

Chronic Spontaneous Urticaria

Etiology and Pathogenesis

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KEYWORDS

• Chronic urticaria • Mast cells • Basophils

KEY POINTS

- Acute urticaria occurs in up to 20% of the population, and may be associated with a drug or food allergy or with infection. It is generally self-limited.
- Chronic urticaria affects up to 1% of the population, and in most cases lesions occur spontaneously without an identifiable external cause.
- Approximately 20% of patients with chronic urticaria have a reproducible physical trigger for their skin lesions, termed physical urticaria.
- There are multiple theories of pathogenesis for chronic urticaria, none of which is clearly established. One theory is that a subset has an autoantibody-mediated disease process.
- Abnormalities in skin mast cells and blood basophils have been described in chronic urticaria.

INTRODUCTION

Urticaria, also known as hives, is a very common condition thought to affect up to 20% of the population in their lifetime.¹ This skin condition is characterized by the appearance of pruritic, erythematous papules or plaques with superficial swelling of the dermis. The major complaint is the symptom of pruritus. Urticaria can be classified by both time course of symptoms and the underlying etiology. Acute urticaria is defined as having skin-symptom duration of less than 6 weeks, whereas chronic urticaria (CU) is generally defined by the presence of urticaria on most days of the week for a period of 6 weeks or longer.

CU is further classified by additional criteria. Approximately one-fifth of CU patients have a clear-cut physical trigger for their skin eruptions, therefore it is termed physical urticaria. These cases are labeled according to the nature of the inciting stimulus

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(Table 1; see also the article by Maurer and colleagues elsewhere in this issue).^{2,3} Among the causative physical factors are dermographism, delayed-pressure urticaria, cholinergic urticaria, cold- and heat-contact urticaria, solar urticaria, aquagenic urticaria, exercise-induced urticaria, and vibratory urticaria. In the remaining 80% of CU, no external allergen or contributing disease process is identified and, thus, the condition is termed chronic idiopathic urticaria (CIU), which has also more recently been labeled as chronic spontaneous urticaria (CSU).⁴ Approximately 40% of patients with CIU/CSU will also report accompanying episodes of angioedema or deeper swelling of dermal or mucosal tissues, whereas 10% have angioedema as their main manifestation.^{5,6} In this review, the terms CSU and CIU are used synonymously. Some guidelines and experts further divide CIU/CSU patients based on serologic evidence of a presumed autoimmune etiology (observed in 30%–40% of these subjects), and call the condition chronic autoimmune urticaria (CAU). In this setting, the remaining 60% to 70% of patients are classified as CIU/CSU.^{4,7}

EPIDEMIOLOGY

Given that the lifetime risk of an episode of urticaria is 20% to 25%, several conditions have been noted to be associated with urticaria. In acute urticaria, 20% of cases have

Table 1 Physical urticaria subtypes, triggers, and testing procedures		
Disorder	Trigger Factor	Test Description
Dermographism (urticaria factitia)	Stroking, scratching, pressure	Mild stroking of skin with tip of pen or tongue blade, or dermatographer
Delayed-pressure urticaria	Application of pressure 30 min to 12 h before onset	Shoulder sling placed for 15 min weighing 7 kg; patient records symptoms over 24 h
Cholinergic urticaria	Elevation of body temperature with exercise, hot water, strong emotion, or spicy food	Exercise with a stationary bike for 15 min beyond sweating Passive heating of one arm to 42°C with water bath Evidence of reaction to sweat antigen
Cold-contact urticaria	Exposure of skin to cold air, cold objects, or cold liquids	Ice cube test for 5 min on arm Temperature test where available
Heat-contact urticaria	Warm object in direct contact with skin	Application of test tube containing warm water at 45°C
Aquagenic urticaria	Skin contact with water at any temperature	Application of water compress at 35°C for 30 min
Solar urticaria	Exposure of skin to sunlight of specific wavelength	Exposure of skin to ultraviolet A, ultraviolet B, or visible light
Vibratory urticaria	Lawn mowing, riding a bike, exposure to vibrating machinery	Vortex platform held to skin for 10 min

Data from Magerl M, Borzova E, Gimenez-Arnau A, et al. The definition and diagnostic testing of physical and cholinergic urticarias-EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. *Allergy* 2009;64:1715–21.

been linked to a potential allergen, such as foods or drugs, 30% of cases are linked to infections, particularly of the respiratory tract, while the remaining 50% appear not to have a trigger.⁸ These associations suggest involvement of the innate immune system via infectious triggers as well as adaptive immunity for cases involving immunoglobulin E (IgE) and allergens.

