

Chronic Urticaria: Mechanisms and Treatment

Roger W. Fox, M.D.

ABSTRACT

Chronic urticaria (CU) is a vexing clinical syndrome. The clinician is challenged by the patient's symptoms. The experienced physician can evaluate the CU patient and prescribe effective treatment. The following review emphasizes the autoimmune mechanisms of CU. Despite this new insight into the pathogenesis of CU, many cases are still categorized as idiopathic. CU patients are a heterogenous group of patients who require an individualized approach to evaluation and management. (Allergy and Asthma Proc 22:97-100, 2001)

The cardinal clinical features of chronic urticaria (CU) are repeated occurrences of short-lived cutaneous wheals accompanied by redness and itching exceeding six weeks. Wheals are lesions ranging from a few millimeters to several centimeters in diameter. Individual groupings of urticaria may become confluent and develop into a large plaque. The individual wheals last less than 24 hours, with the exceptions of delayed pressure urticaria and urticarial vasculitis, which persist for 24-72 hours. Urticaria may occur anywhere on the skin, including the scalp, palms, and soles. There may be only one hive or a generalized outbreak. The itch of urticaria is the hallmark symptom, and it is usually worse in the evening or nighttime. CU typically follows this diurnal pattern. Angioedema (AE) accompanies 40-50% of the cases of chronic urticaria and 10% of the patients experience only AE without hives. AE is a mani-

festation of the same pathogenic process as urticaria. AE is a dermal, subcutaneous, or submucosal extravasation of plasma compared to the superficial dermal process in urticaria involving the post-capillary venules. Prominent AE may persist longer than 24 hours because of the time needed to resorb the tissue fluid. The sites of predilection for AE are dependent regions such as the hands, feet, genitals, face, eyelids, and lips. The alarming nature of oropharyngeal angioedema is rarely life-threatening in CU. AE does not itch; rather, the patient experiences burning or pain.¹

Urticaria and angioedema are common cutaneous manifestations of many different disorders, and 20% of the general population experience hives some time in their lives.² Chronic urticaria occurs in 0.1% of the population;³ when extrapolated to the U.S. population, 250,000 persons would have CU. Twenty percent of CU patients may be symptomatic over 20 years. The average duration of CU is about 3 to 5 years in adults, and a mean symptomatic period for CU of 6 months has been reported. Women are affected twice as often as men, and CU is uncommon in childhood.

The clinician can usually identify allergic type of urticaria, physical urticaria, and urticaria associated with connective tissue diseases by a thorough history and physical exam. The physical urticaria (cold, cholinergic, solar, dermatographia)⁴ can be reproduced with the appropriate cutaneous stimulus and/or present at the time of the exam with the typical lesions. CU is rarely a manifestation of an allergic disorder, such as a 'hidden' food allergy or from a collagen vascular disease (systemic lupus or hypocomplementemic urticarial vasculitis (HUVS)).⁵ Patients with CU are generally healthy and represent a heterogenous group of patients, some of whom experience mild symptoms while others have severe hives that are refractory to antihistamines and other commonly prescribed medications.

Most patients with CU are diagnosed with chronic idiopathic urticaria (CIU), which means that no cause can be identified. Recent research has discovered an IgG autoantibody directed against the alpha subunit of the high-affinity

From the Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Health Sciences Center, Tampa, Florida

Presented at Eastern Allergy Conference, Palm Beach, Florida, May 6, 2000

Address correspondence and reprint requests to Dr. Roger W. Fox, Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Health Sciences Center, 13000 Bruce B. Downs Blvd., VAR 111D, Tampa, FL 33612

IgE receptor on the mast cell.³ Less than 50% of CU patients have evidence of this autoimmune mechanism by immunoblot method or by a positive autologous serum skin test (ASST). An anti-IgE antibody has been implicated in some CU patients. Twenty-five percent of CU patients have associated thyroid autoantibodies (anti-thyroglobulin and/or antiperoxidase).⁶ The laboratory evaluation of CU patients is based upon the history and physical findings. The mainstay of CU treatment includes antihistamines, while some patients require additional therapy to suppress the manifestations. The focus of this review is on the current body of knowledge on the autoimmune mechanisms and the treatment of this vexing, mucocutaneous disorder.

