

Grand Rounds Review

Chronic Urticaria and Recurrent Angioedema: Clues to the Mimics

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Urticaria and angioedema are experienced by up to 1 in 5 people, usually the result of common allergen or medication triggers and infections. Similarly, the majority of recurrent angioedema has an exogenous trigger, for example, angiotensin converting enzyme inhibitors, or is hereditary (type 1 and 2 hereditary angioedema); chronic spontaneous urticaria are most often autoimmune or autoallergic in routine clinical practice. There are, however, several skin and systemic conditions that can imitate the clinical appearance of either angioedema or urticaria, whereas there are several uncommon conditions that have chronic urticaria and/or recurrent angioedema as part of their disease manifestations. Correct diagnosis is paramount to ensuring subsequent tailored therapy for many of these conditions, and in many instances, diagnostic delay can be several years with morbid consequence. In this grand rounds article, we present 2 illustrative clinical cases as the backdrop to discussing a practical diagnostic approach for clinicians to recognize copycat phenotypes and “red flags” that should prompt further investigation of several uncommon mimics. We highlight key diagnostic features, epidemiology, and management for mimics where treatment is distinct from the common phenotypes of recurrent angioedema and chronic urticarias. © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

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ANGIOEDEMA MIMIC—CASE 1

A 43-year-old woman was referred to our tertiary allergy clinic with a 3-year history of intermittent episodes of facial edema, which had increased in frequency in the last 3 months. A provisional diagnosis of recurrent periorbital angioneurotic edema had been made after review by an internist 6 weeks before our initial consultation. Background medical history included hypertension treated with hydrochlorothiazide for 4 years, but no angiotensin-converting enzyme inhibitors or receptor blocker exposure and no other chronic medications including hormonal therapies. She had no history of atopic disease, and food or drug allergy. Family history included a mother deceased at age 40 from an acute respiratory illness; apparently she had also suffered intermittently with facial swellings in the few years before her death. Episodes of swelling had increased over the last 3 months to daily and included symmetrical periorbital and bilateral feet swellings (see Figure 1, A). The swellings felt itchy and painful, and although initially lasting only for 24 to 48 hours, over the last few weeks, they no longer resolved completely between daily worsenings. Systemic enquiry noted intermittent arthralgia of wrists and knees worse in the morning, and no abdominal complaints. Physical examination showed symmetric periorbital edema; violaceous erythema on the elbows; symmetric, tender, and bilateral nonpitting pedal edema; symmetrical mild proximal muscle weakness of the upper and lower limbs; and decreased range of motion in both knees and ankles.

She was admitted to the ward, and investigations confirmed the clinical diagnosis of dermatomyositis with elevated creatine kinase (785 IU/L) and positive antinuclear antibodies (negative anti-Mi-2 and anti-tRNA autoantibodies); a muscle biopsy demonstrated mild atrophy and positive major histocompatibility complex class I staining consistent with an inflammatory myopathy. She was treated with high-dose corticosteroids and cyclophosphamide. Unfortunately, her clinical course was complicated by severe nosocomial sepsis, and she died 26 days after admission.

URTICARIA MIMIC—CASE 2

A 54-year-old woman presented for further evaluation of her hive-like rash associated with systemic symptoms. Her rash began approximately 1.5 years previously with persistent “hives” in limited areas lasting for weeks at a time; the rash had recently become widespread with involvement including her arms, legs, back, chest, face, scalp, and neck. The “hives” lasted for up to a week at a time and then resolved leaving either bruising or brown patches on her skin, some of them disappearing without a trace (Figure 1, B). She described some of them looking “like a ‘bullseye’.” This rash is extremely uncomfortable for her, associated with itching and burning sensations, self-rated as 10/10 in

Abbreviations used

CAPS-Cryopyrin-associated periodic syndrome
CSU-Chronic spontaneous urticaria
EAE-Episodic angioedema with eosinophilia
HUVS-Hypocomplementemic urticarial vasculitis
MC-Mast cell
MCAS-Mast cell activation syndrome
MRS-Melkersson-Rosenthal syndrome
PUPPP-Pruritic urticarial papules and plaques of pregnancy
SLE-Systemic lupus erythematosus

severity, and waking her at night. During a typical day, these lesions are present all day (7 days a week), but some days are worse than others. The burning and itching rash is the worst feature of her illness and has affected all aspects of life—"some days I can't leave my home." She is anxious and depressed, and has missed work because of the symptoms. The associated systemic symptoms included marked fatigue; arthralgias with pain and morning stiffness in the hands, wrists, and feet; back pain; puffy hands; and diminished fist formation, diffuse scalp hair loss, and dyspnoea, but no sicca symptoms or photosensitive eruptions. Background medical history included recurrent oral aphthous ulcers, a history of pleurisy a few years prior, and 1 miscarriage and 2 pregnancies; she smoked e-cigarettes.