At any time, up to 1% of the North American population can be affected by CU.⁹ The overall prevalence is similar in other regions.^{10,11} Both children and adults can develop CU, but it appears to be more common in adults, with women affected nearly twice as often as men.^{10,12–17} The average age of patients suggests that the condition typically begins in the third to fifth decades of life.^{10,15,16} The coexpression of allergic disease in patients with CU appears to be slightly higher than that observed in the general population.¹⁸

PROGNOSIS AND RISK FACTORS

CU is a self-limited disorder in most cases, with an average duration of 2 to 5 years.^{9,19} In patients in whom no trigger is identified, there is a rate of spontaneous remission at 1 year occurs in approximately 30% to 50%.^{13,20–22} However, symptoms persist beyond 5 years in nearly one-fifth of patients.^{13,23}

Factors that predict longer disease duration or more severe disease are limited. In a prospective study of 139 CU patients followed for 5 years, angioedema, features of severe disease, autologous serum skin test (ASST) positivity, and thyroid autoimmunity were associated with longer disease duration.²³ Hypertension and disease severity have been recently identified as factors associated with longer disease duration.¹⁹ However, other studies have not found an association between positive ASST and longer disease duration.²⁰

Autoimmunity

Various autoimmune diseases are noted to be more prevalent in subjects with CU.^{21,24} In a study involving a 13,000-patient database relative to 10,000 control subjects, the following diseases were noted to be increased among CU patients: thyroid disorders, celiac disease, Sjögren syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, and type 1 diabetes²⁵. The diagnosis of autoimmune disease most often appeared in the decade after CU occurrence.

Thyroid Disorders

A higher incidence of thyroid disease in CU patients has been long recognized^{24,26} and was recently confirmed in a large study.²⁵ The overall incidence of hypothyroidism (9.8%) and hyperthyroidism (2.6%) is at least twice that reported in the general population.²⁵ There is also evidence for a higher prevalence of thyroid autoantibodies in CU subjects (antiperoxidase and antimicrosomal) than in the general population,^{14,24,27} but in most CU subjects this is found with normal thyroid function. Some view the significance of a higher frequency of thyroid autoimmunity as a common underlying tendency to form autoantibodies rather than a causal link between the 2 diseases.^{26,28}

Malignancy

There exist conflicting data on whether CIU patients are at increased risk for malignancies.^{29,30} In one Swedish study, 1155 patients with CIU were followed in a dermatology department for an average of 8.2 years. The incidence of malignant cancer during the observation period was compared with the expected number of cancers

from the Swedish Cancer Registry, yielding a relative risk of 0.88 (95% confidence interval [CI] 0.61–1.12). In the second study, a cohort of 12,720 Taiwanese patients was identified as having CU, based on the ICD-9-CM code for urticaria along with use of an antihistamine for at least 6 months over a 2-year period. The rate of malignancies diagnosed in this cohort over an average follow-up period of 5 years was compared with expected rates, obtained from the Taiwan National Cancer Registry. The standardized incidence ratio for patients with CU was 2.2 (95% CI 2.0–2.4). Younger patients appeared to be at higher risk for hematologic malignancies. At present, the identified associations warrant further evaluation.

PATHOPHYSIOLOGY

Skin Pathology

The skin pathology observed in an urticarial lesion biopsy includes degranulation of skin mast cells and a perivascular leukocyte infiltrate composed of lymphocytes, eosinophils, neutrophils, and basophils that have migrated to the skin lesion (**Fig. 1**).³¹ Both mast cells and basophils release histamine and other inflammatory mediators (prostaglandins, leukotrienes, cytokines) on activation, which are capable of causing local vasodilation, itch, and swelling of the skin. In most CIU skin biopsies, there is a lack of leukocytoclasia or fibrinoid deposition such as seen in urticarial vasculitis (UV),^{32,33} complement deposition, or immune deposits.³⁴

Given that pruritus is the major skin symptom in CU and the overall benefits seen with antihistamine therapy, histamine appears to be a central mediator in CU. Skin-blister fluids obtained from lesional and nonlesional skin of CU subjects in a comparison with normal subjects showed greater histamine-releasing activity based on in vitro testing with healthy basophils.³⁵ Elevated skin histamine content was also noted in the CU lesional skin,^{35,36} leading to the idea that local factors may regulate histamine release from skin mast cells in CU.³⁵

