

Cholinergic Urticaria Shows Neutrophilic Inflammation

R. K. WINKELMANN

Department of Dermatology, Mayo Clinic, Rochester, Minnesota, USA

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Three patients with cholinergic urticaria were studied by biopsy and neutrophilic urticaria was observed in two. Direct immunofluorescence was negative in 1 patient, and monoclonal antibody studies identified a large population of OKM-1 antibody positive cells. *Key words: Biopsy; Monoclonal antibody; Immunofluorescence.* (Received January 28, 1985.)

R. K. Winkelmann, Department of Dermatology, Mayo Clinic, Rochester, Minnesota 55905, USA.

Cholinergic urticaria is a unique, whealing response to heat, exercise and, at times, anxiety. The skin will form wheals with intradermal acetylcholine and congeners which show peripheral satellite whealing. Histamine release agents will exhaust the skin capacity for this reaction, and the H₁ blocking agents will suppress a major portion of the reaction.

Histological examination of the skin of these wheals has been limited and of little help in explaining the phenomenon and its differences from the usual acute and chronic urticaria. Illig (1) biopsied 2 of 8 cases and found in both cases perivascular large round cells and in some sections predominant neutrophils with occasional eosinophils. He concluded no difference existed between histologic changes of cholinergic urticaria and other forms of urticaria. James et al. (2) also did not find significant microscopic differences between types of physical urticaria.

METHODS

Biopsies obtained from three patients with cholinergic urticaria were taken from clinical wheals produced by exercise. A positive acetylcholine test was demonstrated in two patients. The patients had had their cholinergic whealing for 1 1/2, 4 and 8 years respectively. Atopic disease was not present in these patients. Blood chemistry, hemogram, erythrocyte sedimentation rate, and serum protein electrophoresis values were normal in two patients. One of two patients had a CH₅₀ of 37 U (normal 41-80), but C₃ and C₄ values were normal. The serum α -1 trypsin inhibitor in this patient was normal. One patient had limited laboratory examinations. Fifty hematoxylin and eosin sections and five aldehyde fuchsin-Giemsa and five alcian blue-PAS sections were available for microscopic study.

RESULTS

Two of the three patients showed neutrophilic urticarial histology: Polymorphonuclear leukocytes in and about the walls of the superficial subpapillary dermal venules (Fig. 1).

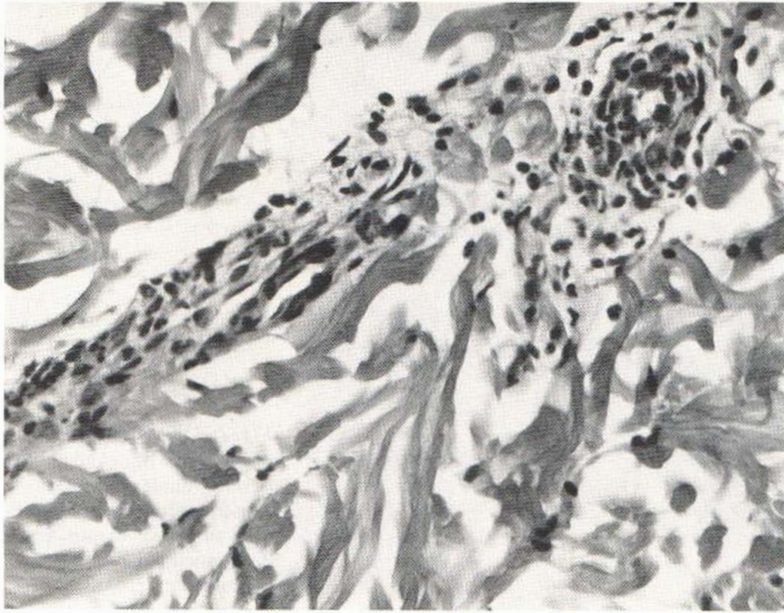


Fig. 1. The neutrophilic urticaria histopathology in a biopsy of an exercise-induced wheal of cholinergic urticaria. Note venules involved and small arteriole free of cellular infiltration. 15 min. Case 2. H & E. $\times 360$.