Neither antihistamines nor oral hydroxychloroquine had been helpful. Treatment with prednisone 40 mg daily resulted in improvement, but on weaning to 10 mg daily, her skin lesions returned. On examination, discrete and confluent urticarial appearing plaques with surrounding blanching of the skin in many areas were noted, measuring from 2 to 4 cm and involving 20% to 30% of the skin. An area of bruising/ecchymosis on the back at the site of a previous urticarial plaque was noted. On her phone, photographs showed the urticarial plaques observed on the clinical examination with many concentric, annular arcuate, and semiarculate plaques (Figure 1, B). The rest of the examination found skin tightening of fingers suggesting sclerodactyly, tender wrists and metacarpophalangeal joints, synovial thickening of the wrists, and a swollen left ankle.

A previous and new skin biopsy showed "urticarial vasculitis." Direct immunofluorescence showed perivascular IgM, IgA, and C3 deposition, and additionally basement membrane zone staining with granular IgM, IgA, and C3 deposition consistent with a lupus band. Laboratory study results showed a modest eosinophilia; a normal erythrocyte sedimentation rate of 22, but slight elevated C-reactive protein at 9.8, elevated alkaline phosphatase of 169 with normal aspartate transaminase and alanine transaminase, normal creatinine, polyclonal hypergammaglobulinemia with no monoclonal protein or protein electrophoresis, borderline elevation in thyroid-stimulating hormone with normal T4 and T3, and unremarkable urinalysis. Serologic testing showed positive anti-nuclear antibody with autoantibodies toward SS-A/Ro, Smith, and ribonucleoprotein. Double-stranded DNA, anti-nuclear cytoplasmic antibody, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies were negative. Complement levels were low: total complement 28 U/mL (normal 30-75), C3 55 mg/dL (normal 75-175), and C4 7 mg/dL (normal 14-40). Chest X-ray shows a mild interstitial change scattered in both lungs suggestive of edema. X-rays of the hands show a minimal degenerative change.

Taken together, a diagnosis of hypocomplementemic urticarial vasculitis (HUVS) associated with systemic lupus erythematosus (SLE) was made. The basis for the diagnosis of the hypocomplementemic vasculitis was her clinical presentation with persistent urticarial plaques, the biopsies showing urticarial vasculitis, and the hypocomplementemia. The diagnosis of SLE was based on the findings of numerous autoantibodies (anti-nuclear antibody, Sjögren's-syndrome-related antigen, ribonucleoprotein, and Smith positivity), skin lesions with alopecia, oral ulcers, history of pleurisy, and polyarthritides. There was no evidence of renal involvement and no cytopenia. It was noted that patients with urticarial vasculitis can have low complement values, and these patients can have features that are quite similar to those of lupus.

Hydroxychloroquine 200 mg BID orally was continued, and she was advised to stop e-cigarettes. Smoking can hasten the systemic clearance of Plaquenil reducing drug efficacy and may exacerbate cutaneous lupus. Repeated failed attempts to wean prednisone were made; however, every time her prednisone was weaned below 20 mg daily, her painful urticarial plaques recurred. Steroid-sparing disease-modifying agents were considered, and in the context of her liver disease (she also had primary biliary cirrhosis), it was felt best to avoid methotrexate or leflunomide. Azathioprine or mycophenolate mofetil was considered. After discussion with the patient and the finding of a normal thiopurine methyltransferase level, azathioprine was introduced 50 mg per day the first week, then increasing to 100 mg per day with a target dose of 1 to 2 mg/kg/day depending on response; over a month the dose gradually escalated to 150 mg daily. On this dose she was able to wean the prednisone completely without recurrence of the urticarial vasculitis. Four years later, she remains under good control with azathioprine 150 mg daily and hydroxychloroquine 200 mg BID orally.

