

Differential diagnosis of chronic urticaria

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Objectives: To review diseases that can present with cutaneous signs and symptoms that mimic those observed in chronic urticaria and to discuss the workup necessary to distinguish these diseases from chronic urticaria.

Data Sources: We performed a PubMed search using the following keywords: *urticaria*, *cryopyrin*, *Sweet syndrome*, *subacute cutaneous lupus*, *urticarial vasculitis*, *urticaria pigmentosa*, *angioedema*, *fixed drug eruption*, *bullous pemphigoid*, and *reticular erythematous mucinosis*. Appropriate chapters in general dermatology textbooks were also reviewed.

Study Selection: Articles that related to disease states, which present with persistent urticarial lesions, were catalogued for use in this review.

Results: Besides acute, chronic, and physical urticarias, there are 2 categories of diseases that have urticarial lesions. The first group includes those in which the skin lesions are almost indistinguishable from those seen in patients with chronic idiopathic urticaria. Thus, the diagnosis relies on a careful history and physical examination, and in some cases laboratory studies are required. The second group are ones that have skin lesions that at one point in their development have an urticaria-like appearance or on rare occasion may have such lesions. These latter diseases are numerous, and we have tried to highlight the ones that most mimic chronic idiopathic urticaria or are more common.

Conclusions: A working knowledge of the diseases that can present with urticarial lesions is essential to accurately diagnose and effectively treat these symptomatic and sometimes serious conditions.

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INTRODUCTION

Chronic idiopathic urticaria (CIU) is a common dermatosis observed in 0.1% of the population.¹ It is characterized by pruritic, evanescent, erythematous papules and plaques of longer than 6 weeks' duration that arise without any obvious cause. Typically, lesions are observed on an almost daily basis, with individual lesions lasting only hours, but on occasion some may last up to 36 hours.² Most lesions have perilesional pallor probably due to vasoconstriction, whereas some have central clearing, giving them a more targetoid

appearance (Fig 1A). Individual lesions can range in size from less than a centimeter in diameter to ones that can affect a whole anatomical region. When lesions have deeper, more extensive edema that extends to the deep dermis and sometimes even subcutaneous tissue, they are referred to as angioedema (Fig 1B). Such lesions may be painful and typically persist longer than urticarial wheals. Approximately 10% to 20% of CIU cases have *only* angioedema lesions, whereas most patients have both urticaria and angioedema or urticaria lesions only.² Although angioedema can be observed anywhere on the body, it is typically observed periorbitally, periorificially, or on palmar and plantar surfaces. Involvement of the mucous membranes and tongue may occur, but this never extends to the larynx. Although this can and does frequently induce considerable anxiety, it rarely poses a serious threat to respiration.

Many patients with CIU also have a physical urticaria; the most commonly associated ones are dermatographism or de-

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Figure 1. Examples of Urticaria and Urticarial Lesions.

