Case in Point

Chronic Urticaria

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The diagnosis of this condition can prove challenging, and treatment—as this case illustrates—may be just as problematic.

Chronic urticaria is defined by the presence of itchy, red, patchy areas of raised erythema and edema of the superficial dermis—often described by patients as swollen, rashy welts, or wheals—for longer than six weeks. In many cases, patients struggle with relapsing prurutic symptoms, which may be resistant to multiple treatments, for months or even years. And while urticaria may occur secondary to a great number of triggers, the chronic condition often goes unexplained even after prolonged investigation involving expensive laboratory tests. As such, chronic urticaria—though usually not life threatening—can be a great source of frustration for both patients and health care providers.

In this article, we present a case of chronic urticaria that ties together the current understanding of the condition's underlying pathophysiology with evidence-based, best practice management.

INITIAL EXAM

A 36-year-old, Hispanic man presented to the medical clinic of a naval unit with a one-month history of worsening urticaria. Wheals first appeared on his face, where they lasted several hours to one day before resolving spontaneously. Later, they reappeared and subsequently resolved in various other locations, including his neck and torso (Figure 1). He reported that, over a period of three days, the wheals appeared all over his body, occurring most frequently on areas covered with clothing and on such pressure points as the beltline. The patient's symptoms were aggravated by hot showers and were most prominent at the end of the day. He experienced swelling of his hands and ankles with intermittently recurring facial and labial swelling (Figure 2). Although he reported having no dyspnea, he did report an itching sensation in his throat when the wheals appeared on his face and neck.

One week prior to symptom onset, the patient had been prescribed methocarbamol and naproxen as needed for upper back strain. He also had been taking two over-the-counter (OTC) herbal substances: green tea extract and a weight-loss formula containing caffeine, green tea, guarana, L-carnitine, and other herbal components. After the onset of urticaria, however, he stopped taking the prescribed medications and the herbal substances and began taking OTC oral diphenhydramine hydrochloride (HCl) in capsule form every six to eight hours. The patient continued use of this medication for one month and made an appointment at the clinic due to increased frequency of facial and labial swelling. By the patient's report, his symptoms persisted despite antihistamine use but worsened each time he attempted to stop taking the antihistamine.

The patient reported no recurrent use of NSAIDs or other herbal medications during this month period. He had no history of atopic diseases, medication allergies, or previous allergic reactions—even during previous use of OTC nonsteroidal anti-inflammatory drugs (NSAIDs). He reported no recent travel; illness (including fever or arthralgias); contact with pets; changes in diet, weight, soaps, or detergents; or use of cleaning agents or solvents. Further, he reported no unprotected sexual intercourse, intravenous drug use, or exposure to blood products.

TREATMENT COURSE

After his first clinic visit, a plan was devised to conduct a trial of dietary and exposure restriction. The patient was instructed to avoid eating nuts, unwashed fruits and vegetables, berries, and seafood and to avoid using cleaning agents, new detergents and soaps, and any herbal and new OTC medications. In addition, he was asked to keep a diary of his symptoms and exposures to chemicals, lotions, new clothing, detergents, arthropods, new foods, and OTC and herbal medications. He was instructed to continue taking diphenhydramine HCl 25 or 50 mg capsules every four to six hours as needed.

Over the next month, the patient attended weekly clinic visits, and his vital signs were found to be normal

Continued on page 22

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Continued from page 19

at each visit. No significant symptom trigger associations were elicited from his diary. The urticaria continued despite the dietary and exposure restrictions and the use of diphenhydramine HCl. Serial examinations of his skin revealed scattered, elevated, erythematous annular wheals that changed in distribution with each successive visit, sparing the mucous membranes of the oropharynx. Angioedema of the labial and periorbital regions, also sparing the mucous membranes, were noted on two separate evaluations. No evidence of hyperpigmentation or peripheral adenopathy was found. Dermographism could not be elicited, but the wheals did blanch with pressure. No other significant physical examination findings were noted.

Due to the repeated recurrence of the patient's angioedema symptoms, the allergy service was consulted one week after his initial presentation. The results of laboratory studies conducted at this time—including a complete blood cell count with differential, erythrocyte sedimentation rate, thyroid profile, and urinalysis—were all normal. As the patient's wheals had a history of resolving in less than 12 hours, biopsy was not indicated. Further laboratory studies, for hepatitis C virus and parvovirus B19, were obtained and yielded negative results.