The leukocyte infiltrate observed in CU skin biopsies and clinical presentation is similar to that seen in allergen-induced late-phase skin reactions. Although both feature mast-cell activation, T cells in the skin late-phase reaction express a T-helper (Th)2 cytokine pattern (interleukin [IL]-4, IL-5), whereas both Th2 cytokines (IL-4 and

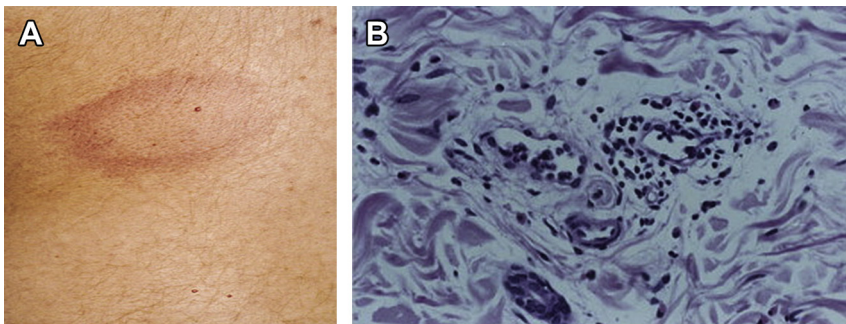


Fig. 1. (A) Image of skin lesion. Superficial swellings of the dermis are called wheals. Wheals are usually pale in the center with a red surrounding flare when they erupt, and become pink as they mature. (B) Biopsy of skin lesion. Photomicrograph of early spontaneous wheal shows perivascular lymphocytes and intraluminal and perivascular neutrophils, with perivascular and interstitial eosinophils. (From Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol* 2002;46(5):645–60. Available at: <http://dx.doi.org/10.1067/mjd.2002.122759>; with permission.)

IL-5) and Th1 cytokines (interferon- γ) are noted in CU lesions.³¹ Of note, little difference is found in the characteristics of skin biopsies of patients with and without serologic evidence for autoimmune urticaria.^{31,37} Increased expression of IL-3 and tumor necrosis factor (TNF)- α in endothelial cells has been detected in the skin biopsies of both lesional and nonlesional skin in CU.³⁸

There is limited understanding of the roles for eosinophils, lymphocytes, and neutrophils in disease pathology. A predominance of neutrophils in the skin-lesion biopsy is termed neutrophilic urticaria, and can lead to alternative disease management.^{39,40} Furthermore, immune features of CIU subjects resistant to high-dose antihistamine therapy relative to antihistamine responders include greater basopenia, higher mean platelet volume, higher levels of C-reactive protein, and higher levels of serum C3, which are features of low-grade inflammation and platelet activation.⁴¹ Other immune profiles described in CIU subjects are summarized in **Table 2**.

Pathogenesis

Although there are several theories regarding the pathogenesis of CU, none have been conclusively established.^{7,52,53} 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 underlying chronic infections.

Autoimmune theory

A widely held theory is that 30% to 40% of CIU patients have an autoimmune disease, also referred to as CAU. These patients have circulating immunoglobulin G (IgG) autoantibodies to either IgE or the high-affinity IgE receptor that are believed to be pathogenic by directly activating mast cells and basophils (**Fig. 2**).⁷ This theory arose from the earlier recognition of increased incidence of thyroid autoimmunity and dysfunction in patients with CU (**Fig. 3**).^{24,25,54} A correlation between thyroid autoimmunity and the presence of autoimmune serum factors in CIU is often cited as evidence for a common

Table 2
Immune profiles of CIU subjects relative to controls

Immune Cell Type/Tissue	Profile
Lymphocytes	Altered signaling through the p21Ras pathway ⁴² Increased frequency of IL-10+ peripheral T cells ⁴³
Peripheral blood mononuclear cells (PBMC)	Increased stimulated production of TNF- α , IL-10, MIP-1 α , and RANTES ⁴⁴ Reduced IL-4 ⁴⁵
Peripheral blood dendritic cells (pDCs)	Impaired TLR9 induced interferon- α production ⁴⁶
Serum	Increased levels of TNF, IL-1 β , IL-6, IL-13, IL-12p70, IL-10, and B-cell activating factor (BAFF); similar among those with CIU and CAU ⁴⁷⁻⁴⁹ Increased IL-6, CRP in CU subjects with NSAID sensitivity after aspirin challenge ⁵⁰
Coagulation	Extrinsic coagulation pathway activated with increased levels of D-dimer and prothrombin fragments ⁵¹