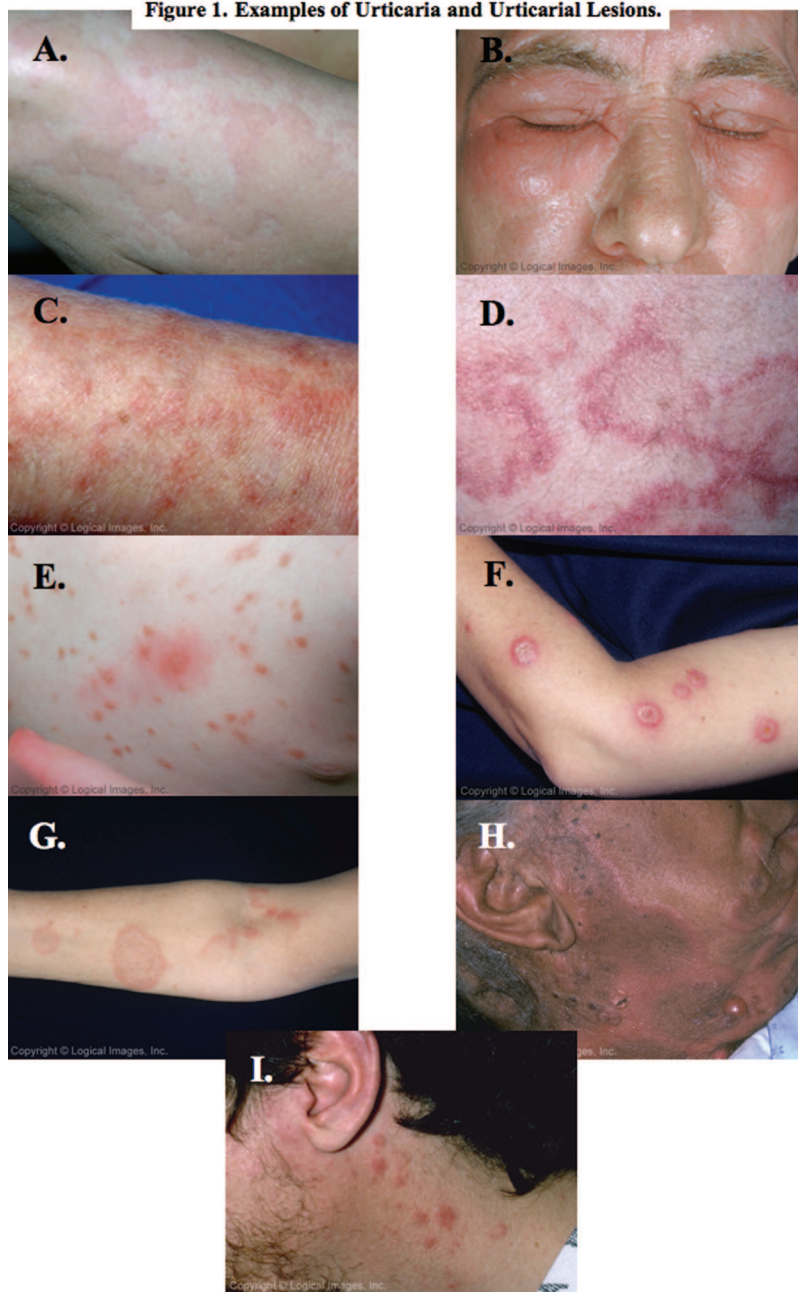


Figure 1. Examples of urticaria and urticarial lesions. Representative clinical photographs of urticaria with central pallor (A), angioedema in the periorbital area (B), subacute cutaneous lupus erythematosus lesions with some epithelial change (C), Rowell syndrome or multiform-looking lupus erythematosus (D), urticaria pigmentosa with salmon-colored lesions (E), Sweet syndrome or acute febrile neutrophilic dermatosis (F), fixed drug eruption (G), urticarial phase of bullous pemphigoid (H), and reticulated erythematous mucinosis (I). All images are copyright protected by Logical Images Inc.

layed pressure urticaria.³ Dermatographism can be elicited by stroking the skin, causing a characteristic symptomatic urticarial lesion to develop within 15 minutes. Delayed pressure urticaria lesions typically develop 1 to 12 hours after sustained pressure to the skin, such as might be seen with tight-fitting clothing or after wearing a heavy backpack. This form of physical urticaria may

be seen in up to 40% of patients with CIU and when present confers a greater disruption in quality of life.³ Some patients with recurrent urticaria have a pure physical urticaria, which can be diagnosed based on the appropriate challenge testing, which has been previously reviewed by Black et al⁴ and will not be discussed further in this review.