Per the recommendations of the allergy service clinicians, diphenhydramine HCl was discontinued and replaced with loratadine 10 mg at bedtime; ranitidine 150 mg twice a day; and a short course of prednisone, starting at 60 mg once a day and tapering over a nine-day period. Mild intermittent recurrence of urticarial symptoms was noted while the patient was taking the prescribed medications.

Two weeks later, after the patient had completed the prednisone taper, his symptoms recurred and worsened.

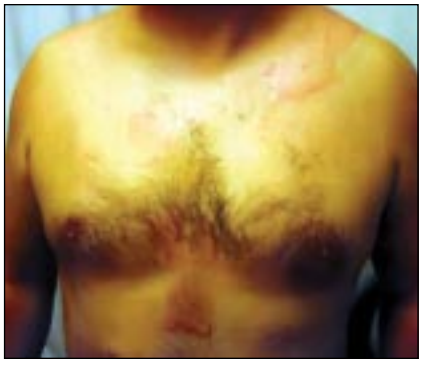

Figure 1. Urticaria appearing on the patient's neck and torso at initial presentation.

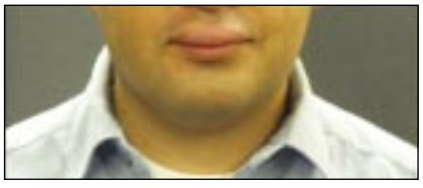

Figure 2. Labial angioedema, which the patient experienced intermittently along with facial swelling.

Consequently, he was prescribed a second course of prednisone with an extended taper, fexofenadine HCl 180 mg in the morning, cetirizine 10 mg at bedtime, montelukast sodium 10 mg at bedtime, and ranitidine 150 mg twice a day. Despite these changes to the patient's medication regimen, his symptoms did not resolve completely.

Various adjustments were made to his medication regimen: fexofenadine HCl and montelukast sodium were discontinued after two months and he was instructed to continue taking cetirizine once a day and ranitidine twice a day. He also received three more tapering courses of prednisone, with the final taper lasting four weeks.

Four months after his initial presentation, the patient has not been prescribed more corticosteroids nor has he been rechallenged with NSAIDs or muscle relaxants since they were discontinued. He continues to experience urticarial symptoms intermittently, without concurrent angioedema. As of this writing, the patient is still taking cetirizine and ranitidine. His urticarial symptoms have become less pronounced and he generally is able to tolerate them.

ABOUT THE CONDITION

Urticaria occurs due to a release of immune mediators and vasoactive substances that lead to localized edema of the superficial dermis. Angioedema progresses through similar mechanisms, but it involves deep dermal and subcutaneous tissues.

Almost a quarter of the general population will experience urticaria or angioedema at least once in their lifetime. The majority of chronic urticaria cases occur in adults, and women are twice as likely as men to be affected.[4] Angioedema occurs concurrently in up to 40% of patients with urticaria, though it can present as an isolated finding in about 20% of cases.[1,2]

Typically, angioedema involves the face (cheeks and periorbital area), lips, tongue, pharynx, and extremities. The presence of angioedema in patients with chronic urticaria can serve as a prognostic indicator in that it may signify an increase in severity and duration of symptoms.[3] Since hereditary or acquired angioedema generally presents without concurrent urticaria,[1] patients with repeated bouts of isolated angioedema should be evaluated for a hereditary deficiency of C1 esterase inhibitor.

Etiology

With conflicting opinions expressed in various guidelines and little supporting evidence, causative factors for chronic urticaria are a matter of dispute. The cause of immune mediator and vasoactive substances release may be autoimmune in nature

Continued on page 27

Continued from page 22

or may be physically induced. In the majority of cases, however, the cause remains unknown.