Abbreviations: CAU, chronic autoimmune urticaria; CIU, chronic idiopathic urticaria; CRP, C-reactive protein; CU, chronic urticaria; IL, interleukin; MIP, macrophage inflammatory protein; NSAID, nonsteroidal anti-inflammatory drug; RANTES, regulated on activation, normal T-cell expressed and secreted (chemokine ligand 5); TNF, tumor necrosis factor.

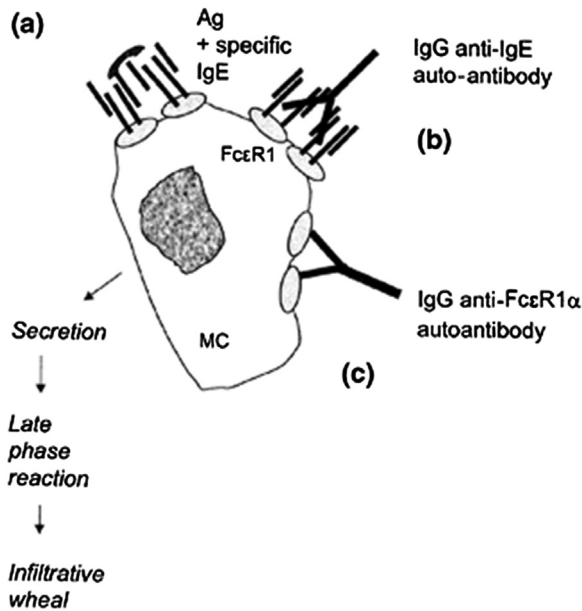


Fig. 2. Proposed pathogenic antibodies in CIU/CSU disease. Ag+, antigen-positive; Ig, immunoglobulin; MC, mast cell. (Data from Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. Clin Exp Allergy 2009;39(6):777–87.)

underlying autoimmune diathesis in a subset of CU patients.^{27,54} Furthermore, increased clustering of human leukocyte antigen (HLA) class 2 DR antigen expression is noted in subjects with CIU and, in particular, those with evidence for serum autoimmune factors.⁵⁵

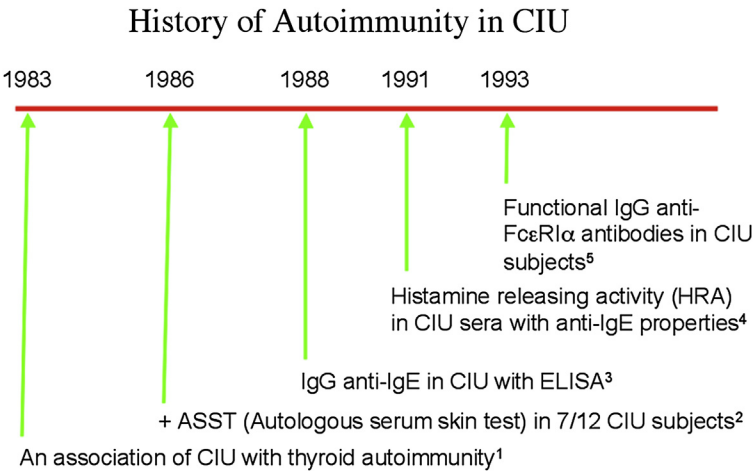


Fig. 3. Timeline for autoantibody theory. ELISA, enzyme-linked immunosorbent assay. (Data from Refs. ^{24,56,57,61,62})

The evolution of the autoimmune theory began in the 1980s when a serum factor that behaved similarly to a cross-linking anti-IgE was detected in the serum of CU patients.^{56,57} At the same time a serologic factor was also identified, based on an *in vivo* skin-test response called the ASST (Fig. 4). In an early report it was noted that 7 of 12 (58%) CU patients developed wheal and flare reactions within 30 minutes at the site of intradermal injection of their own serum or ASST.⁵⁶ The serum fraction responsible for ASST positivity was originally described as being in the 10- to 15-kDa range.⁵⁸ The skin pathology of an ASST reaction resembles that of an IgE-mediated late-phase reaction, supporting the notion that mast-cell degranulation also occurs in the ASST reaction owing to a presumed CIU disease-related factor.⁵⁹ However, more recent work has shown positive ASST to occur in subjects with allergic respiratory disease and healthy controls, raising the issue of the specificity of this test to CU disease.^{53,60}