CIU develops as the consequence of plasma leakage from dermal blood vessels into surrounding connective tissue mediated at least in part by histamine.⁵ This is thought to have an autoimmune basis in more than 40% of patients, although most cases are still best characterized as idiopathic (see the CME Review Article by Brodell et al in this issue of the *Annals*).² Patient history and extensive laboratory evaluation often fail to identify a specific underlying cause; therefore, practice guidelines have suggested that extensive laboratory testing in these patients is not enlightening.^{6,7} The diagnosis of CIU requires exclusion of other disease processes, and sometimes this necessitates laboratory studies. History may suggest a physical stimulus, such as trauma, pressure, exercise, cold, heat, and water-induced lesions, and these are referred to as physical urticarias. Occasionally, recurrent incitement of acute urticaria by exposure to foods, medications, inhalants, or possibly infectious agents give the appearance of a chronic urticarial process.^{8,9} Biopsy is generally not required for the diagnosis, but when performed, histopathologic analysis can help support the diagnosis of CIU and more importantly can rule out other diagnoses. When routine laboratory studies are performed (complete blood cell counts, urinalysis, complement levels, and blood chemical analyses), the results are usually normal.

The characteristic histopathologic feature of a CIU lesion is a superficial and deep perivascular and interstitial mixed cell infiltrate composed primarily of lymphocytes, occasional eosinophils, and very rarely neutrophils. No epidermal changes are seen, such as spongiosis or hyperkeratosis, although there are variable degrees of superficial and sometimes deep dermal edema (eg, angioedema).¹⁰ Although some authors have referred to this pattern as a “necrotizing vasculopathy,” it is important to recognize that a leukocytoclastic vasculitis is never observed in biopsy specimens taken from urticaria. Therefore, the results of direct immunofluorescence studies, which look for the cutaneous deposition of complement or immunoglobulin, are typically negative.¹¹ The presence of vasculitis indicates an underlying immune complex disease and is an important differential to consider in persistent urticarial lesions or lesions that heal with purpura and/or dyspigmentation. Neutrophils can be the predominant cell in approximately 10% of CIU cases and are more commonly observed in biopsy specimens of delayed pressure urticaria or Schnitzler syndrome^{12,13} or in some of the urticaria mimickers (Sweet syndrome, Muckle-Wells syndrome [MWS], leukocytoclastic vasculitis, and bullous pemphigoid [BP]).

The clinical and histopathologic features described herein are collectively pathognomonic for CIU, but occasionally some atypical features are found. When the diagnosis is in question, a more extensive history and physical examination and/or a skin biopsy of a representative lesion or targeted laboratory studies may be necessary. A number of conditions produce erythematous, edematous, pruritic plaques, which could be mistaken for CIU. Usually though, these lesions are more chronic in nature or have associated clinical fea-

Table 1. Differential Diagnosis of Chronic Urticaria

Diseases or syndromes with classic urticarial lesions
Cryopyrin-mediated autoinflammatory disorders
Familial cold autoinflammatory syndrome
Muckle-Wells syndrome
Chronic infantile neurologic cutaneous articular syndrome
Schnitzler syndrome
Diseases with fixed atypical urticarial lesions
Cutaneous lupus erythematosus
Urticarial vasculitis
Cutaneous mastocytosis, urticaria pigmentosa
Sweet syndrome
Fixed drug eruption
Bullous pemphigoid
Reticular erythematous mucinosis

tures that help to distinguish them from CIU. We will cover in this review those diseases that have urticarial lesions but are not CIU. The differential diagnosis of CIU includes 2 categories of diseases (Table 1). First are the diseases or syndromes that have lesions that faithfully mimic those seen in CIU, such as cryopyrin-mediated autoinflammatory disorders and Schnitzler syndrome. The second category of diseases are those with often fixed urticarial lesions that on careful scrutiny have some atypical features, such as duration greater than 24 hours, relative lack of itch, epithelial changes (eg, hyperpigmentation or hypopigmentation, vesicles or blisters, or scaling), or an inconsistent histopathologic appearance, that direct the astute clinician to the right diagnosis. We discuss many of these diseases and identify the clinical features and/or laboratory studies that will help clarify the diagnosis and ultimately lead to a more effective and targeted treatment approach.

