Chronic Urticaria: Diagnostic and Therapeutic Challenges

Case Study and Commentary, Stephen A. Tilles, MD, Jenny Walter, MA, and Matthew Lodewick, MD

INSTRUCTIONS

The following article, “Chronic Urticaria: Diagnostic and Therapeutic Challenges,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 60.

OBJECTIVES

After participating in the CME activity, primary care physicians should be able to:
1. Describe the clinical and histopathological differences between chronic urticaria and acute urticaria
2. Describe the leading identifiable causes of chronic urticaria
3. Understand how to perform diagnostic workup of chronic urticaria
4. Understand the available medical treatments of chronic urticaria

Approximately 20% of the population will develop urticaria (hives) at some point in their lifetime [1]. The majority of cases of urticaria are acute and self-limited and have a readily identifiable cause. Chronic urticaria develops in approximately one quarter of all patients who have hives and, in contrast to acute urticaria, is usually idiopathic [2]. Acute urticaria typically involves mast cell degranulation and mediator release without subsequent histopathologic inflammatory changes. In contrast, chronic idiopathic urticaria results in both mast cell degranulation and a “late phase” non-necrotizing perivascular mononuclear cell infiltrate [3]. Thus, despite their transient nature, the hives of chronic idiopathic urticaria reflect more than the immediate effects of histamine release from mast cells.

Chronic urticaria is defined as raised, pruritic wheals that recur on most days for at least 6 weeks. The wheals are often pale and surrounded by reddened skin, although occasionally the wheals themselves are red. The individual wheals typically last less than 24 hours, and symptoms are often worse at night. Approximately one half of chronic urticaria patients experience coexistent angioedema. Angioedema is nonpruritic and consists of edema in the subcutaneous, submucosal, and dermal layers. As with urticarial wheals, angioedema lesions typically last less than 24 hours. Many patients also report mild dermatographism and increased sensitivity in areas of the body subjected to pressure (eg, belt line, bra line) [3]. Chronic urticaria is twice as common in women as it is in men, and symptoms usually begin in the fourth or fifth decade of life. Most patients with this condition improve spontaneously within several years (typically between 6 months and 5 years). However, the quality of life during symptomatic periods is often dramatically compromised, and symptoms may be extremely challenging to control.

CASE STUDY

Initial Presentation

A 28-year-old woman presents to her primary physician with a complaint of urticaria that has persisted for 8 weeks.

- What is the approach to the initial evaluation of the patient with persistent urticaria?

Investigating the cause of chronic urticaria requires consideration of a broad range of potential etiologies, including several with life-threatening implications (Table 1). For example, chronic urticaria is occasionally part of the initial presentation of leukemia, lymphoma, and carcinoma of the lung, liver, or colon [4]. On the other hand, approximately 80% of cases of chronic urticaria are idiopathic [5,6], so the yield and cost-effectiveness of an elaborate workup is poor in the vast majority of cases. Thus, performing a thorough history and physical examination combined with restrained but thoughtful diagnostic testing based on the history and physical findings is a reasonable approach. The most important elements of the history include obtaining an exact

From the University of Washington School of Medicine, Seattle, WA (Drs. Tilles and Lodewick), and ASTHMA, Inc. Research Center, Seattle, WA (Dr. Tilles and Ms. Walter).
description of the urticarial lesions, including clarifying whether individual lesions are raised, pruritic, or transient. Identifying potential triggering factors also helps to establish the diagnosis of chronic urticaria. These include airborne, ingested (medications, food), or physical (heat, cold, pressure, exercise) factors. Sometimes the patient is unaware of important urticaria triggers. For example, ingesting nonsteroidal anti-inflammatory drugs (NSAIDs), opiates, or angiotensin-converting enzyme inhibitors may worsen urticaria without triggering acute symptoms. An algorithm detailing a clinical approach to chronic urticaria is presented in the Figure.