In parallel with early studies of serum ASST, a report emerged that CU serum contained IgG antibodies against the Fc region of IgE, and led to a dose-dependent histamine release from the blood basophils of healthy subjects.⁵⁷ This activity was termed serum histamine-releasing activity (HRA) (Fig. 5). Initially, serum fractions responsible for HRA (>100 kDa) differed from those fractions described as inducing an ASST (<20 kDa).^{57,58} Later, a single serum fraction (>100 kDa) was capable of inducing both a positive ASST and positive HRA.⁶¹ These findings culminated in a landmark report identifying IgG anti-Fc ϵ R1 α autoantibodies as the main serum factor responsible for HRA.⁶² In this study, 26 CU subjects with a positive serum ASST were studied, and 17 of 26 also had HRA present in the IgG fraction of their serum. In a small subset of these subjects, increased serum HRA activity was seen after

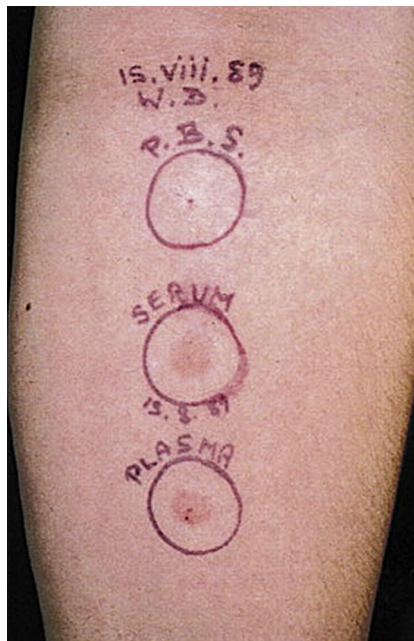


Fig. 4. An autologous serum skin test (ASST) reaction. Phosphate-buffered saline (P.B.S.), saline solution negative control, serum, and plasma are injected in a volume of 0.05 mL and the reaction read at 30 minutes. Here both serum and plasma have given positive responses. (From Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000;105(4):664–72; with permission.)

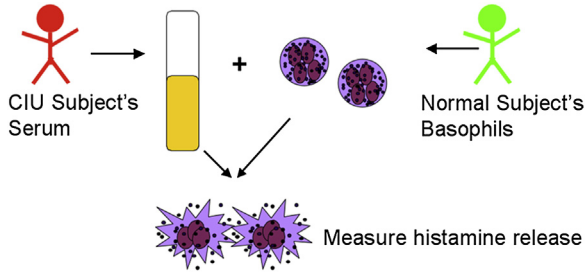


Fig. 5. Serum histamine-releasing assays. (Adapted from Brodell LA, Beck LA, Saini SS. Pathophysiology of chronic urticaria. *Ann Allergy Asthma Immunol* 2008;100(4):294; with permission.)

stripping native IgE from the donor basophils. This finding implied that the IgE bound to the high-affinity IgE receptor (FcεRI) inhibited the ability of some anti-FcεRIα IgG autoantibodies to release histamine from basophils. It remained unclear as to how some of these antibodies would be functional *in vivo*, given the high affinity of IgE for its receptor and the overall high occupancy rate (>95%) of surface IgE receptors on basophils and mast cells.

Subsequent studies focused on describing the frequency of HRA in CU subjects, and characterized whether HRA activity targeted IgE, unoccupied IgE receptors, or occupied IgE receptors on healthy, donor basophils.^{61,63–65} Although early reports suggested that HRA activity and ASST reactions decreased in disease remission,^{56,65} later reports noted persistence of ASST in remission and even after IgG-depletion of the serum used in the ASST.^{66,67} A direct comparison of serum ASST results with those of HRA testing in 163 CU subjects found ASST positivity in 60% of subjects, but only half of the ASST-positive sera evoked serum HRA from basophils.⁶⁸ This finding highlighted that ASST reactivity reflected skin mast-cell-specific serum factors that differed from those (IgG anti-IgE, or anti-FcεRIα) shown to activate donor basophils.⁶⁹ HRA-defined IgG anti-FcεRIα autoantibodies are estimated to occur in 30% to 40% of CU patients, whereas IgG anti-IgE autoantibodies occur in 10%.⁷ A recent modification of the HRA assay examines CU serum for the ability to increase levels of basophil surface activation marker CD203c rather than histamine release.⁶⁴ The exact nature of CU serum factors, their role in CU disease, and the optimum test strategy for detecting such factors continues to be debated.^{53,70} Concerns with the present assays are the variability of the donor basophils for both traditional and newer HRA assays, the confounding of results by other factors in serum that can trigger normal basophils (IL-3, complement), and the occurrence of positive HRA activity in the serum of healthy subjects and those with SLE.^{71–73}

