

Histopathology of Chronic Urticaria

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Abstract

Urticaria of undetermined cause persisting longer than 6 wk is known as chronic idiopathic urticaria (CIU). The differential diagnosis of CIU is lengthy and a skin biopsy may be of value in making a more precise diagnosis. The histopathologic feature that differentiates chronic urticarial lesions from acute urticarial lesions is the presence of a mixed cellular perivascular infiltration, composed mostly of mononuclear cells, surrounding the dermal postcapillary venules. Mast cell numbers in CIU lesions may be increased compared to normal dermis. Various patterns of histopathologic findings have been described in CIU. An understanding of these patterns of infiltrating cells, mediators, cytokines, chemokines and adhesion molecules may provide insight into the mechanism of the cutaneous disease and provide valuable information that will help in the selection of a more effective therapeutic intervention.

Index Entries: Chronic idiopathic urticaria; histopathology; hives.

Urticaria and angioedema are common skin manifestations of many different causes. The incidence of all types of urticaria in the general population is estimated to be between 15% and 20% (1). When urticaria persists for longer than 6 wk, and no identifiable cause has been discovered, chronic idiopathic urticaria (CIU) becomes the diagnosis. Individual lesions of chronic urticaria typically last less than 24 h (usually less than 12 h), but new lesions may appear and resolve sporadically.

The differential diagnosis of chronic urticaria is provided in Table 1. In the majority of cases (80–90%), however, the etiology remains unknown. A skin biopsy is recommended in the evaluation of the patient with refractory, severe chronic urticaria and in the evaluation of the patient suspected of having urticarial vasculitis.

Table 1
Differential Diagnosis of Chronic Urticaria

1. Urticaria: Chronic/Recurring
Raised erythematous plaques in a dynamic state of waxing and waning
Frequent annular or gyrate appearance
Urticaria secondary to allergen (food, drug)
Autoimmune urticaria (antithyroid autoantibodies, anti-IgE receptor autoantibodies).
2. Urticaria-like lesions
Erythema multiforme
Bullous pemphigoid
Dermatitis herpetiformis
Papular urticaria
Pruritis urticarial plaques and papules of pregnancy
3. Urticarial Vasculitis
Lesions may persist beyond 24 h
Purpuric component with residual hyperpigmentation
Hypersensitivity vasculitis
Hypocomplementemic urticarial vasculitis syndrome
Henoch-Schönlein purpura
Serum sickness reaction
Associated with connective tissue diseases

Adapted from Charlesworth Ernest N., The Spectrum of Urticaria: All that Urticates May Not Be Urticaria in *Immunology and Allergy Clinics of North America.*, Vol 15, No. 4, Nov. 1995.

Normal skin consists of an outer epithelial layer known as the epidermis and an inner layer of connective tissue termed the dermis or corium. The interface between these two layers is comprised of numerous upward projections of the dermis known as papillae, which interdigitate with downward evaginations of the epidermis referred to as the epidermal ridges. The epidermis is made up primarily of stratified squamous keratinized epithelium, and it normally contains abundant numbers of melanocytes, Langerhans' cells, and Merkel cells. The dermis is separated from the epidermis by a periodic acid-schiff stain (PAS)-positive basement membrane, which is composed of a basal lamina and the lamina reticularis. Two layers of the dermis are identified: the thin, papillary layer is loose connective tissue with fibroblasts, mast cells, macrophages, and extravasated leukocytes being the predominant cells; and the thicker reticular layer is an irregular, dense connective tissue. The dermis is richly supplied with blood and lymph vessels. In the papillary region, surrounding the epidermal ridges, there is a rich network of capillaries. The overlying epidermis contains no blood vessels of its own. The dermis also contains hair follicles, the sweat and sebaceous glands, and nerves (2).

Histopathologic findings among patients with CIU vary depending upon the site of the biopsy (lesional vs uninvolved skin), as well as the length of time that the urticaria has been present. Typically, as in acute urticaria, localized edema with separation of collagen fibers and blunting and widening of the rete pegs is observed.

Edema formation results from increased small-vessel permeability that occurs primarily in small venules ranging from 20–30 μ in diameter. The smallest capillaries (4–7 μ in diameter) are not involved. The majority of the small blood vessels in the skin are postcapillary venules.

The histopathologic feature that differentiates chronic urticarial lesions from acute urticarial lesions is the presence of a mixed cellular perivascular infiltration surrounding the dermal postcapillary venules. This infiltrate is composed of mostly mononuclear cells (3). Mast-cell numbers in chronic urticarial lesions may be increased as much as 10-fold over that of normal dermis (4). Increases in the combined T-cell/monocyte population have also been reported. The T-cells are primarily CD4+ (5–7). A few eosinophils and/or neutrophils may be identified in the perivenular infiltrate and within the lumen of the venules. The presence of eosinophils in most cases of CIU is substantiated by the presence of major basic protein (MBP) utilizing immunohistochemical techniques. Electron microscopy demonstrates the presence of degranulated eosinophils. Neutrophils are not typically identified in most cases of CIU, although occasionally, a predominantly neutrophilic infiltrate is present without the findings of leukocytoclastic vasculitis (3,8). This pattern of neutrophil infiltration is indicative of severe chronic urticaria.

In 1983, Jones studied 24 subjects with chronic urticaria, and categorized these patients—based on histopathologic findings—into three groups. The implication is that each group responds to specific therapeutic intervention (9).

