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Chronic urticaria: Pathophysiology and treatment approaches

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Urticaria, a cutaneous reaction pattern, varies clinically and histopathologically. The origin of acute urticaria can be detected in some cases; in patients with chronic urticaria, however, the cause is rarely identified. Thus, most patients with chronic urticaria are considered to have idiopathic disease. The dermal mast cell and its mediators may play a central role in chronic idiopathic urticaria. Other inflammatory cells, including lymphocytes and polymorphonuclear cells, have also been implicated. Treatment is based on identification of the inflammatory cells within skin lesions and blockage of the effects of histamine in the skin. Urticaria in which a lymphocyte-predominant infiltrate is seen often responds to one or more H_1 antihistamines. Recently, a new generation of nonsedating or mildly sedating H_1 antihistamines has proved useful in the management of these cases. Antihistamine use alone may be unsuccessful in urticaria in which polymorphonuclear neutrophils predominate; frequently, the addition of agents that alter polymorphonuclear neutrophil function, such as colchicine or dapsone, is required. During the introduction of antihistamine and anti-polymorphonuclear neutrophil therapy, a simultaneous brief course of systemic corticosteroid therapy may be necessary, but the extended use of systemic corticosteroids should be avoided because of significant adverse effects. As the pathophysiologic mechanisms responsible for chronic urticaria are better defined, more effective therapeutic agents should become available. (J Allergy Clin Immunol 1996;98:S325-30.)

Key words: Urticaria, corticosteroids, H_1 antihistamines, cetirizine, chronic disease, drug therapy

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The treatment of patients with chronic urticaria, or hives, can present a significant challenge to the most experienced physicians. Urticaria is a common disorder that affects as many as 25% of all people at some time during their lives.¹ It is not a single disease but a cutaneous reaction pattern for which there are multiple potential causes. The clinical expression of this disease varies from patient to patient, as do its duration of

Abbreviations used

H₁: Histamine H₁
PMN: Polymorphonuclear

activity, the morphologic features of the lesions, and its histopathologic basis.²

Patients with urticaria may have daily or intermittent attacks of hives over a period of <6 weeks, defined empirically as acute urticaria. Other patients have repeated attacks of urticaria over a >6-week period, classified as chronic urticaria. Although urticaria appears in all age groups, acute urticaria is more common among children and young adults, whereas chronic urticaria occurs more often in adults, especially middle-aged women.¹⁻⁴

Typical urticarial lesions appear as pruritic papules and plaques with normal skin surface markings without scaling and with normal pigmentation. Individual lesions usually last <24 hours. Lesion color may vary among patients, and lesions may appear either as erythematous papules or as elevated lesions with white centers and surrounding erythema. Individual hives differ in their size and shape, ranging from a few millimeters to several centimeters in diameter even in the same patient. Classic lesions are round or oval in shape but may assume annular, arcuate, or serpiginous configurations.² While variations in the morphologic features of the lesions are well recognized, correlation of these differences with defined causes or responses to therapy has not been successful.

The histopathologic mechanisms of urticaria also can vary among patients. In 24 patients with chronic idiopathic urticaria in whom a skin biopsy was performed,⁵ 11 had characteristic histopathologic changes consisting of a sparse perivascular mononuclear cell infiltrate, dilatation and engorgement of superficial blood vessels, and associated dermal edema. In an additional 10 patients, skin biopsy revealed a dense perivascular infiltrate consisting of neutrophils, eosinophils, and mononuclear cells, with no evidence of vasculitis. Histologic findings of small-vessel vasculitis were noted in lesional skin biopsy specimens from the remaining 3 patients. Further characterization of these distinct histopathologic groups demonstrated differences in their clinical course and response to therapy. Patients with a mild perivascular lymphocytic infiltrate (lymphocyte-predominant) on skin biopsy had pruritic urticarial lesions responsive to antihistamine therapy. Patients with polymorphonuclear (PMN)-cell-predominant urticaria without vasculitis often had more active disease that was relatively resistant to histamine antagonists.⁵

Thus identification of the type of inflammatory cells in lesional skin of patients with chronic urticaria may prove very useful in formulating a treatment plan.

CLINICAL PRESENTATION

Most patients with chronic urticaria have moderately to intensely pruritic cutaneous lesions and appear to have a lymphocyte-predominant infiltrate in lesional skin biopsy specimens. Individual urticarial lesions usually last for only several hours with no associated purpura or residual hyperpigmentation. Patients with PMN-cell-predominant urticarial lesions without vasculitis, on the other hand, appear to have a more severe clinical course. Often they report itching, stinging, and burning. In addition, their lesions tend to be slightly larger and the duration of the lesions longer (as long as and sometimes longer than 24 hours) than are lymphocyte-predominant urticarial lesions.^{2,5}

On the basis of these symptoms and signs, some clinical differences exist between patients with a lymphocyte-predominant infiltrate on skin biopsy samples and those with a PMN-cell-predominant infiltrate in lesional skin.