INTRODUCTORY APPROACH

Urticaria and angioedema are characterized by swelling in the superficial and deep layers of the skin, caused by a sudden increase in endothelial permeability with extravasation of intravascular fluid into the interstitial tissues.¹ A variety of mediators and mechanisms trigger this process.²⁻⁴ Acute, intermittent urticaria and angioedema are very common affecting up to 1 in 5 people. Chronic urticarias affect approximately 1% of the world's population⁵ and, together with episodic and recurrent angioedema, are an everyday feature of general and specialist allergy and dermatology practice. Although the pathophysiology continues to be elucidated, the majority of chronic urticarias, either spontaneous or inducible, fall into defined autoallergic or autoimmune phenotypes.⁶ Similarly, recurrent angioedemas without urticaria includes those with a clear exogenous trigger, for example, angiotensin converting enzyme-Inh, hereditary forms—with either strong family histories or known genetics, and a well-recognized histaminergic angioedema only group.^{7,8} However, there are several skin and systemic conditions that imitate the clinical appearance of either angioedema or urticaria (see case 1),⁹ whereas there are several uncommon conditions that have chronic urticaria and/or recurrent angioedema as part of their disease manifestations (see case 2). It is critical that alternative skin and multisystem diseases are recognized as increasingly tailored therapy for many is becoming available, and diagnostic delays can be several years with morbid consequence.¹⁰ In this



FIGURE 1. A, Periorbital edema associated with dermatomyositis. **B,** Widespread urticarial plaques involving the abdomen, and resolving urticarial plaques with residual ecchymotic arcuate and semiarculate patches in urticarial vasculitis.

grand rounds article, we have presented 2 illustrative clinical cases. Figure 2 outlines high-level practical diagnostic approaches to aid clinicians to recognize the copycat phenotypes and “red flags” that should prompt further investigation when faced with a patient with recurrent angioedema or chronic urticaria. Further details and discussion are provided highlighting key diagnostic features, epidemiology, and management for known mimics where treatment is distinct from the common phenotypes.

RECURRENT ANGIOEDEMA MIMICS

Given the wide heterogeneity of angioedema phenotypes,^{11,12} the first step to recognize multiple possible mimickers is the collection of a detailed clinical history and examination, answering the questions: (1) Is this angioedema at all?, and (2) is this angioedema but with atypical features? front of mind. Family history, long-lasting versus episodic features, presence or absence of associated wheals, anatomical location, and associated skin or systemic symptoms and signs are of pivotal importance to hypothesize nonangioedema (infectious, infiltrative, neoplastic, autoimmune) conditions and guide the diagnostic workup. Key red flags that should alert to a possible angioedema mimic and prompt further investigations include: (1) involvement of a single anatomical location or dependent area, (2) prolonged duration (>72 hours) without resolution, (3) other skin signs, for example, infiltration or nonangioedema rash, for example, heliotrope rash, and (4) systemic symptoms or signs, for example,

muscle weakness, arthropathy, or weight loss (Figure 2, A). However, the pathway will not always be linear, and in many instances, standard angioedema diagnoses need to be carefully considered and excluded with standard testing, such as C4, antigenic, and functional C1-inhibitor levels and even genetics; sometimes even the response to variable treatment regimens will be required to provide useful clues to the correct diagnosis. In the below section, we highlight certain mimics mentioned in Figure 2, A, that warrant additional awareness.

Infiltrative Causes

Common disorders such as cellulitis and abscesses may be misdiagnosed as angioedema, when the whole clinical picture, including risk factors for skin and soft tissues infections, such as diabetes mellitus or immunosuppression, is not considered. Local signs of underlying inflammation, such as erythema and warmth, and associated systemic signs such as fever are clinical clues to avoid confusion.

Skin infiltration often with surrounding tissue oedema, including from granulomas, malignant cells, and extracellular matrix, is an important mimic to exclude, as introduced in case 1. Tissue diagnosis via skin biopsy is usually key to making the diagnosis, with adjunctive lab and imaging as indicated (Figure 2, A).

Periorbital and facial locations are the commonest site for infiltrative mimics. Periorbital edema and proptosis are key signs of Graves' orbitopathy, often associated with conjunctival