CHRONIC URTICARIA; AUTOIMMUNITY

The histopathology of CU is different from acute urticaria (caused by an allergic reaction to a drug, venom, or food). In addition to the dermal edema seen in both types of urticaria, a mixed cellular perivascular infiltration of the dermal postcapillary venules is present in CU. The infiltration predominantly consists of CD4+ T cells and monocytes, with a prominent neutrophilic and/or eosinophilic infiltration in some cases.⁷ The mast cell has a central role in the initiation of the process by releasing its mediators and cytokines and by activating and interacting with resident cutaneous cells and infiltrating cells. Epithelial (increased expression of TNF alpha), and endothelial cells (increased expression of adhesion molecules and IL3) play a supporting role in the pro-inflammatory process.⁸ The infiltrating cells (T cells, monocytes, neutrophils, and eosinophils) amplify the urticaria response by releasing additional mediators, cytokines, and chemokines. CU represents a dynamic process involving a complex interplay of a number of cells, mediators, cytokines, chemokines, and adhesion molecules. The entire integument is activated in CU.

An initiating event for CU had been elusive, but in 1986 Grattan et al.⁹ reported the presence of a serum factor that caused whealing on autologous intradermal injection or the ASST in some, but not all, patients with CU. In 1993, Greaves' laboratory identified this factor as an IgG with specificity for the alpha subunit of the high-affinity IgE receptor.¹⁰ Subsequent studies have demonstrated this histamine-releasing receptor antibody as a causative factor in 30–45% of CU patients and another 5–10% have a pathogenic anti-IgE autoantibody. Anti-IgE receptor antibody is ubiquitous, and it is a nonpathologic antibody in several other cutaneous diseases and in normal controls. The IgG subtypes in CU are predominantly IgG1 and IgG3, both of which bind complement. Complement activation is required in CU along with the anti-IgE receptor antibody. The complement byproduct, C5a, is necessary for mast cell histamine release.¹¹ Only cutaneous mast cells have the receptor for C5a, explaining why mast cells in the lung or GI tract aren't activated in CU.

Less than 50% of CU patients react to an autologous serum skin test. Of these patients, 80% have a positive

immunoblot test demonstrating the presence of IgG to the alpha subunit of the IgE receptor. A histamine releasing factor (HRF) has been identified in the serum of CU patients, and HRF induces a wheal and flare response in some cases of CU.¹² Plasmapheresis removes the IgG anti-IgE receptor antibody, and results in temporary clinical improvement.¹³ Intravenous gamma globulin induces a partial remission in CU, presumably by increasing the degradation of the pathogenic IgG.¹⁴

CHRONIC URTICARIA: URTICARIAL VASCULITIS

The incidence of chronic urticaria as a manifestation of a systemic connective tissue disease is <1%.¹⁵ The most common immunologic disorders associated with urticarial vasculitis are serum sickness, chronic hepatitis C, HUVS,¹⁶ and systemic lupus erythematosus (SLE). Immune complexes are deposited in the dermal post-capillary venules. Activation of the complement cascade results in the leukocytoclastic vasculitis changes in the skin (neutrophilic infiltration, nuclear debris, destructive changes of the involved venule). These patients are usually identified by the appearance and duration of the individual lesions (palpable purpura or persistent urticaria lasting 24–72 hours), associated hypocomplementemia, and elevated sedimentation rate. Other constitutional symptoms, such as fever or organ involvement (kidney, lung) are typical with these systemic disorders. Rarely, urticarial vasculitis can be an isolated manifestation involving only the skin. The histological findings of cutaneous vasculitis can usually be differentiated from the intense neutrophilic infiltration found in some patients with CU. The treating physician is concerned about missing the diagnosis of urticarial vasculitis, despite the rarity of these diseases causing chronic urticaria. Such physicians may order numerous, often unnecessary, laboratory studies (ANA, ESR, complement levels, hepatitis profiles). An extensive workup is indicated in the severe refractory cases of CU.

CHRONIC URTICARIA: THE THYROID CONNECTION

Seventeen to twenty-seven percent of euthyroid CU patients have thyroid autoantibodies (TA), antithyroglobulin, and/or anti-peroxidase.⁶ TA are found in <6% of the general population. The precise role for these IgG autoantibodies in CU is unclear. Case reports of two CU patients have identified an IgE antibody for thyroid antigens which may be causative.¹⁷ Thyroid hormone treatment has been reported to control the chronic urticaria in a small group of CU patients, although not all CU patients in the study responded to thyroid hormone. The thyroid autoantibody titers are not reduced by the thyroid hormone treatment. The association of thyroiditis, usually Grave's disease, with CU is cited in the literature. Not all patients' urticaria presenting with hyperthyroidism responds to treat-

ment of the underlying thyroid disorder. In addition, patients develop CU with a longstanding thyroid disorder who are stable on thyroid treatment, thus there appears to be no relationship between CU and TA in these cases.