Table 1. Classification of Chronic Urticaria

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<thead>
<tr>
<th>Manifestation of Systemic Illness</th>
<th>Malignancy</th>
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<td>Autoimmune Diseases</td>
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<td>Physical Urticarias</td>
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<td>Cold</td>
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<td>Delayed Pressure Urticaria</td>
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<td>Autoimmune</td>
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<td>IgG Targeting the IgE Receptor</td>
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<td>IgG Targeting IgE</td>
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<td>Thyroid Autoantibodies</td>
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Physical Examination

On examination, the patient is pleasant-appearing and in no apparent distress. Review of vital signs reveals a height of 64", weight of 189 lb, blood pressure of 120/70 mm Hg, pulse of 75 bpm, and respiratory rate of 8 breaths/min. HEENT, neck, cardiovascular, pulmonary, abdomen, lymphatic, and extremity examinations are normal. Skin examination reveals multiple macular erythematous lesions on the arms, legs, abdomen, and chest, especially along the bra line. The individual lesions are basically round, ranging from 5 to 30 mm in diameter.

- What are possible causes of chronic urticaria, and what is the approach to their workup?

When evaluating patients with chronic urticaria, the physician must consider the possibility that the hives are a manifestation of an underlying systemic illness. Although a standard approach to testing has not been established, a reasonable screening test battery might include a complete blood count (CBC) and measurement of erythrocyte sedimentation rate (ESR) and hepatic transaminases. As mentioned, on rare occasions malignancy may present with chronic urticaria. However, in most patients with chronic urticaria no specific malignancy workup is indicated unless the history or physical examination raises suspicion. For example, an elderly smoker with recent onset of chronic urticaria and cough should have a chest radiograph performed. Similarly, if the history and physical examination reveal an enlarging axillary mass, a biopsy procedure should be considered.
Patient presents with lesions and/or history consistent with chronic urticaria

Are individual urticarial lesions morphologically consistent with urticarial vasculitis and do they persist for more than 24 hours?

No

Evaluate for vasculitis:
• Consider ESR
• Consider cryoglobulin assays
• Consider biopsy

No

Detailed history including review of systems:
• Medications
• Food
• Infection
• Physical sensitivity

Physician examination
Consider basic lab tests:
CBC, UA, ESR, LFTs
Consider appropriate tests based on history, physical examination, review of symptoms

Yes

Don't patient have urticarial vasculitis?

Manage vasculitis

Specific management
Remove factors that may augment or induce urticaria
Specific pharmacologic management

No

Does patient have cold urticaria?

No

Are history, physical examination, and/or laboratory tests indicative of an underlying cause?

No

More detailed evaluation
As appropriate:
• additional history
• additional physical examination and/or
• additional laboratory tests
• consider skin biopsy

Yes

Is additional evaluation suggestive of etiology?

No

Treat patient for idiopathic urticaria

Specific management
Remove factors that may augment or induce urticaria
Specific pharmacologic management

Figure. Algorithm for chronic urticaria. CBC = complete blood count; ESR = erythrocyte sedimentation rate; LFT = liver function test; UA = urinalysis. (Adapted with permission from Wanderer AA, Bernstein IL, Goodman DL, et al. The diagnosis and management of urticaria: a practice parameter. Ann Allergy Asthma Immunol 2000;85:532.)
CHRONIC URTICARIA

Autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis are a more common category of systemic illness that presents with chronic urticaria. Alternatively, these disorders or others such as Sjögren's syndrome and autoimmune hepatitis may present with urticarial vasculitis. Urticarial vasculitis classically presents with pruritic, raised wheals persisting for more than 24 hours, often developing a purpuric appearance before resolving. However, urticarial vasculitis is sometimes indistinguishable from chronic urticaria unless biopsy analysis is performed. Therefore, when individual lesions persist for more than 48 hours, additional workup should be considered, including testing for cryoglobulins and skin biopsy. If cryoglobulins are demonstrated, there is an increased likelihood of systemic illness such as hepatitis B or C or lymphatic malignancy.

Chronic infection is responsible for chronic urticaria in a small subset of patients [7]. Infectious entities reportedly responsible for chronic urticaria include hepatitis B and C virus [8], herpes simplex virus, sinusitis [9], intestinal parasites, Candida, and Helicobacter pylori [10]. The likelihood of identifying the underlying cause of urticaria using screening tests for these infections is exceedingly low unless the infection is suggested by history or physical examination [7].

Physical urticarias are caused by application of a physical stimulus to the skin, and they may coexist with idiopathic chronic urticaria or occur alone. Typically, the physical stimulus (eg, hot shower in cholinergic urticaria) results in immediate local mast cell degranulation and transient hives without additional signs of inflammation. An exception to this rule is delayed pressure urticaria, which results in a perivascular mononuclear cell infiltrate indistinguishable from chronic idiopathic urticaria. Because cold urticaria is occasionally associated with cryoglobulinemia secondary to another systemic disease process, testing for cryoglobulins is warranted in patients with this condition [7]. The other physical urticarias are typically localized to the skin and do not require additional workup.