HOW NOT TO MISS AN IMITATOR OF RECURRENT ANGIOEDEMA OR CHRONIC URTICARIA: AN APPROACH

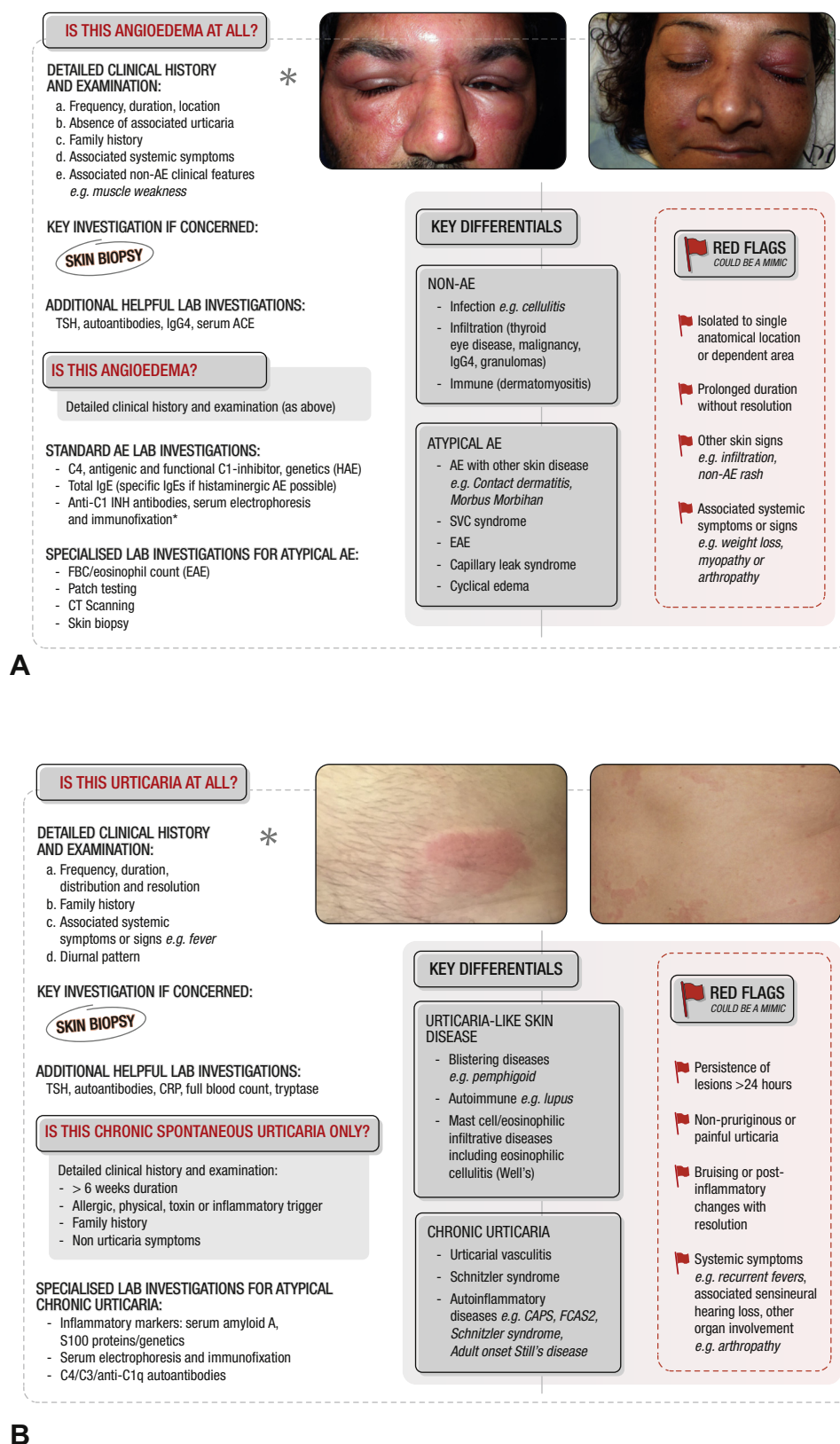


FIGURE 2. Overview of a practical approach, workup, and clues or red flags to (A) recurrent angioedema and (B) chronic urticaria mimics.

inflammation, eye or retroocular discomfort or pain, excessive tearing, and vision alterations (and even blindness). Interestingly, periorbital edema may precede the onset of hyperthyroidism in approximately 20% of patients. Besides the obvious evaluation of thyroid function, noncontrast computed tomography or novel magnetic resonance imaging techniques help to detect signs of optic nerve compression or best evaluate inflamed extraocular muscles.¹³ Involvement of the skin, eyes, lacrimal, parotid, and submandibular glands may occur in granulomatous disorders, such as sarcoidosis and granulomatosis with polyangiitis. Moreover, it is known that up to 25% of cases previously diagnosed as nongranulomatous idiopathic orbital pseudotumor are to be ascribed to immunoglobulin G4-related disease,¹⁴ an immune-mediated fibroinflammatory condition, usually characterized by subacute development, which may involve the head and neck, the pancreato-hepato-biliary system, the retroperitoneum, and/or the aorta, or even show systemic manifestations (Mikulicz syndrome). Other conditions that cause subcutaneous swellings usually restricted to periorbital and facial areas include acute contact dermatitis and Morbus Morbihan—a rare complication of rosacea associated with erythematous edema restricted to the forehead, glabella, upper eyelids, and cheeks.¹⁵