Thirty-five percent of CU patients with a positive ASST have thyroid autoantibodies, whereas 15% of the CU patients without a positive ASST test positive for TA. In accordance with the proposed autoimmune basis of this subset of CU patients, a positive association with HLA-DR and -DQ alleles, known to be associated with autoimmunity, has been described.¹⁸ Some experts believe that the observation of TA in some CU patients represents an unrelated, although parallel autoimmunity and the TA are only markers of autoimmunity.

CHRONIC URTICARIA: THE EVALUATION

Most CU patients are healthy individuals by history and physical exam, and no inciting cause is revealed by detailed questioning.¹ The CU patients are looking for answers to their chronic problem. Routine laboratory evaluations and vasculitis workups rarely uncover an etiology or change the treatment plan of the usual CU patient. Physical urticaria and urticarial vasculitis are diagnosed at the time of the physical exam by the experienced physician. There is no routine CU laboratory panel. A limited workup for CU can be ordered, which includes a CBC with differential, UA, ESR, and liver function studies. This approach may satisfy patients when they are told that "everything is normal." Specific studies can be ordered based on the clinical findings for vasculitis or hereditary angioedema. Food allergy tests or double-blind food/food additive provocation testing are rarely required in the CU patient, except in the rare case. Evaluations for chronic infections such as chronic sinusitis, *H. pylori*, *Trichophyton*, or *H. simplex* are futile endeavors.³

The typical CU patient should be screened for thyroid autoantibodies, and an autologous serum skin test can be easily done. In the refractory, severe CU patient, an autoimmune workup and skin punch biopsy are performed to evaluate for cutaneous vasculitis. For the angioedema-only patient who isn't taking an angiotensin converting enzyme (ACE) inhibitor, an evaluation for C1 esterase inhibitor (C1INH) deficiency is needed. Order quantitative and functional C1 INH, C1, C3, and C4 levels. Low or undetectable C1 INH and C4 make the diagnosis of hereditary angioedema. A low C1 level distinguishes the acquired type of C1 INH deficiency from the hereditary types of angioedema.¹⁹

CHRONIC URTICARIA: THE TREATMENT

The first prescription for all CU patients is an H1 antihistamine. The selection and dose of an H1 antihistamine depend upon the patient's response to the antihistamine. The ideal choice is an antihistamine that controls the pruritus and suppresses the wheal and flare without side effects. The less sedating antihistamines, Claritin, Allegra, and Zyrtec, are considered the first line treatments, since

each is well tolerated at standard doses as well at higher doses that may be necessary for symptom control. For example, Allegra 60 mg b.i.d. may suffice, but Allegra 180 mg b.i.d. is recommended for the more refractory patient. Likewise, Claritin and Zyrtec are often prescribed at double the standard dose. Benadryl or hydroxyzine are commonly prescribed for the CU patient and each is effective, but sedation is a limiting factor. Hydroxyzine is often considered the drug of choice for CU in doses up to 50 mg every 6 hours. The physician may choose to prescribe a less sedating antihistamine in the morning and a sedating antihistamine in the evening. This combination achieves the desired goal of providing 24 hour antihistamine suppression of the symptoms with the fewest side effects. Another strategy is to give sedating antihistamines in low initial doses and gradually increase the dose until control of the hives is achieved. What is the optimal dose of an antihistamine or combination of antihistamines? The patient who doesn't respond to recommended doses or even double doses probably will not benefit by increasing the antihistamine dose or adding another antihistamine, particularly if the histamine skin test is suppressed by the prescribed antihistamine(s).