Acute skin manifestations of immunoglobulin E (IgE)–mediated allergic reactions due to exposures from medications, foods, preservatives, and additives are well documented (Table 1). An exhaustive list of medications may cause or exacerbate histamine release and urticarial or angioedema symptoms through allergic or pseudoallergic reaction pathways. These pathways rarely cause chronic urticarial symptoms but may aggravate symptoms that are present already.[5] For example, NSAIDs may act as a nonallergic trigger of acute urticaria, possibly causing direct release of histamine from mast cells. These medications exacerbate chronic urticarial symptoms in a dose dependent fashion.[6] Patients exhibiting symptoms of urticaria or angioedema should avoid NSAIDs and other medications associated with these conditions, such as angiotensin converting enzyme inhibitors. New evidence suggests that aspirin-induced urticaria or angioedema is associated with human leukocyte antigen allele variations.[7]

Herbal substances also may cause or worsen urticaria. Some examples are echinacea, feverfew, garlic, glucosamine, and valerian.[8]

Reactions to food or food additives, immediately or shortly after exposure, are experienced in a minority of patients. For example, Zuberier and colleagues found that approximately 14% of 64 patients with chronic urticaria had confirmed reactions to food additives when given oral challenges.[9] Therefore, placebo-controlled food challenges can be performed based on a patient's suggestive history. These challenges should not be performed during acute or severe exacerbations of urticaria, however.[10] Skin testing for food allergies only detects IgE-mediated sensitization and will miss non–IgE-mediated reactions.[11]

A less clear and much debated association has been suggested between urticaria and chronic infections, such as with *Helicobacter pylori*. The presence of *H. pylori* bacteria in this patient population may be a coincidental finding, however. Conflicting recommendations exist regarding eradication in patients who have chronic urticaria and are colonized with this bacteria type.[12,13]

Table 1. Associated or aggravating conditions and exposures for chronic urticaria[11]

- Foods and food additives*
- Medications, including NSAIDs† and ACE‡ inhibitors
- Herbal substances, including echinacea, feverfew, garlic, glucosamine, and valerian
- Systemic diseases, including autoimmune diseases—particularly Hashimoto or Grave disease
- Physical stimuli, such as exposure to the sun, heat, and cold
- Allergens, such as molds and *Candida albicans**
- Other or idiopathic (approximately 60% of cases)

*Limited supporting evidence in chronic urticaria. †NSAIDs = nonsteroidal anti-inflammatory drugs. ‡ACE = angiotensin converting enzyme.

NSAIDs may act as a nonallergic trigger of acute urticaria, possibly causing direct release of histamine from mast cells.

Research in the past decade has broadened understanding regarding an immunogenic basis for some cases of urticaria. In fact, a substantial percentage (35% to 40%) of chronic urticaria cases appear to be autoimmune in nature, with the rest remaining idiopathic.[14] An association has been found with immune activation in a subpopulation of these patients. Hashimoto disease and Grave disease are acknowledged examples.

Abnormal thyroid function and the presence of antithyroglobulin antibody and antimicrosomal antibody occurs more commonly in patients with chronic urticaria than in general population.[15,16] While not directly causative of this condition, the circulating antibodies may be a sign of an undiscovered autoimmune pattern for chronic urticaria. A percentage of affected patients have circulating immunoglobulin G antibodies against either the alpha subunit of IgE or alpha subunit of the IgE receptor.[17] Basophils and mast cells are activated by these antibodies to release histamine. The presence of anti-IgE–related antibodies correlates with increased severity of disease.[18]

Research into the pathology of autoimmune-related chronic urticaria is ongoing. Areas of interest include

cellular infiltration of tissues; complement fixation, notably C5a; histocompatibility complexes; cytokines; and expression of adhesion molecules.[5]

Diagnosis

Given the transient nature of urticaria, it is useful diagnostically to have patients capture images of the wheals using digital cameras. Such images can reduce the likelihood that health care providers will misinterpret patients' observations. (In the case presented here, the patient reported to the medical department daily, thus precluding the need for photography.) It is also important to question patients regarding their recent activities and exposures to the elements, food, and medications (including nonprescription medications and herbal products).

The individual wheals of urticaria may be extremely pruritic and vary in size. They are transient in nature, lasting from four to 36 hours (though they usually resolve within 24 hours). A remitting and relapsing course characterizes chronic urticaria and it is generally worse at night.[2,3,19] Erythematous changes are sometimes confluent, and affected skin areas return to normal appearance with resolution. Coloration of the wheals may vary depending on the patient's skin pigmentation and central pallor may be seen.

