Chronic Spontaneous Urticaria: The Devil's Itch

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Learning objectives:

1. To describe the cytokine profile and cellular infiltrates found in the biopsy of a chronic spontaneous lesion.

2. To apply therapeutic strategies for refractory chronic spontaneous urticaria (CSU).

3. To describe the identified features of blood basophils in patients with CSU.

4. To use clinical features to distinguish CSU from other entities such as vasculitis or autoinflammatory disorders.

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Chronic urticaria **is defined as the presence of urticaria for a period exceeding 6 weeks, assuming symptoms for most days of the week. It is divided into chronic inducible urticarias and chronic spontaneous urticaria, previously termed chronic idiopathic urticaria. The latter designation emphasizes that patients can experience urticaria independent of any exogenous stimulus even if one can define circumstances that may worsen symptoms. A search for such an external "cause" is fruitless because the underlying abnormality is "intrinsic," whether it is autoimmune, or some unknown process. Approximately 40% of patients with chronic spontaneous urticaria report accompanying episodes of angioedema, whereas 10% have angioedema as their primary manifestation. In most cases, it is a self-limiting disorder, persisting for 2 to 5 years in most cases, although 20% of patients suffer for more than 5 years. The treatment that has evolved is largely empiric, based on double-blind, placebo-controlled studies whenever possible, but is not yet targeted to any particular pathogenic mechanism. In this article, we review the current status regarding pathogenesis, discuss the diagnostic workup, and update the approach to treatment including consideration of published guidelines, our own experience, and guideline updates that are being prepared.** © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1097-106)**

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Abbreviations used
CSU- Chronic spontaneous urticaria

INTRODUCTION

Chronic urticaria is defined as the presence of urticaria for a period exceeding 6 weeks, assuming the presence of symptoms for most days of the week. It is divided into chronic inducible urticarias (also called physical urticarias) and chronic spontaneous urticaria (CSU), previously termed chronic idiopathic urticaria.[1,2] Chronic inducible urticarias are identified on the basis of history of a consistent stimulus that initiates lesions, which are typically short-lived and fleeting, lasting a few minutes up to 2 hours. When biopsied, there is no cellular infiltrate. In contrast, the term CSU emphasizes that patients can experience urticaria independent of any exogenous stimulus even if one can define circumstances that may worsen symptoms. Thus, a search for such an external "cause" in CSU is a fruitless effort because the underlying abnormality is "intrinsic." Approximately 40% of patients with CSU will report accompanying episodes of angioedema or deeper swelling of dermal or mucosal tissues, whereas 10% have angioedema as their primary manifestation.[3,4] In most cases, it is a self-limiting disorder, persisting for 2 to 5 years in most cases, although 20% of patients suffer for more than 5 years.[5-7]

The treatment for CSU that has evolved is based on double-blind, placebo-controlled studies whenever possible, but is not yet targeted at any particular pathogenic mechanism. Although the efficacy of omalizumab in disease has implicated IgE and IgE receptors in disease pathogenesis, a clear biomarker that segregates responders from nonresponders remains elusive. In this article, we will review the current status regarding pathogenesis, discuss what are the essentials of a diagnostic workup, and update the approach to treatment including consideration of published guidelines, our own experience, and guideline updates that are being prepared.

PATHOGENESIS

Wheals and angioedema in CSU appear to involve the degranulation of skin mast cells, which release histamine, proteases, and cytokines with generation of platelet-activating factor and other arachidonic acid metabolites (prostaglandin D2, leukotrienes C4, D4, and E4). These mediators induce vasodilatation, increase vascular permeability, and stimulate sensory nerve endings that lead to swelling, redness, and itch.[8] A lesion site or wheal is characterized by edema, mast cell degranulation, and a perivascular infiltrate of cells—CD4+ lymphocytes, monocytes, neutrophils, eosinophils, and basophils—and has similarities to the infiltrate seen in the allergen late-phase reaction.[9-12] The lesion cytokine profile shows T-cell expression of IL-4, IL-5, and IFN-γ, suggesting a mixed T_H1/T_H2 response.[10] More recently, epithelial-derived cytokines that favor the T_H2 profile including IL-33, IL-25, and thymic stromal lymphopoietin are detected in the dermis of lesional skin along with the vasoactive agents vascular endothelial growth factor and calcitonin gene-related peptide, but these factors were not observed in uninvolved skin.[13,14] Although several theories exist regarding the pathogenesis of chronic urticaria, none have been conclusively established.[15] Many studies have examined the autoimmune theory of disease and also the validity of serologic tests to establish an autoimmune basis. Additional theories include abnormalities of tissue mast cells and basophils as well as other serologic factors.

Mast cells

A role for mast cells is supported by tissue biopsy evidence of mast cell degranulation, elevated histamine content[8] measured from over CSU skin lesions, and the clinical response to antihistamines.[16] Whether skin mast cells in CSU are increased or not remains controversial. Some studies reported an increase,[11,17,18] whereas other studies reported numbers similar to levels in healthy skin.[9,19] In addition, indirect measures of mast cell presence such as total serum tryptase are within the normal range but higher than the average measured in atopic and nonatopic controls.[20] However, patients with CSU who report extracutaneous systemic symptoms have a higher average tryptase than those with skin-limited symptoms.[21] Mast cells express multiple receptors that are susceptible to activation (eg, chemokine, prostaglandin, Toll-like, or immunoglobulin receptors).[15,22] The exact mechanism for mast cell activation in CSU is still not clear, but several theories are discussed below.

Various autoimmune diseases are more prevalent in subjects with CSU.[23,24] Based on the recognition of increased thyroid disease expression in CSU, the concept of underlying autoimmunity as the cause of disease emerged in the 1980s along with a potential role for IgG class autoantibodies. Specifically, it is thought that autoantibodies to IgE or IgE receptors exist in 30% to 40% of individuals, leaving 60% without a proposed pathogenic mechanism.[25] Of note, a recent study has provided the first evidence for the presence of autoreactive CD4+ T cells to the IgE receptor alpha chain in a subset of subjects with CSU, and that most of these autoreactive T cells secrete IFN-γ.[26] In a recent database survey of 13,000 patients relative to 10,000 control subjects, the following diseases were noted to be increased among patients with chronic urticaria: thyroid disorders, celiac disease, Sjogren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type I diabetes.[27] This IgG autoantibody theory and its controversial clinical significance, and association of CSU with autoimmune diseases has been the topic of a recent review and will not be covered in depth here.[15,28-30]

Another theory is that enhanced skin mast cell releasability occurs in active CSU. For example, compound 48/80-induced histamine responses via skin chambers have been shown to be increased in patients with CSU as compared with healthy controls and this enhanced releasability resolves with CSU remission.[19,31] Recently, levels of Mas-related gene X2, a novel G protein−coupled receptor expressed on human mast cells that binds basic proteins including compound 48/80, are known to be increased in the skin of patients with CSU.[32,33] It has also been noted that CD34+-derived mast cells of subjects with CSU spontaneously release histamine upon sensitization by IgE.[34] However, the cause of this heightened release state of mast cells remains elusive.

Several studies have shown that the blood coagulation cascade is active in CSU and may mirror disease activity (see below). Recent work by Yanase et al[16,35] has proposed a new pathway for tissue mast cell activation. Recognizing the evidence for coagulation system activation, they demonstrated that intravascular histamine release along with an infection stimulus producing Toll-like receptor activation (via Toll-like receptor 3, 4, 5, or 6) can synergize to stimulate endothelial cells to express tissue factor