

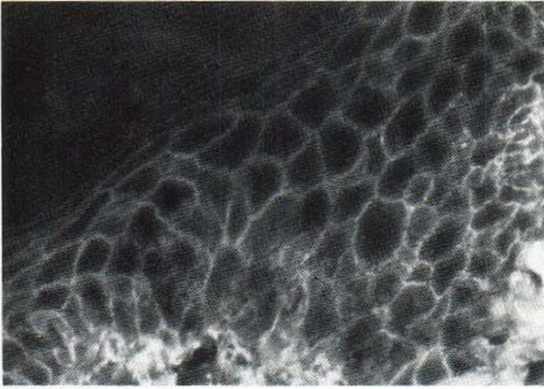


Fig. 3. Direct immunofluorescence demonstrating intercellular IgG deposits.

appearance of bullae on the palms and soles. Histologic examination of a bulla from the palm was not helpful, but by the immunofluorescence technique, IgG deposits intercellularly in the epidermis were demonstrated, thus revealing Pemphigus foliaceus (Fig. 3). Avlosulfon® was discontinued, prednisone 60 mg a day was started and the eruption subsided rapidly. Prior to prednisone treatment the patient had an eosinophilia of 51% of a total of 8000 leukocytes per microlitre. Following 2 weeks of prednisone treatment that was gradually reduced to 40 mg a day, the eosinophilic count dropped to 2% of a total of 6900 leukocytes per microlitre. Azathioprin (Imurel® Wellcome) 50 mg a day was added and prednisone further reduced to 25 mg a day. This combination was successful in preventing recurrence within the observation period of 3 months.

DISCUSSION

Clinically our patient presented as a case of dermatitis herpetiformis, yet she did not respond to Avlosulfon®. The skin biopsy in this preacantholytic stage showed eosinophilic spongiosis as first reported to be the presenting sign in Pemphigus by Emmerson & Wilson-Jones (2), later by others (1, 3, 4). In addition, our patient had a pronounced eosinophilia with 51% eosinophilic leukocytes in the peripheral blood. Osteen et al. (4) and Sneddon & Church (5) also found eosinophilia amounting to 15–24% in peripheral blood.

The combination of a dermatitis herpetiformis-like eruption and eosinophilic spongiosis in an early skin biopsy should suggest Pemphigus. The demonstration of intercellular IgG deposits in the epidermis by direct immunofluorescence microscopy, however, is essential for the establishment of the diagnosis of Pemphigus foliaceus.

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Delayed Cold Urticaria

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Abstract. Five patients with delayed cold urticaria are described. The urticarial skin response was present between 24 and 72 hours after ice challenge. In two of the patients the cold sensitivity was of clinical relevance. Some of the patients displayed low alpha₁-antitrypsin and increased C4 levels in their serum. Our findings may justify the introduction of cold provocation as a routine procedure in the investigation of a patient with chronic urticaria.

Key words Cold urticaria; Delayed cold urticaria; Chronic urticaria.

In cold urticaria the symptoms usually develop within minutes after cold exposure and subsequent warming. In most cases the clinician is able to establish the diagnosis in his office. There are, however, a few reports of delayed cold urticaria

where the localized skin symptoms did not appear until 24–48 hours after cold exposure (8, 9). Delayed cold urticaria may not be so rare, as during the last 6 months we have had the opportunity to see 5 patients. In some of them careful inquiry indicated cold sensitivity, but in others the results of routine cold provocation were quite unforeseen.

CASE REPORTS

Case 1. Thirty-nine-year-old mechanic with fishing and hunting as passionate hobbies. He had a 10-year history of urticaria. The skin symptoms mostly appeared on the face, the neck and on the hands. The urticaria developed gradually and persisted for 3–4 days. The symptoms were often most pronounced on Mondays and Tuesdays, especially in the winter. He had been taking salicylates and indomethacin repeatedly because of arthralgia. When hospitalized and kept on a strict diet he did not react to salicylates, benzoates or other food additives. On the other hand, cold provocation with an ice cube gave no immediate reaction, but after 24 hours there was erythema and deep swelling with itching and burning. The skin lesions were worst after 48 hours and were still perceptible 72 hours after ice challenge. Skin biopsy at 48 hours showed edema in the corium and a slight infiltration of lymphoid cells around the blood vessels.

The patient's α_1 -antitrypsin level was low, 1.7 g/l (normal, 2.0–4.0), there was cryofibrinogen, 0.3 g/l and cryoglobulin, 0.7 g/l. The C4 level was increased, while C3 and total hemolytic activity were normal, as were the following laboratory tests: blood count, urinalysis, serum creatinine and immunoglobulins.

Case 2. A 27-year-old housewife, mother of three children. She has had periods with urticaria since she was 15 and attacks of supraventricular tachycardia during the last 8 years. For several years she has had a history of allergic rhinitis, especially in the spring and the autumn. Her father suffers from allergic rhinitis and her mother from migraine. The urticaria usually appeared on the neck and the shoulders and on the inner sides of her thighs. She was admitted to hospital, put on a diet and tested with salicylates and food additives, all in vain. However, cold provocation gave a delayed response with erythema and a small wheal after 24 hours, followed by more widespread erythema and deep infiltration and tenderness. The skin lesions were easily reproduced and biopsy showed edema of the dermis and small numbers of mononuclear cells around the vessels.

The α_1 -antitrypsin level was 2.0 g/l (normal, 2.0–4.0). Normal or negative laboratory studies included: complete blood count, urinalysis, serum transaminases, serum creatinine, serum protein electrophoresis, immunoglobulins, cryoglobulins, cryofibrinogen, cold agglutinins and complement factors.