A variety of solid and hematologic malignancies may induce skin infiltration with oedema (eg, orbital and ocular lymphoid hyperplasia or adnexal lymphoma). Remarkably, systemic or more localized oedema may sometimes be iatrogenic, due to capillary leakage secondary to chemotherapy, surgery, or engraftment syndrome. In the context of malignant associations with angioedema, clinicians should also be aware of the scenario of late-onset angioedema in the absence of family history and should raise the suspicion of an acquired C1-inhibitor deficiency, with an underlying lymphoproliferative disease (especially splenic marginal zone lymphoma), and this should warrant investigations including anti-C1 inhibitor autoantibodies, serum electrophoresis and immunofixation, and possibly even bone marrow or splenic biopsy, flow cytometric immune phenotyping, and cytogenetics.¹¹

The diagnosis of autoimmune mimics, such as dermatomyositis (case 1), is often aided by associated systemic symptoms and signs such as additional nonangioedema rashes, myopathy, and/or arthropathy, some of which may display pathognomonic cutaneous findings, such as the pruritic pink-violaceous papules overlying interphalangeal and metacarpophalangeal joints (Gottron's papules) and erythema overlying other joints (Gottron's sign) in dermatomyositis. Case 1 illustrates though that these additional features and systemic signs may develop later in the course of illness making the initial presentation more difficult to distinguish from angioedema.

Melkersson-Rosenthal Syndrome

Melkersson-Rosenthal syndrome (MRS), first described in 1928, is a rare (probably underestimated) neuromucocutaneous disorder of unknown etiology that presents with the triad of orofacial edema, recurrent facial nerve palsy, and fissured tongue. The disease shows a female predominance and onset usually between 25 and 40 years, with few pediatric cases.¹⁶ There are no specific biomarkers, and usually symptoms do not occur simultaneously, making recognition of the classic triad complicated with prolonged diagnostic delay frequent. Thus, it is critical that clinicians are aware of this syndrome as a differential for

hereditary and acquired angioedemas. Edema most commonly affects the lower lip, tongue, eyelids, nose, upper arms, genitalia, and larynx, with a nonpitting feature and no associated pain or pruritus. Sometimes it does not resolve completely and may evolve to fibrosis, with permanent disfigurement of the face. Unilateral or bilateral facial palsy may precede orofacial edema even by years, and its duration may increase as disease progresses. The diagnosis of MRS is also possible when the presence of one clinical feature (isolated orofacial edema) is associated with histopathologic confirmation of non-necrotizing granulomatous cheilitis in the biopsy of the lip or eyelid (Miescher's cheilitis granulomatosa). However, caution is needed when making the diagnosis based on histology, because sometimes frank granulomas may be absent and nonspecific inflammatory patterns may be found, especially if sampling is not performed during an acute crisis. Besides the classical triad, a wide spectrum of symptoms may be identified, including headache, facial paraesthesia, aphthous ulcers and secondary infections, conjunctival congestion, and visual disturbances and involvement of other cranial nerves.

The mainstay for the treatment of MRS is corticosteroids (even though we cannot rely on randomized controlled trials for indications of posology and duration), but other treatment strategies, such as intralesional injections of triamcinolone or betamethasone, oral doxycycline, immunosuppressants, photobiomodulation, and even surgical interventions (eg, surgical decompression of the facial nerve), have been described in the literature.^{17,18}

Episodic and Nonepisodic Angioedema With Eosinophilia

Episodic angioedema with eosinophilia (EAE), also known as Gleich syndrome since its first description in 1984,¹⁹ is a rare disease characterized by recurrent episodes of angioedema (usually affecting the face and the limbs), wheals, pruritus, fever, weight gain, oliguria, leukocytosis with marked eosinophilia, and increased serum monoclonal or polyclonal IgM levels. Abdominal symptoms, arthralgia, lymphadenopathy, and splenomegaly may also be present. The interval between attacks is usually of 3 to 4 weeks, and each crisis lasts a few days. The mean age of onset is 35 years, with a slight female predominance, but pediatric cases have been described.²⁰

According to the classification endorsed by the International Cooperative Working Group on Eosinophil Disorders, it can be considered as a subgroup of hypereosinophilic syndromes, when alternate diagnoses have been excluded. The pathophysiology is unknown, but T helper cells, with production of eosinophilopoietic cytokines (as IL-5) that activate blood and tissue eosinophils, are considered to drive the disease. T-cell immunophenotypes may be abnormal in a subset of patients, for example, clonal TCR γ gene rearrangement, and are associated with shorter time to flare, and occasionally transformation to high-grade lymphoma.²¹

IgM as well as cryoglobulinemia, associated with serum hyperviscosity, may also be important in pathogenesis. Non-EAE, usually associated with normal IgM levels and single crisis, has also been reported.²²