An enzyme-linked immunosorbent assay (ELISA) approach to detect IgG anti-FcεRIα offered a promising alternative to the use of bioassays such as the ASST or HRA for autoantibody detection.⁷⁴ Complement-fixing subclasses IgG₁ and IgG₃ were the main subtypes found by ELISA in the serum of CU subjects. By contrast, non-complement-fixing subclasses IgG₂ and IgG₄ were detected in other autoimmune diseases (pemphigus vulgaris, dermatomyositis, SLE, and bullous pemphigoid) at a similar frequency to CU, but were nonfunctional in HRA assays. However, a later study failed to demonstrate a correlation between CU serum containing immunoreactive IgG antibodies and FcεRIα by Western blotting and serum positive for HRA.⁷⁵ Also, broader IgG subclass anti-FcεRIα presence in CU serum was noted in serum that possesses HRA (IgG₁, IgG₃, IgG₄)⁷⁶ and, anti-FcεRIα was noted in serum of

normal subjects.^{77,78} The lack of concordance between ASST, HRA, and other detection platforms such as ELISA/Western blotting remains a problem in identifying the proper test to define the entity of CAU.⁶⁹ Furthermore, the relationship of antibody titers to CIU disease activity has not been clearly demonstrated.⁷⁹ The significance of autoimmune classification as a marker of disease severity^{80,81} or predictor of response to certain therapeutic agents lacks sufficient evidence-based trials.

Summary of autoimmune theory

Summary of Points Favoring Autoimmune Hypothesis

- Functional autoantibody testing by ASST declines with effective therapies such as plasmapheresis and intravenous immunoglobulin^{82,83}
- HLA-DR clustering and increased thyroid autoimmunity^{24,25,54,55}
- Detection of IgG autoantibodies by HRA, Western blot, and ELISA⁷

Summary of Points Unresolved in the Autoimmune Hypothesis

- ASST lacks sensitivity and specificity for CIU^{60,84}
- ASST may indicate the presence of other vasoactive factors rather than IgG autoantibodies⁶⁷
- HRA testing results depend on the donor used for basophils and are confounded by other serum active factors⁷¹
- HRA positives are seen in healthy subjects and SLE subjects^{72,73}
- Skin biopsies and clinical phenotype do not differ between CAU and CIU^{31,37}
- Differential targeting of anti-FcεRI antibodies to occupied versus unoccupied receptors raises issues regarding functional role in disease in vivo
- It is unclear as to why IgG anti-IgE leads to only skin-limited disease and not anaphylaxis

Skin mast cells

Mast-cell degranulation is a central event in lesion development in urticaria,³¹ and elevated histamine levels are noted in skin biopsies.^{35,36} However, the number of skin mast cells is not increased in either lesional or nonlesional CIU skin biopsies relative to the skin of healthy controls.⁸⁵ Likewise, total serum tryptase levels, an indirect measure of total body mast-cell numbers, is only slightly elevated in CU subjects relative to healthy and atopic subjects, but well within the normal range.⁸⁶ Evidence supports that heightened histamine presence detected in CU skin lesions could be due to either enhanced quantitative release of histamine from skin mast cells or from blood basophil infiltration of CU skin tissues.⁸⁷ Elevated skin mast-cell releasability in active CU has been shown by skin challenges with compound 48/80 and codeine.^{88,89} Recently, culture-derived mast cells grown from peripheral blood CD34+ cells of CU subjects showed elevated spontaneous histamine release when compared with mast cells grown from healthy donors.⁹⁰

