinded challenge tests were performed to assess the possibility of internal reactivation.

RESULTS

During history taking, 40.0% of the 120 patients explained that they had a tendency to palmar-plantar hyperhidrosis compared with 7.0% of the controls, and 12.5% thought it could be a facilitating factor of pompholyx. Of the 120 patients, 48.3% smoked, compared with 28.0% of the controls; 24.1% suspected the role of stress. The responsibility of a specific contact was evoked by 20.0% of patients; 8.0% of controls without pompholyx considered themselves as having contact allergy. Of the patients, 5.0% believed they had detected an internal cause linked to food or drug; 46.7% of patients had an atopic condition vs 20.0% of controls (**Table 1**). Interdigital dermatitis was observed in 5.0% of controls without pompholyx and in 15.8% (19 of 120) of patients, because of a dermatophyte in 80.0% of cases and *Candida*

Table 1. Causative Study of Pompholyx According to Number of Patients^a

Cause of Pompholyx	Patients With Suspected Causation	Relevance Analysis
Intertrigo	19 (15.8)	13 (10.8)
Patch test positive result	89 (74.2)	80 (66.7) ^b
Tobacco patch positive result	5 (4.2)	2 (1.7)
Idiopathic and atopic	0	18 (15.0)
Endogenous cause	13 (10.8)	8 (6.7)
Nickel	6 (5.0) ^c	2 (1.7)
Drugs	3 (2.5) ^c	3 (2.5)
Food	4 (3.3) ^c	3 (2.5)

^aData are given as number (percentage) of the 120 patients.

^bThis included cosmetics (31.7%) and metals (16.7%).

^cThere was suspicion in these patients.

in 20.0% of cases. After a 3-week treatment with topical imidazole salicylate, clinical remission without later recurrence of pompholyx symptoms was obtained in only 13 of the 19 patients. Therefore, the fungal cause was attributed only to these 13 patients, which represents a little more than 10% of all surveyed patients. In 3 of these patients, a simultaneous recurrence of pompholyx and intertrigo was observed during the next 6 months.

A contact allergy was found in 74.2% of patients presenting 1 or several positive epicutaneous test results, with an average of 2.2 tests, for 193 positive test results. Listed by decreasing order, test results were positive to nickel, shower gel, chromium, fragrance, shampoo, balsam of Peru, lanolin, cobalt, thiuram, lauryl sulfate, *p*-phenylenediamine (PPD), fresh tobacco (5 times), formaldehyde, parabens, and octyl gallate. In 97 cases of the 193 positive test results, there was a concordance between external application and disease recurrence. For cosmetic products, the relevance of positive test results for shower gel was confirmed 28 of 30 times; for shampoo, 14 of 17 times. The relevance analysis confirmed the diagnosis of what might be considered allergic contact pompholyx in 67.5% (81 of 120) of patients. The specific involvement of contact allergens was confirmed by the eviction test regarding any positive patch test results, including personal cosmetics. Regarding shower gel and/or shampoo, the main allergens were fragrances (14 times) and preservatives (2 times), in consideration of other associated positive patch test results (**Table 2**). More in detail, 16.7% of surveyed patients had pompholyx related to metals, 18.3% linked to other allergens of the standard panel, and 31.7% to a cosmetic allergy. As a whole, contact pompholyx cases were broken down into hygiene product intolerance (46.7%), metal allergy (25.0%), and reaction to various other allergens, such as rubber, formaldehyde, lanolin, PPD, and balsam of Peru (28.3%). Hygiene product allergy was related 10 times to a fragrance allergy and 4 times to a balsam of Peru allergy (**Table 2**).

Internal cause regarding possible metal, food, drug, or tobacco allergy was identified from data on the questionnaires and clinical history. None of the 75.0% of patients with a negative patch test result to metals demonstrated flare-up of pompholyx after metal oral intake.

Table 2. Data for Contact Pompholyx

Allergen	Patch Test Positive Result (n = 193) ^a	Clinical Relevance (n = 97) ^b
Nickel	32	12
Chromium	25	6
Fragrance	18	12
Balsam of Peru	15	8
Lanolin	12	4
Cobalt	10	2
Thiuram	8	3
Lauryl sulfate	7	0
PPD	6	3
Isothiazolinone	4	1
Octyl gallate	3	2
Parabens	3	0
Formaldehyde	3	2
Shower gel	30	28
Shampoo	17	14

Abbreviation: PPD, *p*-phenylenediamine.

^aA positive result was found in 89 of the 120 patients (74.2%).