The mainstay of treatment is short courses of corticosteroids, and this can be increased if relapse occurs while maintenance therapy is ongoing. Steroid-sparing therapeutic options, such as anti-IL-5 monoclonal antibodies, have been beneficial in some cases.^{23,24}

TABLE I. Key differentiating features of classical urticaria, urticarial vasculitis, Schnitzler syndrome, and cryopyrin-associated periodic syndromes (CAPS)

Disease	Clinical features	Accompanying symptoms	Laboratory results	Skin biopsy	Response to treatment
Classical urticaria	Circumscribed, raised, erythematous plaques, often with central pallor intensely itchy. Pruritus symptoms often seem most severe at night	Angioedema in minority of patients	No specific abnormalities	Dermal edema, blood vessel dilatation, and a mild perivascular infiltrate predominantly consisting of monocytes and CD4 ⁺ lymphocytes	Good response to antihistamines. Good response to corticosteroids
Urticarial vasculitis	Painful and itching urticarial plaques often last >24 h and may be accompanied by signs of leukocytoclastic vasculitis; residual dusky pigmentation at the site of plaques	May be associated with concurrent angioedema, purpura	Hypocomplementemia (complement studies [total complement, C3, C4], C1q levels); may be associated with anti-C1q antibody	Both signs of urticarial (dermal edema) and vasculitis (superficial and deep perivascular and interstitial polymorphonuclear infiltrate with nuclear dust, leukocytoclasia, and red blood cell extravasation); direct immunofluorescence shows immunoglobulin and complement deposition in or around blood vessels of the upper dermis and/or at the dermal-epidermal junction	Variable response to antihistamines, hydroxychloroquine, colchicine, corticosteroids, immunosuppressive medications (azathioprine, mycophenolate mofetil, or cyclophosphamide, rituximab)
Schnitzler syndrome	Chronic recurrent urticarial rash on trunk and upper extremities. Nonpruriginous. Persists between 4 and 36 h	Fever, arthralgias, hepatosplenomegaly, lymphadenopathy	Monoclonal gammopathy, increased inflammatory parameters	Heterogeneous findings: neutrophilic urticaria is most common, spongiotic dermatitis	No response to antihistamines, partial response to high-dose corticosteroids, rapid and complete response to anti-IL-1 therapy
CAPS	Daily, nonpruriginous urticarial rash on trunk extremities and face. Exacerbated by exposure to cold	Fever, arthritis/arthralgia, sensorineural hearing loss, aseptic meningitis, type AA amyloidosis	Increased inflammatory parameters	Predominantly neutrophilic, perieccrine, and perivascular infiltrates throughout the dermis. There is no evidence of vasculopathy or vasculitis	No response to antihistamines, limited/no response to corticosteroids, rapid and complete response to anti-IL-1 therapy

Adapted from Davis and van der Hilst.²⁵

CHRONIC URTICARIA MIMICS

In the majority of cases, a diagnosis of chronic spontaneous urticaria (CSU) is easily established by the history and clinical signs of recurrent pruritic wheals with or without accompanied angioedema for more than 6 weeks. However, there are a number of differential diagnoses that need to be considered especially in those patients who present with unusual or extracutaneous symptoms and do not respond to standard treatments of CSU. [Figure 2, B](#), outlines an overall approach similar to consideration of angioedema mimics, highlighting both nonurticarial mimics and disorders where chronic urticaria is only a part of the disease phenotype. The below sections detail further key conditions where treatment approaches differ substantially from CSU, with [Table 1](#) summarizing key mimics: highlighting clinical presentations, histologic features, and treatments.

Nonurticarial Diseases

A few chronic inflammatory skin conditions may imitate the clinical picture of CSU and should therefore not be overlooked. These include a heterogeneous group of disorders such as eosinophilic disorders that were already mentioned in the context of angioedema, premonitory bullous pemphigoid, and pruritic urticarial papules and plaques of pregnancy (PUPPP). Despite their clinical similarity with CSU, they are clearly differentiated by a routine skin biopsy.

Bullous pemphigoid is an autoimmune disease of the skin that preferentially affects the elderly population. Although the main clinical findings are vesicles, in some patients, it may present with urticarial plaques only accompanied by severe pruritus. Skin histopathology shows subepidermal blistering and dermal inflammatory infiltrates as well as complement and immunoglobulin deposits at the dermoepidermal junction.²⁶

PUPPP is a disease restricted to pregnant women, usually presenting during the third trimester or the early postpartum period. Its clinical findings are heterogeneous ranging from pruritic abdominal papules and small vesicles to generalized urticarial lesions. Histopathologic findings show perivascular cellular infiltrates with dermal edema and negative immune histology.²⁷

