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Neutrophilic Urticaria

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Eight patients with neutrophilic urticaria were identified in a 5-year biopsy experience (1980–1984). All patients had a neutrophilic venulitis without fibrinoid necrosis, hemorrhage, or leukocytoclasia. Four patients had a history of angioedema, and two had a personal history of atopic disease. Results of laboratory studies, including complement and protein values and antibody serologic tests, were normal. All patients responded to antihistamine agents. Despite occasional clinical or histologic diagnoses of vasculitis for such cases in the past, the clinical, laboratory, and histologic features and the therapeutic course of these patients are compatible with a phase or type of chronic urticaria. (Received April 28, 1987.)

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The histopathologic features of urticaria usually have been considered to be nonspecific or nondiagnostic (1, 2). Biopsies of urticaria have become more frequent only because it is possible to recognize cases of urticarial vasculitis histologically and by direct immunofluorescence. Russell Jones et al. (3) recognized a histologic pattern of urticaria with neutrophils between cases of true vasculitis and of true urticaria, and other authors (4, 5) have told us of recognizing leukocytes in urticaria. In 1985, Peters & Winkelmann (6) presented 10 cases of clinical chronic urticaria with the finding of neutrophils in and about the venules of the dermis. Leukocytoclasia, hemorrhage, and fibrinoid necrosis were absent, and results of direct immunofluorescence studies were nonspecific or negative. The laboratory data, course, and response to antihistamine therapy confirmed the clinical diagnosis of chronic urticaria.

We have now identified eight additional cases which indicate that this pathologic picture of "polys in the wall" does not indicate vasculitis but may be a phase or type of urticaria.

MATERIALS AND METHODS

We reviewed the 321 biopsies of urticaria and erythema from 1980 through 1984 in the files of St. John's Hospital, London. Five or more hematoxylin-and-eosin-stained sections were available in the cases selected. Sections stained with the periodic acid-Schiff method also were studied. The histories were reviewed, and follow-up data, up to 1 year or current time, were obtained. The laboratory data were summarized for review. Specific attention was given to the response to treatment.

RESULTS

Eight patients with the typical pathologic features were found (Fig. 1). Neutrophils were observed in the walls of the dermal veins, particularly in the superficial venous plexus. The endothelial cells were swollen but not necrotic. Around the vessels, leukocytes were observed, and mixed round cells were also present. Leukocytoclasia was minimal or