^bClinical relevance was found in 50.2% of the 193 tests and in 81 of the 120 patients (67.5%).

Of the 30 patients presenting with a positive patch test result to metals, challenge testing elicited a vesicle palmar-plantar eczema flare-up in only 2, although 6 had been suspected of having possible internal reactivation through metallic denture material. The fact that the dorsal aspect of the hands was spared in these 2 patients during those provoked palmar-plantar pompholyx flare-ups was suggestive of a sudoral elimination of the nickel concentrated in perspiration.

Of 58 smoking patients, tobacco gave a positive contact reaction in only 5. The effect of smoking avoidance or the smoking test confirmed the exclusive responsibility of tobacco smoking as a triggering factor in only 2 patients. Drug allergy was suspected on clinical history and confirmed by oral intake or chronology in 3 patients (amoxicillin in 2 and intravenous immunoglobulin in 1). In the 2 patients suspected of having an amoxicillin allergy, the blinded challenge test result to amoxicillin was positive. In the patient whose pompholyx had appeared on 4 occasions the day after an intravenous immunoglobulin injection for dermatomyositis, chronology allowed the conclusion of a causation relationship without challenge testing.

Concerning the hypothesis of food-related pompholyx, food involvement was suspected in 4 cases (paprika in 2, orange juice in 1, and crustaceans in 1), leading to an open oral challenge. A double oral test performed with an in-between period of 3 weeks demonstrated that pompholyx was reactivated in 3 of the 4 cases. The concordant presence of specific IgE was found in all these 3 cases (2 for paprika and 1 for orange juice). Therefore, the total number of internal cause pompholyx amounted to 8 (6.7% of all surveyed patients).

To sum up, the causative study found 67.5% of contact pompholyx, including cosmetic products (31.7%) and metals (16.7%); interdigital-plantar intertrigo (10.0%); and internal cause (6.7%), which left 15.0% of idio-

pathic cases of pompholyx concerning exclusively atopic patients (Table 1). (Percentages do not total 100 because of rounding.) In comparison, the control population of patients without pompholyx presented with interdigital dermatitis in 5.0%, contact allergy in 8.0%, hyperhidrosis in 7.0%, smoking in 28.0%, and atopy in 20.0%.

The mean age of the patients included in the present study confirms that the peak of frequency of pompholyx is between the ages of 30 and 40 years.^{3,4} In addition, the predominance of isolated hand pompholyx (70.0%) vs the mixed palmar-plantar lesions (20.0%) and the isolated plantar manifestations (10.0%) is consistent with the literature, which gives figures of 80%, 12%, and 3%, respectively.⁵

COMMENT

The present study allows the classification of the classic causative hypotheses formulated in the literature by order of frequency. The initial hypothesis of pompholyx triggered by sudation had led Fox¹ to choose the word *dysidrosis* from the Greek *idros* in 1873, but later the histological features of spongiosis definitively discarded this theory and linked pompholyx to the eczema family.⁶ However, the great frequency of hyperhidrosis (40.0% of patients) must be underlined. The responsibility of fungal interdigital-plantar intertrigo is known as a classic cause of pompholyx, but is perhaps overrated.⁷⁻⁹ In the present series, this cause has been proved in 10.0% of cases, whereas 15.8% of all patients experienced interdigital-plantar intertrigo. Recently, an epidemiologic study¹⁰ of 198 patients with a history of hand eczema confirmed statistically the relationship between palmar vesicular flare-up and the presence of tinea by establishing 3.58 as the relative risk of vesicle eruption in case of intertrigo. With regard to internally reactivated pompholyx, nickel allergy described in the literature¹¹⁻¹³ has been formally accepted in only 2 patients presenting aggravation or elicitation of intense vesicle flare-ups. Nevertheless, the number of reactions of internal origin remains minor compared with contact pompholyx; still, it concerns 8 of 120 patients, including these 2 cases of nickel allergy, 3 cases of pompholyx triggered by foods, and 3 cases elicited by drugs. A drug origin has been reported in the literature,¹⁴ with reactivation of contact dermatitis after intake of neomycin sulfate. Other drugs have been presented as responsible for pompholyx: iodine products, salicylic acid, paracetamol, oral contraceptives,¹⁵ mycophenolate mofetil,¹⁶ and intravenous immunoglobulins.¹⁷⁻²⁰