Chronic Urticaria “Plus” Conditions

Urticarial vasculitis. Urticarial vasculitis describes a clinical presentation with urticarial plaques that are persistent and are associated with clinical signs of vasculitis; it is a very important diagnosis to consider in patients with chronic urticaria. As in our illustrative case that outlined several key features, clinicopathologic correlation is essential to confirm the urticarial and vasculitic changes. Urticarial vasculitis may be suspected in patients with more than 6 months of urticaria combined with unexplained systemic inflammation such as recent onset shortness of breath or proteinuria.²⁸ The key red flags in our case were the longstanding (years), widespread, and persistent urticarial plaques (lasting for >24 hours) that the patient described as painful, rather than pruritic, together with signs of vasculitis (purpuric patches and plaques/palpable purpura). In approximately one-third of cases, resolution of the plaques leaves purpuric patches (often patterned) and postinflammatory hyperpigmentation.²⁹ The urticarial plaques may be associated with angioedema (approximately 51%) and livedo reticularis (14%).³⁰ Skin biopsy confirms the diagnosis, frequently showing histologic features of both urticaria and vasculitis.

Urticarial vasculitis likely is a description of a continuum of disease, from urticaria to frank multisystem vasculitis, from mild to severe disease. Similarly, the histologic signs of vasculitis may vary from a sparse perivascular infiltrate with no leukocytoclasia to a dense infiltrate with frank signs of blood vessel destruction including leukocytoclasia and fibrin deposition.^{25,30} Like other forms of vasculitis, involvement of the skin may be just the tip of the iceberg—multiple other organs may be involved, including renal, gastrointestinal, pulmonary, and musculoskeletal. Systemic involvement is highly variable. In normocomplementemic urticarial vasculitis, often there is no systemic involvement. In HUVS, one series of 57 patients described the following systemic involvement: constitutional symptoms in 56%, musculoskeletal involvement in 82%, ocular involvement in 56%, pulmonary involvement in 19%, gastrointestinal involvement in 18%, and kidney involvement in 14%.³¹ The severity of systemic involvement often correlates inversely with complement levels (low complement levels correlate with more severe disease); hence, HUVS is more severe than normocomplementemic urticarial vasculitis.³²

Urticarial vasculitis is a rare entity, more prevalent in women and middle age. Much depends on the definition of vasculitis used in studies, but estimates of 5% to 20% of biopsies from patients with chronic urticaria have been described to show features of urticarial vasculitis.³³ Studies have mostly described the epidemiology of the hypocomplementemic form of urticarial vasculitis. In a study from Sweden, the point prevalence on December 31, 2015, was 9.5 per million (95% confidence interval: 4.5, 14.5).³⁴ The etiology is similar to the causes of urticaria and the causes of vasculitis. Although often idiopathic, underlying etiologies such as infection (eg, hepatitis B and C), medications, connective tissue disease, and malignancy need to be investigated. The most common association is with SLE as in our case, and some consider HUVS to be a feature of SLE.³⁵ A collagen-like region on C1q has been implicated as the antigenic target in the hypocomplementemic form; indeed, HUVS has been described to be anti-C1q vasculitis.³⁶ Lab testing often reveals a raised sedimentation rate, a positive antinuclear factor (anti-nuclear antibody), low complement levels (C1q is low in hypocomplementemic vasculitis, but may also be low in other connective tissue diseases such as SLE), and abnormal laboratory values suggesting that specific organ involvement may be observed.³⁴

The management is based on limited evidence and anecdotal reports; there have not been randomized controlled studies to guide treatment. Systemic corticosteroids and steroid-sparing medications are often used.³⁷ For predominantly urticarial presentation, antihistamines are used. Nonsteroidal anti-inflammatory drugs are often helpful, whereas other medications that are used include dapsone, colchicine, hydroxychloroquine, and pentoxifylline. For more severe disease, methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, rituximab, anakinra, canakinumab, and omalizumab have all been used.³⁷ Whereas normocomplementemic urticarial vasculitis is associated with a benign course, HUVS is often associated with increased morbidity, but is rarely life-threatening.³⁰

Autoinflammatory syndromes. In patients presenting with recurrent wheals and signs of additional organ involvement, several systemic inflammatory diseases need to be considered.

Besides HUVS, urticarial autoinflammatory diseases are the other important differential diagnoses. Autoinflammatory diseases are characterized by chronic inflammation at various organs most often including the musculoskeletal system and the skin. In contrast to autoimmune diseases, autoinflammatory disorders are driven by activation of innate rather than T-cell- or antibody-specific immune responses.³⁸

Autoinflammatory diseases are rare entities that can be divided into early-onset monogenic diseases and complex acquired diseases that may present during childhood or later in life.