DISEASES WITH URTICARIA AS ONE OF THE CUTANEOUS MANIFESTATIONS

Cryopyrin-Mediated Autoinflammatory Disorders

The cryopyrin-mediated autoinflammatory disorders (familial cold autoinflammatory syndrome [FCAS], MWS, and chronic infantile neurologic cutaneous articular [CINCA] syndrome) are rare autoinflammatory diseases associated with recurrent urticaria. These syndromes are dominantly inherited on chromosome 1q44 and are due to mutations in the cold-induced autoinflammatory syndrome 1 (*CIAS1*) gene, which encodes for the protein cryopyrin.^{14,15} Other names for the *CIAS1* gene are nacht domain-, leucine-rich repeat-, and PYD-containing protein 3 (*NALP3*) or pyrin domain-containing APAF1-like protein 1 (*PYPAF1*).^{16,17}

Common features of the cryopyrin-associated periodic fever syndromes include a nonpruritic, urticarial rash (induced by cold in FCAS) beginning in infancy or the first 2 decades of life and fever.¹⁴ Patients with FCAS and MWS typically have conjunctivitis, and patients with MWS and CINCA have sensorineural hearing loss and secondary amyloidosis.¹⁸ The hallmark features of MWS, also known as the urticaria-

deafness-amyloidosis syndrome, are recurrent inflammatory episodes that consist of urticarial skin lesions accompanied by fever, arthralgia, arthritis, and malaise.^{19,20} The attacks normally resolve after 12 to 36 hours and recur every few weeks.¹⁶

The diagnosis of a cryopyrin-associated periodic syndrome is made on the basis of the physical findings listed herein. No test or biopsy currently exists that is both sensitive and specific enough to make the diagnosis.¹⁸ Elevated erythrocyte sedimentation rate, elevated C reactive protein level, polymorphonuclear leukocytosis, and polyclonal hypergammaglobulinemia may all be noted both during attacks and/or periods of remission. Interestingly, cryoprecipitates are typically never identified.²⁰ Cold provocation tests with ice cubes will initiate urticaria in persons with FCAS but may not initiate an urticarial episode in patients with MWS or CINCA. General exposure to colder temperatures may bring on flares in patients with MWS. Skin biopsy specimens from patients with a cryopyrinopathy may show amyloid deposits in sweat glands but more typically show a dense perivascular and/or interstitial neutrophilic and monocytic infiltrate in the papillary dermis.²¹

The treatment of these diseases has been greatly improved with the recent use of the recombinant interleukin 1 (IL-1) receptor antagonist anakinra (Kineret).^{17,22} Anakinra inhibits the binding of IL-1 to its cell surface receptors and thereby prevents its proinflammatory actions. Anakinra decreases the frequency of attacks and has been shown to halt symptoms and normalize renal involvement when present.²³ Glucocorticoids can be used for acute attacks, but adverse effects from chronic glucocorticoids limit its usefulness.

Schnitzler Syndrome

Schnitzler syndrome was first described by a French dermatologist in 1972, and since that time more than 50 cases have been reported in the literature.²⁴ Schnitzler syndrome is characterized by a chronic urticarial rash, fever, arthralgias or arthritis, bone pain, lymphadenopathy, and IgM gammopathy.²⁵ There is a delay in diagnosis (usually 5 years or longer) because most patients are instead labeled as having antihistamine-unresponsive CIU.²⁶ The urticarial lesions can last longer than typical CIU lesions (eg, 12 to 36 hours), and they tend to come in crops. The pruritus is often less intense than in CIU, and angioedema lesions are uncommon.²⁶

The skin lesions frequently are biopsied because of their long-lasting nature and typically reveal mild to moderate dermal neutrophilia without overt vasculitis.²⁶ Direct immunofluorescence results are commonly negative but if positive usually show IgM deposition around blood vessels and occasionally along the dermoepidermal junction.²⁶ A monoclonal IgM gammopathy is typically seen, although there have been a few reports of cases with an IgG gammopathy. Other laboratory findings typically observed include an elevated sedimentation rate, normal complement levels, and occasionally leukocytosis, thrombocytosis, and anemia. The disease has a chronic course with no spontaneous remissions. The

major concerns are systemic amyloidosis (relatively rare) and the evolution into a lymphoproliferative disorder, which occurs in approximately 15% of patients.²⁶