Concerning tobacco and its responsibility, it has been reported in the present study that 58 patients (48.3%) smoked regularly, which is consistent with the epidemiologic observations of Edman¹⁵; only 5 of them evoked a chronology suggestive of causation. Nevertheless, the fact that 58 of 120 patients were smokers leads to questioning about the role of tobacco. The few patients with a positive test result to tobacco do not exclude the possibility that smoking might intervene through a nonallergic adjuvant mechanism. This hypothesis is sug-

gested by the absence of contact eczema on the smokers' fingers and the conclusions of the epidemiologic study of Linneberg et al.²¹ They observed that contact allergy to nickel had more severe manifestations in patients smoking 15 pack-years, and they established a significant dose-response relation that was independent of exposure to nickel. Given that the elimination challenge test results confirmed only 2 cases of tobacco-induced pompholyx of 120 (1.7%) in the present series, it seems that the direct role of tobacco is accessory compared with its real indirect aggravating potential. The few cases of pompholyx exclusively related to tobacco do not exclude the possibility that smoking may act as an aggravating cofactor in many more cases.

Although pompholyx is generally considered to be an endogenous dermatosis, this series points to the importance of contact allergy representing the exclusive cause in up to 81 of 120 patients. It may be speculated that the small percentage of cases of internal reactivation is not representative of the real proportion of endogenous pompholyx, but the main point of these results is to confirm the existence of so-called contact pompholyx that has already been mentioned in the literature. Indeed, several articles report that hand eczema may present a pompholyx form in percentages varying from 7%²² to 30%.⁹ Direct contact is one of the most important causes of pompholyx in the present series, with 67.5% of contact pompholyx. In 1979, Meneghini and Angelini⁹ evaluated contact pompholyx at 30%, listing by order of frequency various chemical molecules (PPD, chromium, cobalt, mercaptobenzothiazole, nickel, and formaldehyde). Among metallurgists, for whom pompholyx represents half of the observed dermatoses, cutting oil is massively at the origin of the lesions,²³ but the literature considers nickel the dominant allergen of pompholyx,³ before cobalt and chromates (28% and 16%, respectively).²⁴ Other studies have confirmed the disappearance of cases of pompholyx during nonworking periods, with a percentage evaluated at 7%.²⁵ Generally speaking, the allergens involved in pompholyx are PPD (9.3%), chromium (7.4%), cobalt (3.0%), mercaptobenzothiazole (2.7%), nickel (1.7%), and formaldehyde (1.8%).⁹ In the present series, the responsibility of pompholyx has been attributed to metals in 16.7% of all patients, representing 24.7% of cases of contact pompholyx. But the most significant conclusion of the present study is the importance of pompholyx related to personal hygiene products, which represent 47.2% of contact pompholyx and 31.7% of all cases of pompholyx. The cause of pompholyx remained unknown in 15.0% of cases at the end of the present study, but all these patients were atopic or had hyperhidrosis. Of the patients in the present study, 46.7% had an atopic condition. These figures are close to those reported in the literature, which vary from 41% to 50%.^{3,26} and suggest that pompholyx could represent an equivalent of atopic palmar plantar dermatitis.²⁷

The existence of observed hyperhidrosis in 33.3% of the 120 patients led us to consider hyperhidrosis as an important cofactor. Other researchers have reported the coexistence of hyperhidrosis in smaller proportions, varying between 7.5% and 19%,^{3,13} but iontophoreses have already been proposed with success in the treatment of

pompholyx.²⁸ The possibility of a concentrated flux of inflammatory cytokines in sweat has been advocated.²⁹ For this reason, the use of antiperspirants may represent an interesting adjunct treatment in refractory idiopathic pompholyx.

In conclusion, this epidemiologic study confirms the existence of pompholyx triggered by interdigital-plantar fungal intertrigo and by endogenous nickel, but in smaller proportions than contact pompholyx (67.5%), in which cosmetic and personal hygiene products play a predominant role. The high rate of contact pompholyx is noteworthy because patients with pompholyx are generally considered to have a lower incidence of contact dermatitis than those with common hand eczema. This study points to a major decrease of so-called idiopathic and internally reactivated pompholyx, with a high level of cases induced by personal hygiene products. In light of these statistics, it seems that the role of metals might have been overrated during the past years³⁰ because there is no argument to think that this series is not representative of the overall condition of pompholyx. Of the cases, 6.7% are related to an internal reactivation from food, drug, or haptenic origin. Although it is impossible to state that idiopathic pompholyx represents an equivalent of atopy, its association with atopy leads logically to planning additional causative investigations³¹ before undertaking more expensive or extensive treatments of refractory pompholyx.³²

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