ETIOLOGY

Although the etiologic basis of acute urticaria sometimes can be determined, a precipitating cause is often difficult to establish in patients with chronic disease. In a study of 226 patients with chronic urticaria,⁶ a cause was identified in only 21%, indicating that the majority of patients had idiopathic, chronic urticaria. Nevertheless, it is clear that identification and elimination of the cause of chronic urticaria constitute the most effective form of therapy.

Several agents and factors that have been implicated in provoking urticarial reactions should be considered when a patient with chronic urticaria is examined; these agents include medications, foreign sera, foods, food additives, infections, insect bites and stings, contactants, inhalants, and physical factors as heat, cold, light, pressure, vibration, and water. Urticarial reactions also have been associated with some genetic and systemic diseases (Table I). Associations with systemic disease, however, are uncommon.

PATHOPHYSIOLOGY

An understanding of the mechanisms responsible for urticaria should improve the effectiveness of therapeutic approaches. Numerous studies indicate that cutaneous mast cells and their mediators play a central role in urticaria; for example, the vascular changes observed in urticarial lesions can be attributed to the release of the preformed mast-cell mediator, histamine. When introduced in the skin, this mediator causes a wheal-and-flare reaction similar to urticarial lesions.⁷ The finding of elevated histamine levels in skin-blister fluids and cutaneous biopsy specimens of urticarial lesions^{8,9} further supports the significance of histamine in the pathogenesis of urticaria.

The skin mast cell generates other important vasoactive molecules, prostaglandin D₂ and leukotriene C₄, which can cause urticarialike reactions when injected in the skin.¹⁰ Although the contributions of

TABLE I. Potential causes of urticarial reactions

Medications
Sera
Foods
Food additives
Infections
Insect bites and stings
Contactants and inhalants
Physical agents
Heat
Cold
Light
Pressure
Vibration
Water
Diseases
Systemic lupus erythematosus
Serum sickness
Cryoglobulinemia
Juvenile rheumatoid arthritis
Hyperthyroidism or hypothyroidism
Muckle-Wells syndrome
Neoplasms
Mastocytosis

prostaglandin D₂ and leukotriene C₄ to the development of urticaria are not well established, it is known that histamine antagonists do not block the effects of these mediators.^{2, 5, 7} Mast-cell-derived chemotactic factors for neutrophils and eosinophils, including tumor necrosis factor- α also may account for some urticarial reactions, particularly, in PMN-cell-predominant urticaria.^{6, 7}

Several immunologic and nonimmunologic factors trigger mast-cell degranulation and mediator release in vitro and in vivo (Table II). Stimulation of cutaneous mast cells by the binding of antigen to specific surface-bound IgE antibodies may result in an immediate wheal-and-flare reaction and in a late-phase reaction. After an immediate response to antigen in the skin, the late-phase reaction slowly develops at the antigen challenge site. It consists of burning, pruritus, erythema, and induration that peak at 6 to 8 hours and typically resolve by 24 to 48 hours.¹¹ Histologically, late-phase reactions are characterized initially by vasodilation and a perivascular infiltrate consisting primarily of neutrophils and eosinophils with scattered mononuclear cells. This PMN-cell-rich reaction persists for approximately 24 hours but is replaced by a CD4⁺ (helper/inducer) T-lymphocyte reaction by 48 hours.¹¹⁻¹³

In studies of chronic urticaria, late-phase-like reactions were seen in patients with circulating IgG autoantibodies against mast cell and basophil IgE receptors who were injected with autologous serum.^{14, 15} Serial skin biopsies showed the early appearance of PMN cells, which were replaced by lymphocytes within 24 hours.

TABLE II. Potential mast-cell degranulators

Immunologic
Antigen
Anti-IgE autoantibodies
Anti-IgE-receptor autoantibodies
Anaphylatoxins C _{3a} and C _{5a}
Eosinophil major basic protein
Leukocyte-derived histamine-releasing factors
Nonimmunologic
Neuropeptides
Substance P
Calcitonin gene-related peptide
Vasoactive intestinal polypeptide
Neurokinin Y
Adenosine triphosphate
Hormones
Gastrin
Estrogen
Corticotropin
Medications
Acetylsalicylic acid
Nonsteroidal antiinflammatory agents
Opiates
Curare
Succinylcholine
Polymyxin B
Thiamine
Physical stimuli
Heat
Cold
Light
Pressure
Venoms
Radiocontrast media

These autoantibodies may play an important role in chronic urticaria, especially in persistent PMN-cell-predominant urticaria.