These lesions tend to be remarkably unresponsive to standard therapies, including antihistamines, corticosteroids, dapsone, colchicine, and most immunosuppressive agents. Recently, several reports have been made of a significant and sustained response to the recombinant IL-1 receptor antagonist anakinra (Kineret), although it is too early to say whether this therapy will affect progression to lymphoproliferative disorders or systemic amyloidosis.²⁵

DISEASES WITH ATYPICAL URTICARIAL LESIONS

Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) is a spectrum of rheumatologic diseases that are more common in women.²⁷ CLE can be divided into 3 primary reaction patterns. Patients with acute cutaneous lupus erythematosus (ACLE) present with erythematous macules in sun-exposed areas of the body, most typically a malar or butterfly rash over the central part of the face. Chronic cutaneous lupus erythematosus (CCLE) is a chronic, scarring condition, which produces discoid plaques that are notable for their dyspigmentation. Neither of these cutaneous lupus patterns are typically confused with CIU. However, subacute cutaneous lupus erythematosus (SCLE) can present with urticarial-like lesions that typically burn more than they itch and fluctuate in appearance (Fig 1C). These nonscarring lesions appear predominantly on sun-exposed areas of the body, hours to days after significant sun exposure, but can on occasion be mistaken for CIU. SCLE lesions do not wax and wane in hours and in fact typically last for days to weeks. In addition, they usually have subtle epithelial changes that are noted clinically as fine scale (often on the periphery of the lesions), which helps the clinician distinguish these lesions from CIU.²⁸ Rowell syndrome is an unusual clinical variant of SCLE that is characterized by erythema multiforme–like lesions that can also mimic CIU lesions (Fig 1D).²⁹

A skin biopsy can be helpful in defining each of the reaction patterns of lupus erythematosus, although the findings in ACLE and SCLE are less marked than those observed with the scarring form of lupus CCLE. The histopathologic findings consist of a sparse dermal infiltrate of mononuclear cells, dermal mucin deposition, and vasculopathy of basal cells of the epidermis. Direct immunofluorescence on a skin biopsy specimen typically demonstrates granular deposition of IgG and complement along a thickened basement membrane zone, which can solidify the diagnosis if the routine histopathologic findings are not classic. Antinuclear antibody and complete blood cell count with differential should be performed when SCLE is suspected because most cases with ACLE or SCLE will fulfill the American Rheumatism Association criteria for systemic lupus erythematosus.³⁰ Other more specific antibodies can be obtained (double-stranded

DNA, RNP, Sm, Ro [SS-A], La [SS-B]), but their prevalence is not high.³⁰

Treatment of cutaneous lupus involves the use of topical and/or systemic corticosteroids, antimalarials, and other immunosuppressive drugs³¹ and highlights the need for an accurate diagnosis. Using broad-spectrum sun block and promoting smoking cessation can significantly reduce the severity of CLE and increase the efficacy of treatments.

Urticarial Vasculitis

Urticarial vasculitis is a form of small- to medium-vessel leukocytoclastic vasculitis that presents with urticarial wheals, and up to 40% of these patients have angioedema.³² The lesions differ from CIU because they tend to be painful or burn, last for several days, and heal with dyspigmentation or purpura. Systemic symptoms are not uncommon and include arthralgias, respiratory symptoms, fevers, and abdominal discomfort. Urticarial vasculitis most commonly develops in association with connective tissue diseases, autoimmune disorders, viral hepatitis, or as a paraneoplastic syndrome.³³ If the patients have hypocomplementemia and significantly elevated erythrocyte sedimentation rates, they tend to have a more severe, multiorgan disease.³⁴ The presence of urticarial vasculitis in patients with systemic lupus erythematosus is a harbinger of more active disease.³⁵