No leukocytoclasia, hemorrhage or fibrinoid change was observed. The third patient showed only lymphocytes about the dermal blood vessels.

Direct immunofluorescent studies of the skin biopsy in patient 2 utilizing antibody to IgG, IgM, IgA, C₃, and fibrinogen were negative. This patient showed neutrophilic urticaria histology.

Monoclonal antibody studies in patient 2 utilizing antibodies to leu-1, leu-2a, leu-3a, OKT-6, B₁, and OKM-1 showed only rare lymphocytes positive with leu antibodies. OKM-1 positive cells were found in large numbers about the venules, probably identifying granulocytes as well as monocytes (Fig. 2). This is in contrast to the studies of chronic urticaria and dermatographism, in which it was found that lymphocytes were the predominant cell.

COMMENT

Neutrophilic urticaria is a term recently used to describe nonleukocytoclastic neutrophil infiltration of dermal blood vessels, usually veins (3). It has been shown not to be a form of vasculitis by clinical correlation, immuno-fluorescence, and by a positive response to H₁ blocking agents. Similar neutrophilic vascular states are found in cold urticaria (4), and in trafuril-induced cutaneous erythema and dermatographism (5).

The presence of neutrophils in cholinergic urticaria gives a clue to the mediators involved. Cold urticaria, which has neutrophilic urticarial histology, is associated with the release of a neutrophil chemotactic factor in the circulation (6). One may suppose that the trafuril neutrophilic vessel change may be related to prostaglandin release as the whole process is suppressed by acetylsalicylic acid (5). Leukotrienne B₄ has been shown to produce neutrophilic chemotactic histology (7). The effects of salicylates on cold urticaria and cholinergic urticaria have not been specifically documented.

At present, four states have been documented to have the histology of neutrophilic

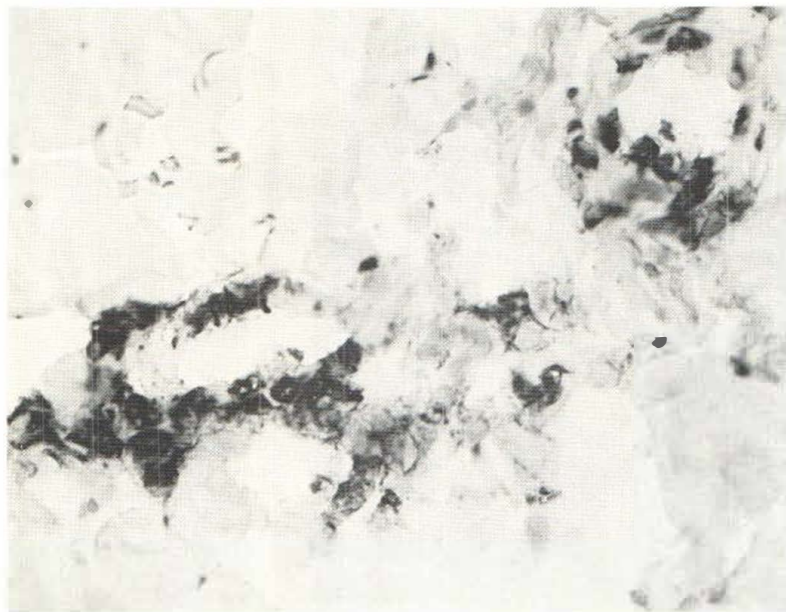


Fig. 2. OKM-1 positive macrophages within and about dermal venules of an exercise-induced lesion of cholinergic urticaria. 15 min. Case 2. Monoclonal antibody peroxidase-antiperoxidase method, $\times 450$.

urticaria: Cholinergic urticaria, cold urticaria, trafilur erythema, and the rare group of chronic urticaria and dermographism patients usually mistaken for urticarial vasculitis because of this histology (3). The current patients indicate that the neutrophilic urticaria may be a phase of the urticarial inflammatory reaction in patients with cholinergic urticaria. Two groups of dermographic patients were found: one with mild neutrophile histology in early lesions and one with lymphocyte perivascular histology in later lesions (8). Additional time sequence and pharmacologic mediator-related studies are needed to clarify this relationship.

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