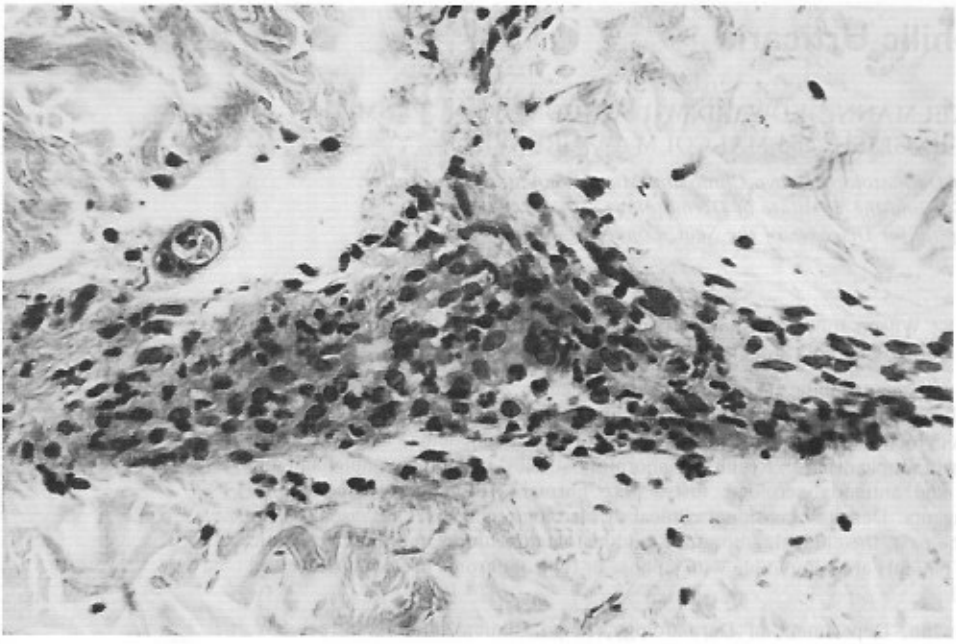


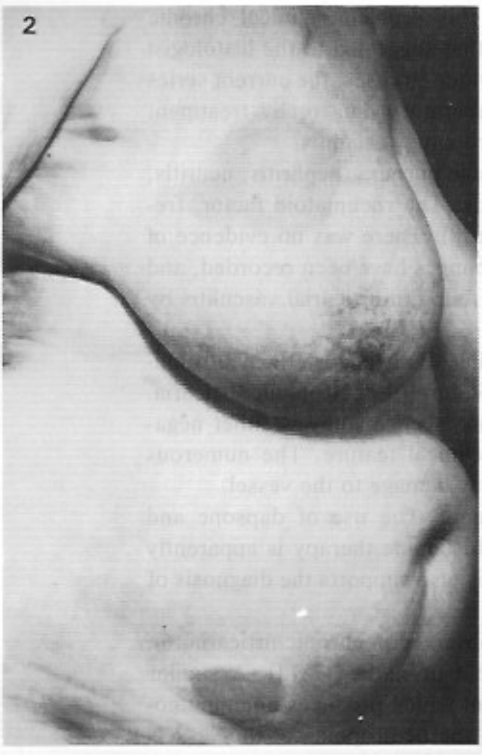
Fig. 1. Neutrophilic urticaria. A subpapillary venule demonstrates "polys in the wall". (Hematoxylin and eosin; ×360.)

absent. Hemorrhage was not observed, and fibrinoid deposits were not identified with either hematoxylin-and-eosin or periodic acid-Schiff stain. Eosinophils were present in all cases and were scattered within and about the vessels. In three cases there was significant tissue eosinophilia (more than 5 cells/high-power field). The subpapillary and papillary capillaries showed no inflammation. The epidermal and appendageal structures were normal. Dilated lymphatics were present in all specimens.

The patients were equally divided between males and females; the age range was broad and many occupations were represented. The duration of the disease varied from 4 months to 11 years. Four patients gave a history of individual lesions lasting all day. The gross appearance of the lesions is shown in Figs. 2 and 3. Four patients gave a history of angioedema. One of these patients had an atopic disease, hay fever; a second atopic patient did not give a history of angioedema.

Dermographometer-induced mild dermographism has been reported in four patients (7). In our case 6, pressure applied by weight produced a lesion 4 hours after application (delayed pressure urticaria). No patient had a recorded history or diagnosis of specific physical urticaria. No drug allergies were recorded, and no instance of sensitivity to salicylates had been noted.

The hemogram was normal in all but case 4; this patient had a coincidental *Pasteurella multocida* infection after a dog bite and had increased temperature, sedimentation rate, and leukocyte count. Peripheral eosinophilia was less than 5% in all cases. Blood chemistry values were normal, including liver enzymes, electrolytes, calcium, urea, and uric acid. Serum protein values and electrophoresis results were normal. The cryoglobulin test in one case was negative. Results of complement studies, including C3, C4, and C1 esterase inhibitor, were normal in the six patients tested, with the exception of an increased C1 esterase inhibitor value (0.43 g/l; normal, 0.1–0.26 g/l) in case 1 and a temporary depres-



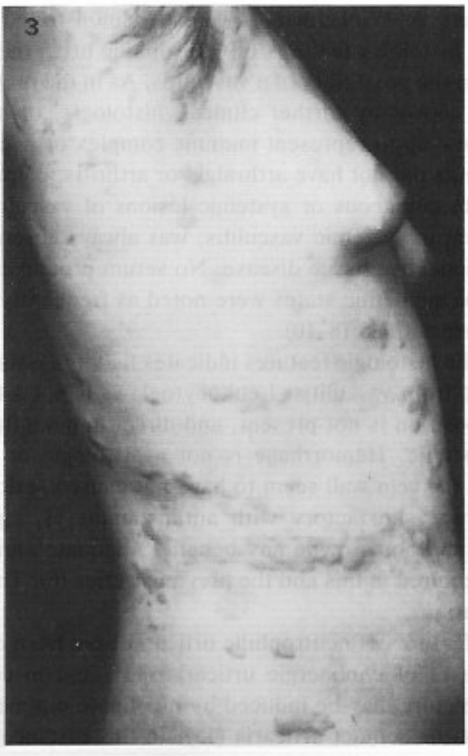


Fig. 2. Edematous and erythematous plaques of urticaria in a patient with neutrophilic urticaria (case 6).