The diagnosis is usually made by histopathologic analysis, which demonstrates leukocytoclastic vasculitis with dense perivascular infiltrate composed of neutrophils, neutrophilic debris, and small vessel damage (endothelial swelling, fibrosis, and fibrin deposition).^{32,36} This reaction pattern is thought to be the result of antigen-antibody complexes, although not all cases have deposition of immunoreactants at either the perivascular or dermoepidermal junctions.^{37,38} Laboratory workup typically includes complement studies, hepatitis B and C serologic tests, serum protein electrophoresis, and measurement of antinuclear antibody (and other relevant extractable nuclear antigens as dictated by the presentation), rheumatoid factor, and cryoglobulins.

Treatment is dictated by the severity of the disease and the degree of visceral involvement. The therapies used include dapsone, colchicine, hydroxychloroquine, nonsteroidal anti-inflammatory agents, systemic corticosteroids, azathioprine, cyclophosphamide, cyclosporine, and most recently Kineret.^{34,39}

Cutaneous Mastocytosis: Urticaria Pigmentosa

Cutaneous mastocytosis (CM) is the most common and benign form of mastocytosis, affecting predominantly children and characterized by increased mast cells in the skin.⁴⁰ Patients with this form of mastocytosis usually have normal serum total tryptase levels, suggesting that there is not a systemic involvement. CM tends to spontaneously regress over time.⁴¹ Based on recent advances in our understanding of the pathophysiology of mastocytosis, a new World Health Organization classification was proposed in 2001 establishing criteria for each of the variants, which include cutaneous

mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma.⁴² There are multiple subvariants of cutaneous mastocytosis, including urticaria pigmentosa, diffuse mastocytosis, and mastocytomas. Urticaria pigmentosa, also known as maculopapular CM, is the one that is a good mimicker of CIU (Fig 1E). The features that help distinguish CM from classic urticarial lesions are the orange to deep brown pigmentation observed overlying the wheal and the ability to elicit urtication by stroking the skin, which is referred to as the Darier sign.⁴³ In addition, the lesions tend to remain small, rarely achieving diameters greater than 1 to 2 cm, and completely spare the face, scalp, palms, and soles. Occasionally, a central vesicle or blister will form within a lesion. CM may be associated with other symptoms of mast cell activation, such as flushing, pruritus, and spontaneous urtication.

The diagnosis of CM is made by the combination of a classic clinical picture and cutaneous histopathologic findings that demonstrate multifocal infiltrates of at least 15 or more mast cells. These are best identified by a Leder stain, metachromatic stain, or antitryptase monoclonal antibodies. Only if patients have an elevated total tryptase level (>20 ng/mL) or constitutional symptoms suggestive of systemic mast cell involvement (recurrent syncope, diarrhea with abdominal pain, peptic ulcer disease, bone pain, severe headaches, and flushing) are more extensive laboratory evaluations warranted (x-ray examination of skeletal system, ultrasonography of abdomen, upper gastrointestinal tract endoscopy with biopsy or bone marrow biopsy).⁴² Therapy for CM is dictated largely by the severity of the symptoms and includes histamine₁ and histamine₂ antagonists, topical corticosteroids, and psoralen-based phototherapy.⁴⁴

Sweet Syndrome: Acute Febrile Neutrophilic Dermatitis

Acute febrile neutrophilic dermatosis was first described in 1964 by Sweet.⁴⁵ Classic Sweet syndrome is associated with infection of the respiratory or gastrointestinal tract or occurs after vaccination.⁴⁶ There is also a paraneoplastic variant most commonly associated with lymphoproliferative disorders but also sometimes associated with solid malignant tumors.⁴⁶