Recently, supernatants taken from mast cell lines (HMC-1, LUVA) after exposure to CU serum, but not to normal serum, caused increased endothelial monolayer permeability. This CU serum-evoked response was independent of IgG serum fractions or dependence on IgE receptor activation of the mast cell lines.⁹¹ Other possible pathways that could activate mast cells, such as innate immune receptors, remain to be established. Mast-cell activation in physical urticarias has been studied using provocation challenge by a specific stimulus challenge to the skin. For example, the application of a cold-water challenge in a patient with cold urticaria showed elevations in blood histamine levels in the draining venous vessels.⁹² Likewise, cold-temperature challenge of isolated skin fragments of cold urticaria subjects led to histamine release.⁹³ Areas of

research in physical urticaria include the role of recently identified transient receptor potential channels that can be regulated via changes in temperature, pH, or osmolality, and produce calcium influx into the cell.⁹⁴ A novel familial cold urticaria syndrome with associated immunodeficiency has been described to have abnormalities in the PLC γ signaling pathway of immune cells, including mast cells.⁹⁵

Blood basophils

Evidence that blood basophils are involved in the pathogenesis of CU has emerged over the past decades.^{52,96} In the 1970s, 2 groups identified that blood basophils of CIU subjects had reduced capacity to release histamine after IgE-receptor activation.^{97,98} This paradoxical reduction in histamine release was attributed to prior in vivo activation and was referred to as basophil hyporesponsiveness or hyporeleasability.⁹⁸ Basophil histamine hyporeleasability was limited to the IgE receptor pathway and was not seen with stimulation by formyl-methionyl-leucyl-phenylalanine, bradykinin, or monocyte chemoattractant protein.^{99,100} Recently, blood basophil IgE receptor responses of CIU subjects were segregated into 2 basophil functional phenotypes, CIU responders (CIU-R) and CIU nonresponders (CIU-NR).¹⁰¹ CIU-R basophils show a histamine degranulation profile similar to that of normal subjects, whereas basophils of CIU-NR subjects do not degranulate to ex vivo IgE-receptor activation and possess elevated levels of the IgE-receptor regulating inhibitory phosphatases, SH2-domain-containing inositol-5-phosphatase (SHIP)-1 and SHIP-2. These 2 functional phenotypes are stable in active CIU disease, are not related to the presence of autoimmune serum factors, and also reflect differences in some clinical features of subjects.^{79,102} Furthermore, hyporeleasability of basophil response improves in disease remission.⁷⁹ The underlying disease mechanisms leading to these distinct basophil phenotypes remains to be elucidated, but supports the idea that basophil responsiveness is relevant to the pathogenesis of urticaria.

Blood basopenia has also been noted in CU subjects for decades, and has been linked to the presence of serum HRA.^{103,104} Skin biopsy studies using basophil-specific antibodies have provided evidence for the presence of basophils in both CIU lesional sites and nonlesional skin tissues, a finding not seen in healthy skin and many other skin diseases.^{31,87,105} The degree of basopenia is correlated to disease severity and appears to reflect blood basophil recruitment to the skin lesions, whereas in CIU remission basopenia improves.^{41,79,98,106} Collectively this work suggests that altered basophil trafficking is present CIU.

Infections

The topic of infections and CIU was recently reviewed.¹⁰⁷ Among infections implicated in CU are *Helicobacter pylori*, but the data are mixed.^{108–110} The role of infections and CU onset is often raised but is difficult to prove. Recent work on staphylococcal nasal carriage also revealed higher levels in CU patients than in controls.¹¹¹ In a small study, nasal carriage of *Staphylococcus aureus* was assessed in 57 CU patients and 25 controls. A positive swab was found in 32 of 57 CU subjects, and all were given empiric antistaph therapy with 28% having complete remission, 12% partial relief, and 60% no benefit from treatment.¹¹²

CLINICAL FEATURES

Urticarial lesions or hives are typically raised erythematous plaques that are circumscribed (Fig. 6). These lesions can assume a variety of sizes, and may be flattened in appearance if a patient is using antihistamines. Any area of the body can be affected, including areas where clothing may compress the skin (waistband).



Fig. 6. Urticaria. (Courtesy of New Zealand Dermatological Society Incorporated. Published online at: <http://www.dermnetnz.org>.)

Most lesions have a life span of less than 24 hours; therefore, photographs of skin lesions are extremely useful in helping to confirm the diagnosis. Lesions with a longer life span or the occurrence of bruising may suggest the presence of vacuities. The severity of the pruritus can be disruptive of both sleep and daily activities.