Thyroid autoimmunity is common in patients with chronic urticaria. However, while approximately 15% of patients with chronic urticaria have detectable serum thyroid autoantibodies [11], the role of these antibodies in the pathogenesis of chronic urticaria is unclear. Clinically, these patients may be hypothyroid, hyperthyroid, or euthyroid. Because the urticaria in hypothyroid and euthyroid patients sometimes resolves with thyroid replacement, thyroid disease is an important consideration in patients with chronic urticaria.

In the past decade a variety of elegant scientific studies have shown that a significant proportion of idiopathic chronic urticaria has an autoimmune basis. IgG autoantibodies that recognize the receptor for IgE are present in 25% to 50% of these idiopathic patients [7]. By binding to the IgE receptor, these antibodies can serve as a continuously applied inflammatory stimulus resulting in complement activation and subsequent mast cell degranulation and histamine release. In contrast to allergic reactions that involve direct mast cell activation by IgE recognition of an allergen, the autoantibody to the IgE receptor causes hives only after generating a complement activation product called C5a, a well-known anaphylatoxin capable of directly degranulating mast cells [12]. Chronic urticaria patients with autoantibodies directed to the IgE receptor may be identified by autologous skin testing (performing a skin test using the patient’s own serum as the “antigen”). While a positive autologous skin test is suggestive of an autoimmune etiology for the patient’s urticaria [7], this testing is not mandatory since its result does not alter the treatment or prognosis in many cases.

• Is skin testing for food allergies recommended in chronic urticaria?

A common misconception among both patients and some physicians is that chronic urticaria results from an IgE-mediated immunologic reaction to either an inhaled or ingested allergen. In fact, patients with chronic urticaria are no more likely to be atopic or to have true food allergies than the general population [13]; therefore, routine skin testing is rarely indicated. However, some food dyes and preservatives appear to exacerbate urticaria in a small minority of patients [14]. Since these associations are not IgE-mediated, a trial of dietary elimination rather than skin testing or serologic IgE tests is appropriate.

• What steps should be taken in the further evaluation of this patient?

The patient’s history strongly suggests the diagnosis of worsening chronic urticaria. The absence of raised lesions on physical examination is consistent with an antihistamine treatment effect causing a blunting of the hive response. The history does not contain convincing evidence suggesting an etiology of her urticaria, but there are 3 concerning issues. First, her urticaria began shortly after she started taking sertraline. While medications (especially β-lactam antibiotics) are a very common cause of acute urticaria, they rarely cause chronic urticaria. Nonetheless, given the time course of
sertraline introduction and the onset of hives, stopping this medication would be prudent in this case.

Second, the patient also frequently takes naproxen, an NSAID. These drugs do not typically cause chronic urticaria, but 20% to 30% of patients with chronic urticaria report worsening of their hives while taking NSAIDs [15]. Therefore, substituting an analgesic without cyclooxygenase-inhibiting properties is appropriate. Should there be an increased need for anti-inflammatory treatment (eg, concurrent inflammatory arthritis), a trial of an NSAID from the COX-2 inhibitor class would be reasonable. While there are no controlled trials addressing the use of COX-2 inhibitors in patients with urticaria, these agents often do not cause adverse events associated with the nonspecific cyclooxygenase inhibitors (eg, aspirin, ibuprofen, and naproxen) [16].

Finally, because the patient is a young woman with ongoing depression and obesity, thyroid assessment is warranted. If she were to have an elevated thyroid-stimulating hormone (TSH) level and measurable thyroid autoantibodies, the urticaria would have an excellent chance of resolving with thyroid replacement. Although there is no suggestion in the history or by physical examination of other systemic illnesses, a simple screening battery is reasonable at this stage.

**Laboratory Evaluation**

The physician orders a CBC, measurement of ESR, TSH level, and hepatic transaminases, and a thyroid autoantibody panel. The results of all tests are normal, including a TSH level of 1.2 µU/mL and an ESR of 6 mm/h. Given the results of these tests, a provisional diagnosis of idiopathic chronic urticaria is made. The physician now begins to focus on possible interventions to relieve symptoms. Since the patient’s urticaria began after the introduction of sertraline, the physician stops this drug and adds a bedtime dose of doxepin 25 mg to the patient’s daily dose of 10 mg of loratadine.