Urticaria caused by physical stimuli—such as exercise; exposure to cold, heat, or stress; or pressure on the skin (such as a tight fitting belt or backpack)—usually last two hours or less, though they may last longer than eight hours occasionally.[1] A chronic urticaria diagnosis requires the presence of spontaneously occurring wheals not attributable to physical pressure. Challenge testing based on the patient's exposure history may lead to the discovery of concurrent physical urticarias.

Practice guidelines on managing urticaria and angioedema—published in 2000 by the Joint Council of Allergy, Asthma and Immunology—emphasize ruling out other potentially treatable conditions before making the diagnosis of chronic idiopathic urticaria (Table 2).[18] Two of these conditions are urticarial vasculitis and urticarial pigmentosa.

Physical examination findings that are suggestive of urticarial vasculitis are pigmentary changes, petechiae or purpura, or persistence of wheals for 36 hours or more. Lesions that blanch with pressure are helpful to exclude vasculitis or infiltrative disease.[2] In addition, urticarial vasculitis is less pruritic in nature than chronic urticaria and may be associated with connective tissue disorders or systemic vasculitis.[19] Less than 1% of all cases of chronic urticaria are due to a cutaneous vasculitis, such as urticarial vasculitis.[20]

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Table 2. Conditions to be considered in the differential diagnosis of chronic urticaria[18]

- Adverse drug reactions
- Urticarial vasculitis
- Connective tissue disorders
- Urticaria pigmentosa
- Idiopathic anaphylaxis
- Immunobullous eruption (urticarial phase)

Urticarial pigmentosa, the most common form of cutaneous mastocytosis and another condition included in the differential diagnosis of chronic urticaria, also is diagnosed primarily by the patient's history and physical examination results. In adults with this condition, cutaneous, pigmented, 3- to 4-mm macules or papules present most commonly in a truncal distribution. Dermographism appears only on these maculopapular areas and not on lesion free skin (a positive Darier sign). Urticarial pigmentosa often is the presenting feature of systemic mastocytosis.[21] A skin biopsy of the wheals is indicated for these findings or if an associated history of arthralgias or fever is elicited.

A biopsy may be obtained to rule out other etiologies of urticaria when the symptoms have been prolonged or severe.[22] Selective laboratory testing, such as erythrocyte sedimentation rate and rheumatologic serology tests, should be obtained based on the patient's history; otherwise, more cost than value is gained. Unfortunately, an inciting cause for chronic urticaria is elicited in only 5% to 20% of cases with extensive laboratory testing.[11]

Research into appropriate screening tests has met with limited success, though a subgroup of patients

with chronic urticaria can be identified by an autologous skin serum test (ASST). This test involves the intradermal injection of the patients' own serum, with a wheal and flare reaction considered a positive result. Such testing may identify autoantibodies in one third to one half of patients with chronic urticaria. The test's sensitivity and specificity for autoimmune urticaria are 70% and 80%, respectively. In a large number of patients, the ASST remains positive after urticarial symptoms have resolved.[23]

Consultation with such specialists as a dermatologist, allergist, or immunologist may aid in diagnosis and management.[24] A review of medical literature did not reveal specific referral criteria for possible chronic urticaria, but specialists may be able to manage further testing (as indicated) and off-label use of medications that may manage the condition more effectively.

Treatment

Regardless of etiology, the foundation of chronic urticaria management consists of avoiding aggravating factors and using antihistamines—specifically nonsedating H1 receptor antagonists—in a maintenance rather than an abortive role (Table 3).[18] In fact, antihistamines are the only medications approved by the FDA for chronic urticaria treatment.

Several studies have evaluated the efficacy of H1 receptor blockers in treating chronic urticaria, both alone and in combination.[25–28] For monotherapy, older antihistamines (such as hydroxyzine) that nonspecifically target H1 and H2 receptors are very effective in managing urticaria. The adverse effect of drowsiness, however, often leads to medication discontinuation. The patient may tolerate the sedating effects of hydroxyzine better if the drug is administered at bedtime. Patients are advised against operating machinery and driving while using these first-generation, sedating antihistamines.