Angioedema involves episodic submucosal or subcutaneous swelling that is asymmetric in distribution (**Fig. 7**). Paresthesia such as numbness or tingling is



Fig. 7. Angioedema. Deeper swellings of the skin and submucosa called angioedema are less well defined and do not necessarily show any difference in color from unaffected skin. (From Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol* 2002;46(5):645–60; with permission.)

common, rather than the pruritus described in urticaria. Body areas commonly involved include the lips, eyes, cheeks, and extremities. In most cases angioedema is coexpressed with urticaria, but can be the sole feature in a limited number of cases.¹¹³ It is important to consider other causes of isolated angioedema such as drugs (angiotensin-converting enzyme inhibitor-induced lesions), hereditary angioedema, or acquired angioedema (see the relevant article by Bork elsewhere in this issue). Among factors that are thought to contribute to disease exacerbations of urticaria are nonsteroidal anti-inflammatory medications (NSAIDs), alcohol ingestion, and stress.^{21,114,115}

Table 3 Key features of diseases that are associated with urticaria		
Disorder	Feature	Evaluation
Urticarial vasculitis (UV)	Painful, long-lived lesions (>48 h), bruising and pigmentation, systemic signs (fever, chills, arthralgias)	Skin biopsy
Systemic lupus erythematosus	Prolonged skin lesions, UV sensitivity, with fever, weight loss, arthritis, lymphadenopathy, other organ system	Skin biopsy and laboratory evaluation
Cryoglobulinemia	Cold-induced lesions, lesions more on extremities, arthralgias	Testing for hepatitis C, cryoglobulins
Schnitzler syndrome	Monoclonal gammopathy (IgM or IgG), fever, urticaria, bone pain, lymphadenopathy	WESR, CRP, SPEP with immunofixation
Mastocytosis	Urticaria pigmentosa, Darier's sign	Skin biopsy, tryptase
Polymorphic eruption of pregnancy (PEP) or pruritic urticarial papules and plaques of pregnancy (PUPPP)	Pruritic dermatitis, erythematous papules with striae, target-like lesions	Seen in 1 in 300 pregnancies, typically resolves postpartum, no specific laboratory abnormalities
Hypereosinophilic syndrome	Urticaria, angioedema, other organ system involvement with eosinophils	Eosinophil count
Cryopyrin-mediated periodic syndromes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome	Periodic fevers, urticaria, and leukocytosis, muscle and skin tenderness post cold exposures	Early onset of symptoms, genetic
Cryopyrin-mediated periodic syndromes: Muckle-Wells syndrome	Periodic urticarial eruptions without cold sensitivity, sensorineural hearing loss, arthritis	—

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; SPEP, serum protein electrophoresis; WESR, Westergren erythrocyte sedimentation rate.

DIFFERENTIAL DIAGNOSIS

Numerous disorders must be considered in the evaluation of patients with chronic idiopathic or spontaneous urticaria. Acute urticaria is often associated with viral and bacterial infections, especially in children. Some pediatric series suggest an infection to be associated with disease, or possibly related to the antibiotic used to treat the illness.^{116–118} Acute urticaria can be observed in the early stages of hepatitis A, B, and C infection, but little evidence exists for hepatitis virus infection causing CU.¹¹⁹ In the past, stool studies to exclude parasites as a cause of urticaria have been recommended, but are only relevant in individuals who have recently traveled to endemic areas.

It is clear that food and drug anaphylaxis often demonstrate skin symptoms within 2 hours of ingestion, and is rarely determined to be the cause of CU. The frequency of NSAID-induced exacerbations of skin disease varies from 25% to 50%.¹²⁰ In some individuals the period of aspirin sensitivity ends when the urticaria disease resolves. There is evidence for genetic variability of prostaglandin E2 receptor subtype EP4 gene in aspirin-intolerant CU.¹²¹

Among the systemic diseases that can be associated with CIU are several rare disorders, which are summarized in **Table 3**.

FUTURE CONSIDERATIONS AND SUMMARY

Further studies are clearly needed to advance the understanding of pathogenic factors that trigger skin symptoms in both acute and chronic urticarial disease. At present, the diverse nature of inciting factors and systemic disease that are associated with urticaria suggest that multiple pathways lead to a common pathway involving mast-cell activation, resulting in infiltration by blood leukocytes. In addition, better biomarkers to predict the course of CIU disease and assist in the selection of therapeutics are needed.

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