The physician at this point must decide whether to add another agent, such as an H2 antihistamine, or a leukotriene receptor antagonist (LTRA), Accolade or Singulair, to the H1 antihistamine. An H2 antihistamine improves the clinical course of a select few CU patients. The LTRAs have been reported to benefit small numbers of patients. Alternatively, the tricyclic antidepressant, Doxepin, is commonly prescribed when the above regimen have failed.¹ Doxepin is an excellent H1 and H2 antihistamine, but it is extremely sedating. Doxepin can be prescribed in the evening along with a less sedating antihistamine in the morning. As mentioned above, L-thyroxine may be used in the patient with demonstrable thyroid autoantibodies. An adequate trial with L-thyroxine for a month is recommended until the hives are controlled or until the TSH is suppressed. Corticosteroids are very effective in the management of severe CU, but the extended use of corticosteroids is not recommended due to their side effect profile. The exceptions to this rule are the severe cases of CU patients who require corticosteroids, because no other treatment has an impact on the clinical course. In these difficult cases all attempts to taper or to utilize alternate day corticosteroid therapy are mandatory. The experienced physician can utilize steroid-sparing agents in the severe CU patient. The drugs reported in the literature or in case studies include Dapsone, Plaquenil, Methotrexate, Stanazolol, and Cyclosporin. The response to each one of these drugs is unpredictable, and the side effects must be considered in the individual patient. The clinical experience with Cyclosporin is very encouraging. Cyclosporin in doses of 3.0–4.5 mg/kg have had good to excellent responses in two-thirds of patients who were treated for 3 months.²⁰ CU patients with anti-IgE receptor antibody have improved transiently after plasmapheresis and IV gamma globulin

infusions, but these treatments are expensive and unwarranted. Each clinical trial with a treatment plan should be carefully monitored for at least a month to determine whether a significant benefit can be determined. Fortunately, most CU patients are easily managed with antihistamines, but a select group of patients is much more difficult to manage, and present a frustrating experience for both the patient and the physician. Further evaluations of new treatments are needed before they can be generally accepted therapies for even the most severe CU cases. Future treatments will be guided by scientific discoveries on the molecular or cellular interactions involved in the pathophysiology in CU.

REFERENCES

1. Fox R. Urticaria and angioedema, Ch. 17. In *Current Practice of Medicine: Allergy and Immunology*, 2nd Ed. Lieberman PL (Ed.) Current Medicine, Inc., 141–150, 1998.
2. Champion R. H., Roberts S. O. B., Carpenter R. G., and Roger J. H. Urticaria and angioedema—a review of 554 patients. *Br J Dermatol* 81:588–597, 1969.
3. Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 105:664–672, 2000.
4. Casale T. B., Sampson H. A., Hanifin J., et al. Guide to physical urticarias. *J Allergy Clin Immunol* 82:758–763, 1988.
5. Greaves M. W. Chronic urticaria. *N Engl J Med* 332:1767–1773, 1995.
6. Leznoff A., and Sussman G. L. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity—a study of 90 patients. *J Allergy Clin Immunol* 84:66–71, 1989.
7. Sabroe R. A., Poon E., Orchard G. E., et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 103:484–493, 1999.
8. Hermes B., Prochazka A. K., Haas N., et al. Upregulation of TNF-α and IL-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol* 103:307–314, 1999.
9. Grattan C. E. H., Wallington T. B., Warin R. P., et al. A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. *Br J Dermatol* 114:583–590, 1986.
10. Hide M., Francis D. M., Grattan C. E. H., and Greaves M. W. Autoantibodies against the high affinity IgE receptor as a cause for histamine release in chronic urticaria. *N Engl J Med* 328:1599–1604, 1993.
11. Ferrer M., Nakazawa K., and Kaplan A. P. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 104:169–172, 1999.
12. Fagiolo U., Cancian M., Bertollo L., et al. Inhibitory effect of heparin on skin reactivity to autologous serum in chronic idiopathic urticaria. *J Allergy Clin Immunol* 103:1143–1147, 1999.
13. Grattan C. E. H., Francis D. M., Slater N. G. P., et al. Plasmapheresis for severe unremitting chronic urticaria. *Lancet* 339:1078–1080, 1992.
14. O'Donnell B. F., Barr R. M., Blac A. K., et al. Intravenous immunoglobulin in chronic autoimmune urticaria. *Br J Dermatol* 138:101–106, 1998.
15. Tong L. J., Balakrishnan G., Kochan J. P., et al. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 94:461–465, 1997.
16. Wisniewski J. J., Baer A. N., Christensen J., et al. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serological findings in 18 patients. *Medicine* 74: 24–41, 1995.
17. Bar-Sela S., Reshef T., and Mekori Y. A. IgE antithyroid microsomal antibodies in a patient with chronic urticaria. *J Allergy Clin Immunol* 103: 1216–1217, 1999.
18. O'Donnell B. F., O'Neill C. M., Francis D. M., et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. *Br J Dermatol* 140: 853–858, 1999.
19. Markovic S. N., Inwards D. J., Frigas E. A., and Phyllyk R. P. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med* 132:144–150, 2000.
20. Grattan C. E. H., O'Donnell B. F., Francis D. M., et al. Randomised double-blind study of cyclosporin in chronic idiopathic urticaria. *Br J Dermatol*, in press. □