Fig. 3. Clinical appearance of chronic urticaria in a patient with histologic features of neutrophilic urticaria (case 5).

sion of C4 (9 mg/dl; later, it was 75 mg/dl; normal, 20–65 mg/dl) in case 2. The rheumatoid factor assay was negative in all five cases tested. The antinuclear antibody assay was negative in all six cases. Platelet agglutination for immune complexes was positive (1:40) in case 7. The streptococcal anti-DNA antibody test was positive (1:240) in case 4 (this was the dog-bite victim who also had *Escherichia coli* in her urine). All other urinalyses gave negative results.

All patients showed partial or total relief of lesions with antihistamine agents (H_1) and, with time, all were considered to be improved. Because of the suggestion of vasculitis, 1- to 2-month courses of dapsone were given to three patients, with no relief. Two patients were given indomethacin for 3 months or more, with no improvement. Patient 8 showed improvement on a low-salicylate diet, but diets low in salicylate, yeast, or tartrazine did not help two other patients. One patient (case 4) received prednisone and had temporary improvement. Additional diagnoses included seborrheic dermatitis and contact dermatitis to metal (proved to be nickel and cobalt in one patient each). The dog-bite infection with *E. coli* cystitis were the only infections recorded.

DISCUSSION

Three of these patients (cases 2, 3, and 6) were given a provisional clinical diagnosis of urticarial vasculitis, and in case 8 a histologic diagnosis of vasculitis was proposed. The 10

cases of Peters & Winkelmann (6) also demonstrated this problem: clinical chronic urticaria with histologic features of neutrophilic urticaria that suggested to the histologist or the clinician the possibility of a vasculitis. As in the previous 10 cases, the current series could not be shown by further clinical, histologic, or laboratory data or by treatment results or follow-up to represent immune complex or necrotizing vasculitis.

These patients did not have arthralgia or arthritis, palpable purpura, nephritis, neuritis, or any definite cutaneous or systemic lesions of vasculitis. The rheumatoid factor, frequently present in systemic vasculitis, was always absent (8). There was no evidence of underlying connective tissue disease. No serum protein changes have been recorded, and no hypocomplementemic states were noted as frequently found in urticarial vasculitis by Soter and other authors (8–10).

Review of the histologic features indicates that it is possible to distinguish the neutrophilia in urticaria from vasculitis. Leukocytoclasia is not a feature of neutrophilic urticaria. Fibrinoid deposition is not present, and direct immunofluorescence study is either negative or nonspecific. Hemorrhage is not a histologic or clinical feature. The numerous leukocytes in the vein wall seem to have not caused serious damage to the vessel.

Treatment was satisfactory with antihistamine H_1 agents. The use of dapsone and indomethacin did not provide any benefit. Adequate antihistamine therapy is apparently all that was required in this and the previous series (6). This also supports the diagnosis of chronic urticaria.

Histologic features of neutrophilic urticaria have been observed in chronic urticaria (6), in isolated cases of cholinergic urticaria (11), and in cold urticaria (12–14). A similar microscopic picture may be induced by nicotinate ointment which produces nonimmunologic erythema or contact urticaria (15). In this instance, the neutrophilia of the vessels persists for 24 hours and is associated with vasopermeability and dermographism (16). The presence of dermographism in the earlier series of these cases (seven of eight patients) and the presence of angioedema, pressure urticaria, and induced dermographism in the present patients may be a unifying feature for this urticarial lesion.

Three of the previous 10 cases had a significant coincidental infection. Only one patient in the current series showed this relationship, but the cases were not specifically investigated for this. It seems that neutrophilic urticaria may occur in patients with demonstrable physical urticaria or, at times, with infection, and these relationships should be carefully documented.

The histologic appearance of chronic urticaria has been stated to be chronic perivascular lymphocytosis with occasional eosinophils (17, 18). The lymphocytes have been shown to be T-helper lymphocytes (19). Some cases have nonspecific pathologic changes in the skin. The neutrophilic urticarial picture could represent a urticarial process in which the neutrophils play the dominant role. However, we believe that the neutrophilia we have identified is best considered as a phase in the development of the urticarial lesion. Dermographism lesions may show early neutrophilia and, later, vascular lymphocytosis (20, 21). Because all the lesions have been biopsied and studied retrospectively, we believe that these may be fortuitous biopsies and that other, older, lesions in the same patients might show the usual lymphocytic vascular reaction. All our biopsied lesions are early ones, as recognized by the dilated lymphatics, a feature lost in older or faded urticarial lesions. It is necessary to identify current patients with this problem so that early and late lesions may be biopsied and the patients studied in prospective fashion.

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