Although the contribution of inflammatory cells to urticarial lesions is not well understood, lymphocytes and neutrophils are known to release a family of histamine-releasing factors that induce mast-cell degranulation.^{16, 17} Similarly, eosinophils store several mediators including major basic protein in their granules, which, when released, can cause mast-cell degranulation.¹⁸

Whereas activation of the mast cell and recruitment and activation of other inflammatory cells may explain the pathogenesis of urticaria, evidence suggests that the local release of neuropeptides from sensory nerve endings also may contribute to these cutaneous reactions. Several neuropeptides, including substance P, vasoactive intestinal polypeptide, calcitonin gene-related peptide, neuropeptide Y, and adenosine triphosphate, have been identified in sensory nerves innervating the skin.¹⁹ When these sensory nerves are stimulated, action potentials develop and move orthodromically toward the central nervous system. Retrograde, or antidromic, impulses

also may develop in some instances and lead to the release of one or more neuropeptides in the dermis. Studies *in vivo* indicate that substance P is the most potent degranulator of human skin mast cells.^{20, 21} The release of substance P from dermal sensory nerves may be responsible for dermatographism, which is often detectable in patients with chronic urticaria, and also may explain episodes of worsening hives in patients during times of emotional stress.

It appears that urticaria results from several pathologic events: mast-cell degranulation, infiltration of inflammatory cells, and release of neuropeptides from sensory nerves. In patients with chronic urticaria, repeated cycles of these proinflammatory events may account for prolonged disease activity.

TREATMENT

Examination of patients with chronic urticaria should focus initially on the identification and elimination of the etiologic agents or factors (Table I). Currently, however, a cause is identified in $\leq 20\%$ of patients with chronic disease.¹⁻⁶ For all patients with urticaria, avoidance of acetylsalicylic acid and nonsteroidal antiinflammatory agents is recommended, because these medications exacerbate existing urticaria approximately 50% of the time.¹⁻⁴ Patients having exacerbations with acetylsalicylic acid also should avoid potentially cross-reacting azo dyes and benzoates.²² Opiates are also known mast-cell degranulators, and patients should avoid their use whenever possible.^{23, 24} Therapeutic strategies for chronic idiopathic urticaria may depend on the histologic findings in a lesional skin biopsy specimen. Lymphocyte-predominant disease appears to respond better to antihistamine therapy than does disease with PMN-cell-rich infiltrates. Patients with PMN cells and urticarial vasculitis on skin biopsy samples have a disease distinct from that of patients without added vasculitis. Patients with urticarial vasculitis require more extensive examination and a different therapeutic approach.^{25, 26}

Most patients with chronic urticaria have the lymphocyte-predominant form of this disorder and may not require a skin biopsy on initial examination. A skin biopsy should be performed in patients who demonstrate clinical signs and symptoms suggesting PMN-cell-rich urticaria or those in whom the disease does not respond to the therapeutic approaches described for lymphocyte-predominant urticaria.

Lymphocyte-predominant urticaria

Histamine H_1 -receptor antagonists are effective therapeutic agents for many patients with chronic idiopathic urticaria, especially those with the lymphocyte-predominant form of this disorder.¹⁻⁵ Antihistamine use is based primarily on the hypothesis that mast-cell histamine plays a central role in urticaria.

Clinically, this choice is supported by the observation that both first-generation and second-generation antihistamines have proven effective in chronic idiopathic urticaria.

Although first-generation H_1 antihistamines are effective, they have the disadvantage of causing significant sedation. Second-generation H_1 antagonists offer the advantage of little or no sedative effects and in general have a longer half-life.²⁷⁻²⁹ Many cases of chronic urticaria can be controlled with a single H_1 antihistamine; however, some respond better to a combination of two H_1 antagonists. The use of a second-generation antihistamine during the day and a first-generation antihistamine in the evening is often an efficacious and practical use of different classes of H_1 antagonists.

Caution should be taken, however, when the second-generation H_1 antagonists astemizole and terfenadine are combined with other medications. Macrolide antibiotic agents, imidazole antifungal agents, and quinine have been reported to inhibit hepatic drug-metabolizing enzymes and thus to increase serum levels of these antihistamines.^{30, 31} Increased serum concentrations of astemizole and terfenadine can induce torsade de pointes, a potentially lethal cardiac arrhythmia.^{32, 33}

The tricyclic antidepressant doxepin, a potent H_1 -receptor antagonist with H_2 -receptor activity, is also useful for the treatment of patients with chronic urticaria.³⁴ However, because of its soporific effects, it is best tolerated at bedtime.