Allergy and Asthma Proceedings

Back issues available at \$15.00 each.
Postage: add \$5.00 for foreign address

16E, Risk Factors and Severity Index
Vol. 20 No. 1(January/February 1999)

Asthma, Latex Allergy, Rhinitis Update
Vol. 20 No.2(March/April 1999)

New Mediators of Inflammation and Corticosteroids
Vol. 20 No.3(May/June 1999)

Avoidable Complications of Allergic Rhinitis(Symposium)
Vol. 20 No.4(July/August 1999)

Allergen Immunotherapy and Asthma Management
Vol. 20 No.5(Sept/Oct 1999)

Advances in Allergy,1999(IRINE Symposium) Nov/Dec 99

Combined Allergy Immunology Meeting 1998
Vol. 19 No. 6 (November/December 1998)

Eosinophil and Chemokines
Vol. 19 No. 5 (September/October 1998)

Allergic Rhinitis Associated with Sinusitis
and Asthma (Symposium)
Vol. 19 No. 4 (July/August 1998)

Chemokines and Asthma
Vol. 19 No. 3 (May/June 1998)

Eosinophilic Cationic Protein in Asthma and Rhinitis
Vol. 19 No. 2 (March/April 1998)

Gustatory Sweating
Vol. 19 No. 1 (January/February 1998)

Hypersensitivity Pneumonitis
Vol. 18 No. 6 (November/December 1997)

Advances in Allergy and Immunology
(Irine Symposium)
Vol. 18 No. 5 (September/October 1997)

A Bimonthly Journal

Begin my subscription with the current issue.

Name _____
(Please print)
Address _____
City _____ State _____ Zip _____

2001 Subscription Rates

	Domestic (U.S.A.)	All Foreign Countries
Institutional	\$200.00	\$230.00
Personal	\$120.00	\$150.00

- ☐ Payment enclosed
☐ Change of address

CHANGE OF ADDRESS

If your
mailing address
is changing show
old address below...and new address above.

Name _____
(Please print)

Address _____

City _____ State _____ Zip _____

Change of address for the _____ issue.

Editor

GUY A. SETTIPANE, M.D.

Participating Allergy Societies

Alabama Society of Allergy and Immunology
Arizona Society of Allergy
Arkansas Allergy Society
Buffalo Allergy Society
California Society of Allergy and Clinical Immunology
Cleveland Allergy Society
Colorado Allergy Society
Connecticut Society of Allergy and Clinical Immunology
Eastern Allergy Conference
Florida Allergy and Immunology Society
Georgia Allergy Society
Greater Kansas City Allergy Society
Greater Washington Allergy Society
Illinois Society of Allergy and Clinical Immunology
Iowa Society of Allergy and Immunology
Kentucky Allergy Society
Louisiana Allergy Society
Maine Society of Allergy and Clinical Immunology
Maryland Society of Allergy
Massachusetts Society of Allergy
Michigan Allergy Society
Mid-South Allergy Forum
Mid-West Forum on Allergy
Missouri State Allergy Assoc.
Nassau-Suffolk Allergy Society (N.Y.)
New England Society of Allergy
New Hampshire Allergy Society
New Jersey Allergy Society
New Mexico Allergy Society
New York Allergy Society
New York State Allergy Society
Ohio Society of Allergy and Immunology
Oklahoma Allergy Society
Orange County Society of Allergy and Clinical Immunology
(California)
Pennsylvania Allergy Association
Rhode Island Society of Allergy
South Carolina Society of Allergy and Clinical Immunology
Southwest Allergy Forum
Tennessee Society of Allergy and Immunology
Texas Allergy Society
Virginia Allergy Society
Washington State Society of Allergy and Immunology
Westchester Allergy Society (N.Y.)
Western Society of Allergy and Immunology
Wisconsin Allergy Society

Return Address

STAMP

Allergy and Asthma Proceedings
95 Pitman Street
Providence, Rhode Island 02906

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.