Table 3. Therapeutic options (both on- and off-label) for chronic urticaria management[18]

Therapy	Comments
Antihistamines*	
• H1 receptor antagonists	
–Nonsedating	Safe adverse effects profile; primary therapy choice
–Sedating	Also peripherally block H2 receptors; adverse effect profile may be difficult to tolerate; nighttime administration an option
• H2 receptor antagonists	Safe adverse effect profile but limited incremental benefit
Tricyclic antidepressants (doxepin)	Frequently discontinued due to adverse effects
Leukotriene antagonists	No more effective than placebo when administered with maximized histamine blockade
Combination therapy with multiple medication classes	Experimental, limited trials conducted to study efficacy
Adrenergic medication	Reserve use for acute treatment of severe angioedema
Beta-agonists	May be used as an adjunct to antihistamines
Corticosteroids	Effective, but symptoms may rebound; multiple complications with high dosages and long-term use
Immunosuppressants	May be used as a corticosteroid sparing agent
Intravenous immunoglobulin	Theoretical benefit for unresponsive cases with associated antibodies, but supporting evidence limited
Plasmapheresis	Use limited by high cost and procedural risks

*Only agents FDA approved for treating chronic urticaria.

The combination of an H1 and H2 blocker can maximize histamine blockade, as both receptor types are present in the skin. Combined treatment with a nonsedating antihistamine in the morning and a sedating H1 receptor blocker before bed has been recommended.[28]

A number of medication classes have been used to treat unremitting cases of chronic urticaria in an off-label manner for added effect. In addition to prescribing for uses beyond the approved indications, off-label uses of medications or therapies include higher than recommended

dosages, combination with other drug classes, alternate prescribing schedules, and novel uses of disease modifying antirheumatic drugs.[11,18] In fact, prescribing antihistamines in excess of normal recommended dosage for these classes of medications improves efficacy slightly and may have actions other than maximal histamine blockade.[18]

The use of tricyclic antidepressants (such as doxepin HCl), for their potent antihistamine properties, has been one off-label consideration. Such use, however, often fails due to adverse effects.[30]

To minimize adverse effects, combination therapy with various classes of medications has been studied. The prescription of antileukotrienes, such as montelukast or zafirlukast, to a patient who is already prescribed maximized histamine blockade adds negligible therapeutic benefit, however. A randomized, placebo-controlled trial comparing desloratadine with montelukast, both as monotherapies and as a combined therapy, found montelukast to be comparable to placebo in efficacy.[31] Results of other research, however, indicate that monotherapy with this class offers improved symptom response.[31,32]

Adrenergic medications (such as epinephrine) should be reserved for cases of severe, life threatening angioedema with airway compromise. Otherwise, the adverse effect profile of this drug class precludes general use in chronic urticaria. Beta-agonists, such as terbutaline sulfate, have been used to treat the condition in small trials with some success.[33]

Corticosteroids can be used for patients whose chronic urticaria is refractory to other treatments. Complications from using corticosteroids in high doses or over the long term, however, are well documented in the treatment of other conditions (including glaucoma, cataracts, hypertension, diabetes, immune suppression, and osteopenia). An attempt to reduce these complications in chronic urticaria management has led to the practice of prescribing low doses and alternate day dosing schedules.[2] Corticosteroids are effective in suppressing inflammatory activation through multiple pathways, but the rebound of urticarial symptoms has been noted.[5]

As a steroid sparing option, the use of immunosuppressants, such as cyclosporine and methotrexate, has been evaluated. These trials were small, but results were promising for these medications.[34,35]

Other novel therapies include intravenous immunoglobulin, such as omalizumab, for use in unresponsive cases of chronic urticaria with associated antibodies.[37] And plasmapheresis has been used as a therapeutic option for recalcitrant cases of urticaria with IgE receptor antibodies,[38] though the costs and procedural risks associated with this therapy limit its benefit as a long-term treatment option. (In the case presented here, the patient's minimal response to any of the therapies attempted suggested that other therpies with unfavorable adverse effect profiles would not produce sufficient benefits to offset the risks.)

Despite the many difficulties posed by chronic urticaria, the aforementioned diagnostic and treatment advances provide good reason to be cautiously optimistic about future management of the problem. Although the majority of cases remain idiopathic, providers now benefit from a dramatically increased understanding of immune activation in a significant subpopulation. And patients who are affected severely by chronic urticaria, who once had long-term corticosteroid treatment as their only option, can now make use of such improved options as immunosuppressants, immunoglobulin, and plasmapheresis. ●

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Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

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Continued on page 33

Continued from page 30

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