Sweet syndrome predominantly affects women, usually between 30 and 50 years of age, and is characterized by the acute onset of pyrexia, leukocytosis, and plaques that may resemble urticaria, although they are more persistent.⁴⁷ Typically, Sweet syndrome lesions begin as erythematous papules and nodules that coalesce to form tender, irregular, sharply bordered urticarial plaques with pronounced edema that can give them a peau d'orange appearance (Fig 1F). Some lesions are studded with indurated vesicle-like papules. The lesions are typically observed on the upper extremities, face, neck, and trunk and have an asymmetric distribution. Arthralgias and constitutional symptoms such as fever, general malaise, headache, and myalgia may also be present.⁴⁸

Histologically, Sweet syndrome is characterized by a dense infiltrate of neutrophils diffusely distributed throughout the upper dermis.⁴⁸ The intensity of the neutrophilic infiltrate and the distribution that is characteristically throughout the upper dermis rather than just perivascular distinguishes Sweet syndrome from neutrophilic urticaria. Edema exists in the upper papillary dermis and fragmented nuclei are common, although vessels are intact. The complete blood cell count often reveals leukocytosis with neutrophilia, and the erythrocyte sedimentation rate is often elevated.⁴⁷

Systemic corticosteroids offer the best treatment for the symptoms and cutaneous lesions, although approximately 25% of cases recur. Other treatment options include potassium iodide, colchicine, dapsone, or cyclosporine.⁴⁶ If the lesions are not treated, they may persist for weeks or months and may heal with scar formation.⁴⁸

Fixed Drug Eruption

Fixed drug eruption (FDE) is an uncommon form of adverse drug reaction typically observed with systemic administration that has distinctive clinical and histologic features.^{49,50} The skin lesions typically occur in the same spot (or spots) with each subsequent exposure to the offending agent. In the earliest phase, the eruption appears as an erythematous, sharply delineated round to oval macule(s) that can become more edematous and classically develops distinct hyperpigmentation, which in some cases never fully resolves (Fig 1G). Less commonly, vesicles or bullae may form within a lesion. It is not uncommon that there may be only one or just a few lesions. The typical location is on the extremities and the perianal, perioral, and genital regions. Many drugs have been implicated and include tetracyclines, sulfamethoxazole, barbiturates, nonsteroidal anti-inflammatory agents, and antihistamines to name but a few. Although the acute lesions of FDE can mimic urticaria, the persistence of the lesions for days (and longer if the inciting agent is not identified), the relative lack of pruritus, and the pronounced hyperpigmentation make the clinical distinction clear.

If the diagnosis is not clear, a skin biopsy may help because the histopathologic features of FDE are different from CIU. FDE has a moderately dense infiltrate of CD8⁺ T lymphocytes along the dermoepidermal margin with hydropic degeneration of the epidermal basal cells, pigment incontinence, and occasionally bullae formation at the base of the epidermis.^{50,51} The treatment is simply to identify and avoid the offending agent.

Bullous Pemphigoid

BP is an autoimmune subepidermal blistering disease that primarily affects older patients, but individuals of all ages have been described. The IgG autoantibodies are directed primarily against the BP 230 and BP 180 antigens, which are components of the hemidesmosome adhesion complex and therefore important for the basal cells of the epidermis to adhere to the basement membrane.⁵² The blister cleft there-

fore develops at the base of the epidermis, giving rise to a tense vesicle or more commonly blister. Blisters typically develop within an erythematous, indurated plaque. Uncommonly, patients may have multiple erythematous, urticarial plaques with no blisters, and they may complain of some degree of pruritus. It is not uncommon that these early, nonblistering lesions have a serpiginous appearance (Fig 1H). This is the clinical variant of BP that masquerades as CIU. Approximately 10% to 35% of patients will have oral ulcers that may precede the skin disease. The presence of such lesions helps suggest the correct diagnosis. The diagnosis of BP requires a skin biopsy and direct immunofluorescence studies. Routine histopathologic analysis demonstrates a superficial infiltrate of lymphocytes and histiocytes with an enrichment of eosinophils classically associated with a subepidermal blister. The direct immunofluorescence of perilesional skin shows immunoreactants (C3 $\pm$ IgG) deposited in a linear pattern at the epidermal basement membrane. Indirect immunofluorescence reveals that 70% to 78% of BP patients have circulating IgG directed against the basement membrane.⁵³ It is believed that the induration and pruritus sometimes observed with BP lesions may be due to complement-mediated mast cell activation. Most patients have an elevated serum total IgE level, and other recent studies have suggested that IgE may play a role in this disease.^{54,55}