Because histamine mediates its effects through both H_1 and H_2 receptors,^{35, 36} H_2 antagonists have been used in combination with H_1 antagonists. Although the efficacy of combined H_1 and H_2 antagonists is questionable, several reports indicate that this combination is effective in the management of some cases of chronic urticaria.^{37, 38}

The calcium channel blocker nifedipine, combined with antihistamines, has been reported to be effective in some cases of chronic idiopathic urticaria in dosages of 10 mg two times per day to 20 mg three times per day.³⁹ Overall, however, this treatment appears to have limited efficacy for patients with chronic urticaria in whom the disease is unresponsive to antihistamines alone.

Because of numerous side effects, long-term use of systemic corticosteroids should be avoided; however, short-term systemic corticosteroid therapy is often effective in controlling active disease. Corticosteroids do not inhibit cutaneous mast-cell degranulation directly, but they do affect the function and cytokine production of various inflammatory cell populations.⁴⁰ Institution of oral prednisone at dosages of 20 to 30 mg/day for ≤ 5 days often controls the symptoms of urticaria effectively and permits successful introduction of antihistamine therapy. Exacerbations of urticaria often occur at the time of corticosteroid withdrawal in patients treated with corticosteroids for > 5 days.

PMN-cell-predominant urticaria

PMN-cell-predominant urticaria is often unresponsive to antihistamine therapy alone.^{2, 5} Nevertheless, because histamine probably plays some pathologic role, first- and second-generation H_1 antagonists should be used as described for patients with lymphocyte-predominant urticaria. The new, second-generation antihista-

mine cetirizine, which is the active metabolite of hydroxyzine, suppresses the histamine-induced wheal-and-flare reaction for ≤ 24 hours.⁴¹ Research in which a skin chamber is used to simulate an antigen-induced late-phase reaction indicates that cetirizine also may have important antiinflammatory effects by suppressing the migration of neutrophils, eosinophils, and basophils into the chamber.⁴² On the basis of its putative antiinflammatory effects, cetirizine may prove useful for the management of PMN-cell-predominant urticaria, but further studies of this possibility are required.

Patients with PMN-cell-predominant urticaria often require agents in addition to antihistamines for disease control. Colchicine at dosages of 0.6 mg two times per day and dapsone at dosages of 50 to 150 mg/day are useful as adjunctive therapy. Because the use of dapsone is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, an adequate serum level of this enzyme should be documented in patients before therapy is instituted. When introducing an H₁ antihistamine in conjunction with colchicine or dapsone, it is beneficial to treat patients initially with prednisone 30 mg/day for 3 to 5 days.⁴³ This combined therapeutic approach permits rapid control of disease activity while allowing time for the achievement of effective tissue levels of antihistamine and anti-PMN-cell agents.

On occasion, urticaria is unresponsive to one or more of the therapeutic regimens described. For these patients, it is important to rule out the diagnosis of urticarial vasculitis by performing a skin biopsy. Urticarial vasculitis is usually resistant to antihistamines and low to moderate doses of corticosteroids but often can respond to a combination of high-dose corticosteroids plus colchicine or dapsone.^{25,26} For patients without urticarial vasculitis, other therapeutic approaches to consider include plasmapheresis and administration of cyclosporine A.^{44,45} Although reported to be effective, these treatments are only short-term solutions, because urticaria often recurs when treatment is withdrawn and because both treatments are extremely costly.

SUMMARY

Chronic urticaria is a cutaneous reaction pattern for which there are many potential causes. Although the disease is most commonly idiopathic, it is important to attempt to identify and eliminate the underlying causes because this approach is the most effective form of therapy. When underlying factors cannot be identified, treatment regimens may be planned on the basis of the type of inflammatory-cell infiltrate present in skin biopsy specimens. As understanding of the pathophysiology of urticaria expands, more effective therapeutic agents and strategies should emerge.

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Risk management in allergen immunotherapy

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The major risk of allergen immunotherapy is the development of systemic anaphylactic reactions. The reported frequency of systemic reactions after allergen immunotherapy varies from <1% in patients receiving conventional immunotherapy to >36% in patients receiving rush immunotherapy. Fatal and systemic reactions to allergen immunotherapy have similar characteristics. The onset of both types of reaction occurs <30 minutes after injection in approximately 70% of patients. The most common risk factors for fatal and systemic reactions to allergen immunotherapy include a history of asthma, increasing allergen dose, high allergen sensitivity, previous systemic reaction, and injection during an active allergen season. On the basis