Group one ($n=3$) was made up of subjects with biopsy findings of neutrophilic vasculitis. Two of the three subjects demonstrated hypocomplementemia, and had evidence of C3 conversion and deposition of immunoreactants in lesional as well as uninvolved skin. This was the only group in which cryoglobulins were detected. All three subjects in group one demonstrated monoclonal rheumatoid factor and positive C1q binding. Immunosuppressant drugs (dapsone, hydroxychloroquine, or prednisone) are required in this group.

The second histologic pattern ($n=10$) consists of a dense perivascular mixed-cellular infiltrate comprised of neutrophils, eosinophils, and mononuclear cells. The group two subjects had normal or increased complement levels, but complement components were rarely identified in the lesions. Other immunoreactants such as fibrin and IgG were

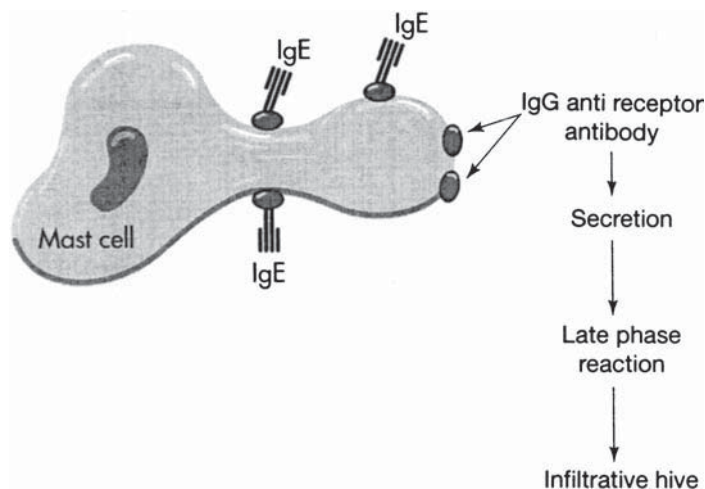


Fig. 1. The activation of cutaneous mast cells by IgG auto-antibody directed to the high-affinity IgE receptor α -subunit. In addition, may involve complement activation with C5a stimulating only cutaneous mast cells with receptors for C5a. Adapted with permission from (12).

detected in lesional, but not normal, skin. These patients did not respond to antihistamines alone.

The third histologic pattern of chronic urticaria identified ($n=11$) was that of a sparse perivascular infiltrate. In these group three subjects, complement was normal and immunofluorescence was essentially negative. These patients responded to antihistamine therapy.

Functional IgG autoantibodies specific to the high-affinity IgE receptor (Fc ϵ RI) alpha subunit or against IgE have been identified in subjects with CIU or now referred to as chronic autoimmune urticaria (10) (Fig. 1). A polymorphic perivascular infiltrate without features of vasculitis are typical in autoantibody-positive chronic urticaria patients. Hide et al. (11) identified anti-IgE-receptor antibodies in 30% to 40% of subjects with chronic urticaria. Another 10% were found to have anti-IgE antibodies. The autologous serum skin test produced a typical wheal-and-flare reaction at the site of the injection, demonstrating the triggering of cutaneous mast cells by the autoantibody found in the patient's serum. An autoimmune etiology is present in 40% to 50% in another group of CIU patients (12). These autoantibody assays are only performed in research laboratories.

Charlesworth (13) proposed a classification of chronic urticaria based on the histopathology and presence or absence of the autoantibodies. The typical CIU patient, who responds to H1-receptor antagonists and is autoantibody-negative, has a relatively sparse perivascular infiltrate composed predominantly of lymphocytes. However, the find-

ings of an intense polymorphic cellular infiltration with eosinophils and neutrophils are associated with the autoimmune type of chronic urticaria. The implication of this observation, based on histologic findings, is to facilitate in the selection of appropriate therapy.

Sabroe et al. (8) examined the cellular infiltration from urticaria wheals in both subsets of chronic urticaria subjects—i.e., those with circulating autoantibodies, and those without—at two different times (wheals of less than 4 h duration and wheals of greater than 12 h duration). Ten of 22 subjects had functional anti-Fc ϵ RI and/or anti-IgE autoantibodies. Neutrophils and eosinophils were present in both short- and long-duration wheals, and there was evidence of degranulation in both groups. No distinctive difference in the histopathology between the two groups (+/– autoantibody) was identified, or between the less than 4-h or greater than 12-h study groups, with the exception of higher numbers of EG2-positive cells (activated eosinophils) in the wheals of the over 12-h duration in subjects without autoantibodies.

Increased levels of IL-6 have been demonstrated in blisters raised over pressure urticarial lesions (14), and an increased expression of migration inhibitory factor has also been demonstrated in several types of urticaria (15). Hermes et al. (16) reported that immunoreactivity for TNF- α and IL-3 was significantly higher on endothelial and perivascular cells of the upper dermis in all urticarial lesions compared with normal skin. TNF- α was found in both lesional and non-lesional skin of subjects with urticaria. This finding indicates that the entire integument is activated in chronic urticaria.

In summary, chronic urticaria is a heterogeneous disorder with varying underlying pathophysiologic abnormalities. The timing of the cellular infiltrate is unknown, largely because it is difficult to establish the duration of one single hive. The infiltrating cells, T-cells, monocytes, neutrophils, and eosinophils release additional mediators, cytokines, and chemokines, amplifying the initial urticarial response that results from the activation of the cutaneous mast cells. Thus, chronic urticaria represents a dynamic process involving a complex interplay of a number of cells, mediators, cytokines, chemokines, and adhesion molecules. Evaluation of the histopathologic features in individual patients may provide insight into the mechanism of their cutaneous disease, leukocytoclastic vasculitis, or intense cellular infiltrate variant type of chronic urticaria, and can provide valuable information that will help in the selection of a more effective therapeutic intervention.

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