The treatment is dictated by the severity of the disease. Localized indolent disease may require nothing more than topical corticosteroids or oral tetracyclines or niacins. More extensive and aggressive disease will often require high doses of systemic corticosteroids (40 to 80 mg/d) and/or immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide.

Reticular Erythematous Mucinosi

Reticular erythematous mucinosis is a rare disorder that primarily affects middle-aged women.⁵⁶ It appears as a pink or erythematous reticulate and sheet-like areas of erythema typically observed on the chest and back (Fig 1I). The disease is cyclical with exacerbations and remissions. Although this is classically asymptomatic, up to 30% of patients will experience pruritus. Photosensitivity and hormonal changes (oral contraceptives, pregnancy, menstruation) are often noted to flare the disease.⁵⁷

A histologic analysis of a lesion reveals a perivascular and often perifollicular mononuclear infiltrate with increase in dermal mucin, which is detected by Alcian blue or colloidal iron stains. Therefore, the identification of mucin distinguishes this condition from that observed in CIU. The results of direct immunofluorescence are negative, and the epidermis appears normal.⁵⁷ The origin of this mucinosis is unclear, although it may be autoimmune because it is often seen in patients with other autoimmune disorders such as systemic lupus erythematosus, Hashimoto thyroiditis, and diabetes mellitus. Treatments tried are topical calcineurin antagonists,

hydroxychloroquine, and pulse dye lasers for the vascular component.

CONCLUSION

The diagnosis of CIU is made based on the clinical presentation of waxing and waning edematous plaques and the exclusion of other conditions. These diagnoses include conditions such as Schnitzler syndrome and cryopyrinopathies, which show classic urticaria in the setting of specific clinical syndromes and other conditions such as lupus erythematosus and acute febrile neutrophilic dermatosis in which red plaques may resemble urticaria, but they are fixed and typically last for days if not longer. This review has highlighted those diseases that mimic CIU, pointing out key features that help to solidify the diagnosis. It is critical to keep these other diseases in mind when viewing an atypical CIU case.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor medical education for physicians. ACAAI designates each Annals CME Review Article for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should only claim credits commensurate with the extent of their participation in the activity.

CME Examination

1–5, Brodell LA. 2008;100:181–188.

CME Test Questions

1. The hallmark features of Muckle-Wells syndrome include urticaria, nephropathy, and:
 - a. blindness
 - b. neuropathy
 - c. deafness
 - d. anosmia
 - e. dysgeusia
2. The most important historical feature of true urticaria is its tendency to:
 - a. wax and wane in hours
 - b. form ever-expanding rings
 - c. remain fixed for days
 - d. recur in the same exact spot
 - e. cycle from red to blue to white
3. A biopsy specimen of fixed urticarial lesions associated with systemic lupus erythematosus is most likely to show:
 - a. vascular thrombosis
 - b. leukocytoclastic vasculitis
 - c. lichenoid inflammation
 - d. interstitial mixed infiltrate with scattered eosinophils
 - e. telangiectasias
4. An important clue to the diagnosis of chronic idiopathic urticaria is the presence of:
 - a. purpura
 - b. blisters
 - c. dermatographism
 - d. lesional numbness
 - e. lesional tenderness
5. A patient with typical urticaria presents with weight gain, fatigue, weakness, and constipation. The most important laboratory test in this patient would be:
 - a. thyroid-stimulating hormone
 - b. antinuclear antibody
 - c. hematocrit
 - d. urinalysis
 - e. liver function tests

Answers found on page 215.