- **What medications are used in the initial treatment of patients with chronic urticaria?**

$H_1$ antihistamines are the mainstay of chronic urticaria treatment (Table 2). First-generation agents such as diphenhydramine or hydroxyzine are generally quite effective, although they must be taken every 4 to 6 hours to achieve their maximal effect. Most patients experience significant sedation from these agents. The second-generation antihistamines cetirizine, loratadine, and fexofenadine are much longer-acting and cause less sedation than the first-generation agents [17]. Cetirizine is the most likely to cause sedation but is usually well tolerated. The addition of a first-generation antihistamine on an as-needed basis is a useful adjunct. If the response to the usual dose of a second-generation antihistamine is inadequate, it is reasonable to try doubling the dose or changing to a different second-generation $H_1$ antihistamine. Use of $H_1$ antihistamines to augment $H_1$ antihistamine treatment is useful in a minority of patients, but $H_1$ antihistamines should not be continued if their benefit is not apparent after 1 to 2 weeks of therapy.

Doxepin, a tricyclic antidepressant with potent $H_1$ and $H_2$ antihistamine effects, is often useful for chronic urticaria that is difficult to control. Doxepin is quite sedating, but a single bedtime dose of 25 mg, increasing to 50 mg if necessary after 1 to 2 weeks, is often well tolerated and cost-effective [18].

**Treatment Response**

Two weeks after discontinuing sertraline, the patient’s urticaria persists, and she reports excessive sedation on doxepin, even after the dose is reduced to 10 mg. Off sertraline the patient’s depression has worsened. Also, after judging that the antihistamine therapy was contributing to her fatigue and somnolence, she discontinued both loratadine and doxepin. Over the ensuing weeks, she urgently presents to clinic several times and receives several short courses of prednisone.

- **What medications are used to treat refractory urticaria?**

### Table 2. Therapeutic Agents for Chronic Urticaria

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<th>H1 antagonists</th>
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<td>First-generation</td>
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<td>Diphenhydramine</td>
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<td>Chlorpheniramine</td>
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<td>Hydroxyzine</td>
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<tr>
<td>Second-generation</td>
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<tr>
<td>Loratadine 10 mg daily*</td>
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<td>Fexofenadine 180 mg daily†</td>
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<td>Cetirizine 10 mg daily‡</td>
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<td>H2 antagonists</td>
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<td>Doxepin</td>
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<td>Corticosteroids</td>
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<td>Cyclosporine</td>
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<td>Plasmapheresis</td>
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<td>Intravenous immunoglobulin</td>
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*Claritin, AW P $68.10/month for tablets or $78.90 for RediTabs.
†Allegra, AW P $60/month.
‡Zyrtec, AW P $56.40/month.
A short course of oral corticosteroids (e.g., prednisone 40 mg daily for several days tapering over 7 to 10 days) is occasionally necessary to control refractory urticaria; however, these agents should be used sparingly because of their potential side effects. There have been several recent case reports on the efficacy of leukotriene antagonists for treatment of chronic urticaria. One retrospective case review series found a benefit of these agents in 10 of 18 patients [19]. The leukotriene antagonists appear to hold some promise, but further research and controlled trials are required.

Allergists and dermatologists often employ more potent immunosuppressive agents in the most difficult cases. Some of these include methotrexate, cyclosporine, intravenous immunoglobulin, and plasmapheresis. The latter 3 may be occasionally necessary to control refractory urticaria; however, these agents should be used sparingly because of their potential side effects. There have been several recent case reports on the efficacy of leukotriene antagonists for treatment of chronic urticaria. One retrospective case review series found a benefit of these agents in 10 of 18 patients [19]. The leukotriene antagonists appear to hold some promise, but further research and controlled trials are required.

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Evaluation Form: Chronic Urticaria: Diagnostic and Therapeutic Challenges

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Part 1. Please respond to each statement.  Strongly Agree  Strongly Disagree

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Additional comments: ______________________________________________________________________________________
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Part 2. Please complete the following sentence.
As a result of reading this case study, I . . .
☐ see no need to change my practice.
☐ will seek more information before modifying my practice.
☐ intend to change the following aspect(s) of my practice: (Briefly describe)
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Signature: ___________________________ Date: ___________________________

Part 4. Identifying information: Please PRINT legibly or type the following:
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