Case 3. A 60-year-old housewife with eczema on the hands over the last 25 years. During the previous 10 months she had suffered from urticaria almost every day. On admission the patient was taking various pills containing dyes or salicylates. After some time on a diet and without pills her urticaria improved. Provocation with

food additives and dyes gave no conclusive information. However, ice cube challenge produced erythema and deep swelling after 24 hours and an even stronger reaction after 48 hours and the biopsy showed a histopathologic picture similar to that in cases 1 and 2.

The laboratory tests showed a low α_1 -antitrypsin level, 1.7 g/l (2.0–4.0) and an increased C4. Other complement factors were normal, as were serum protein electrophoresis, immunoglobulins, serum transaminases, serum creatinine, blood count and urinalysis. Cryoglobulins or cryofibrinogen were not demonstrated.

Case 4. A 20-year-old auxiliary nurse, with pruritus and sometimes itching papules on her arms and shoulders. She was taking contraceptive pills. Her complaints started in the winter and gradually subsided during the summer. Next winter she experienced the same itch but now also on the hands and face. On admission she was expected to have chronic urticaria. Provocation with salicylates and food additives proved negative, but cold exposure gave a positive reaction after 24 and 48 hours. Her cold sensitivity seems to be of clinical importance and of relevance to her history.

The α_1 -antitrypsin value was normal, as were C3 and total hemolytic activity, but C4 was increased. She had cryofibrinogen, 0.3 g/l, but no cryoglobulins. Immunoglobulins, serum protein electrophoresis, serum transaminases, serum creatinine, blood count and urinalysis were all within the normal range.

Case 5. A 27-year-old female animal keeper. She had a verified salicylate hypersensitivity giving urticaria. In order to exclude other food additives from producing urticaria, she was referred to hospital for testing. While on a diet all provocations were negative except for cold challenge which gave erythema and deep infiltration after 36 hours. The clinical relevance of this delayed cold sensitivity is most uncertain.

The laboratory studies revealed low α_1 -antitrypsin, 1.6 g/l (2.0–4.0), increased C4, but normal C3 and total hemolytic activity. She had cryofibrinogen, 0.9 g/l, but no cryoglobulins. Other laboratory tests including blood count, urinalysis, serum creatinine, serum protein electrophoresis, immunoglobulins and serum transaminases were normal.

DISCUSSION

The outcome of the cold provocation tests was not expected, although in two cases, Nos. 1 and 4, it was in accord with the case histories. Patient No. 1 was a keen sportsman and fisherman who spent almost every week-end in the open air. In the winter season he used to drive his snow-scooter. Because of the delayed reaction, his symptoms, localized to face neck and wrists mainly, were pronounced on Mondays and Tuesdays and tapered off during the rest of the week. The delayed cold sensitivity was a satisfactory explanation of his complaints. In case 4 the urticaria started during the winter and disappeared in the summer, only to recur with the next

cold weather season. In the other 3 patients the delayed cold sensitivity was not compatible with their histories. Thus our patients might belong to two groups: one with clinical symptoms of cold urticaria and the other without these symptoms.

In the immediate type of cold urticaria, the skin symptoms have been correlated to a considerable increase of histamine in the blood from the challenged limb. Elevated levels of serotonin or bradykinin were not found, however, (7). When patients were studied by perfusion technique, it was possible to demonstrate the presence of kinins in the perfusate after ice challenge, but no histamine was found (1). These conflicting results may be due to the differences in the techniques employed or to a complex mechanism behind cold urticaria with several critical mediators.

In chronic urticaria an increased reaction to intradermally injected kallikrein has been reported as well as a delayed response to histamine and bradykinin in some patients (6). It was speculated that histamine and bradykinin caused leakage of plasma into extravascular tissues activating kallikrein, to which these patients are sensitive, possibly due to lack of kallikrein inhibitors.

It has also been reported that in some plasmas there is a spontaneous cold activation of factor VII. The activation is correlated to increased production of an arginine esterase (4), presumably kallikrein, as indicated by studies with various inhibitors (5). Factor VII is slowly activated, with a lag time of 5 to 13 hours. This substantial evidence of cold activation of kallikrein is of interest and may offer an explanation for the delayed appearance of the cold urticaria in our patients, through a generation of kinins.

Biopsies of the reactions at 48 hours after cold challenge showed edema in the corium and only a slight increase in mononuclear cells around the vessels. There was no evidence of vasculitis. In the case of delayed cold hypersensitivity reported by Sarkany & Turk (8), there was more pronounced perivascular cuffing with lymphocytes. The histopathological picture was considered typical of tuberculin type hypersensitivity. In spite of this difference in the histopathology, the history of the case presented by Sarkany & Turk is very similar to the history of our case No. 1.

The laboratory studies showed low α_1 -antitrypsin levels in our patients, as has previously been found in patients with cold urticaria of the

immediate type (2, 3). It does not, however, imply that the mechanisms underlying immediate and delayed cold urticaria are the same. The α_1 -antitrypsin is an inhibitor of tissue and leukocyte proteases, as well as of plasmin and kallikrein, exerting its effect mainly extravascularly. The involvement of this inhibitor in various mediator systems could explain the different clinical types of urticaria connected with low levels. Our α_1 -antitrypsin values were measured immunologically, which means that the total amount of inhibitor was calculated, leaving its biological activity open to further variation. The isolated presence of increased C4 in some patients and of cryoglobulins and cryofibrinogen are worthy of note but cannot be evaluated in the few patients at our disposal.

We think that cold provocation with delayed determination should be included as a routine procedure in the investigation of chronic urticaria, for two reasons. First, it is reasonable to assume that patients with unrecognized cold urticaria should receive an explanation of their complaints. Secondly, the delayed reaction to cold provocation may be of relevance to studies on the various mechanisms behind chronic urticaria.

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