In patients with adult onset of recurrent urticarial rash and systemic symptoms, Schnitzler syndrome and adult-onset Still's disease (AOSD) are most relevant. Schnitzler syndrome—with a median symptom onset of 50 years—presents with recurrent nonpruritic or only mildly pruritic wheals that are unresponsive to antihistamine therapy. Typically, skin and systemic symptoms follow a diurnal pattern with a maximum intensity in the evening. Accompanying systemic symptoms include fever episodes, arthralgia, and bone pain, as well as fatigue.³⁹ Laboratory investigations show a monoclonal band in the immune electrophoresis (paraproteinemia), elevated inflammatory markers (eg, CRP, serum amyloid A, and S100 A8/9), and neutrophil-rich dermal infiltrates on skin histopathology.⁴⁰ The etiology of Schnitzler syndrome is unknown, but IL-1 plays a pivotal role, as demonstrated by the favorable clinical response to anti-IL-1 blockers.⁴¹ Still's disease (also known as systemic juvenile idiopathic arthritis [SJIA]) and its adult variant (adult-onset Still's disease) usually present with maculopapular salmon-colored exanthema, but may also show urticarial rashes and similar systemic symptoms to Schnitzler syndromes.⁴² In addition to fever, fatigue, and arthropathy, patients may present with hepatosplenomegaly and high inflammatory markers including serum hyperferritinemia (often >1000).⁴³ Targeted therapy with both anti-IL-1 and anti-IL-6 blockers has been shown to be effective in SJIA and AOSD.^{44,45}

Within the monogenic spectrum of autoinflammatory diseases, cryopyrin-associated periodic syndrome (CAPS) is the best-known and most important differential diagnosis of CSU. CAPS is characterized by similar clinical symptoms as in Schnitzler syndrome and SJIA/AOSD, with recurrent usually nonpruritic wheals (often exacerbated by cold temperatures), and a number of systemic symptoms such as fever, fatigue, and arthropathy.⁴⁶ Patients may also suffer from uveitis, hearing loss, and central nervous system involvement. In contrast to polygenic autoinflammatory conditions, the onset of CAPS is usually early childhood with ongoing symptoms into adulthood. Skin histopathology may show neutrophil-rich infiltrates and elevated inflammatory markers as in Schnitzler syndrome and SJIA/AOSD. In addition, patients respond well to anti-IL-1—targeted drugs.⁴⁷ If the patient history and clinical symptoms including early onset suspect CAPS, genetic analysis (routinely performed by Sanger sequencing) may confirm the diagnosis by a heterozygous mutation in NLRP3.⁴⁸

Mast cell activation syndromes. Recurrent wheals may result from clonal and nonclonal expansion of mast cells (MCs); thus being a symptom as part of the complex of symptoms associated with MC activation.⁴⁹ Mastocytosis—defined by abnormal clonal MC expansion and accumulation in tissues such as bone marrow and skin—can present with recurrent wheals, although typically cutaneous mastocytosis presents with

hyperpigmented macules that become urticarial when rubbed (Darier's sign).⁵⁰ Skin biopsy (Figure 2, B) is useful in differentiating these urticaria-like lesions. The presence of additional systemic features associated with either severe MC activation, for example, anaphylaxis, or chronic MC activation, for example, neurologic and gastrointestinal symptoms, should alert clinicians to consider systemic mast cell activation syndromes (MCAS)—either clonal such as systemic mastocytosis or nonclonal idiopathic forms of MCAS.^{49,51} In the latest World Health Organization classification of mastocytosis, critical diagnostic criteria involve visualization of dense MC infiltrates (≥ 15 MCs in aggregates) in bone marrow or other extracutaneous organs, KIT D816V mutations, and baseline serum tryptase levels >20 ng/mL.⁵² In contrast, consensus diagnostic criteria for nonclonal idiopathic MCAS with multisystem features are lacking with opposing views in the literature around the scope of patients included, and the need for biochemical confirmation of tryptase increases, for example, 20% + 2 ng/mL from baseline.^{51,53} In the context of differentiating MCAS from CSU, a detailed history, serial serum tryptase measurements, and targeted tissue sampling should be sufficient.

CONCLUSION

In the majority of instances, detailed clinical history and examination, coupled with awareness of key differential diagnoses, is sufficient to recognize the majority of the mimics of angioedema and chronic urticaria presented in this grand rounds review. Where red flags are identified, standard investigations are nonconclusive, and/or where response to standard treatments is unsuccessful, it is critical to think and investigate further. Finally, it is important for clinicians to be aware that in many of the systemic diseases presented above, including in the illustrative cases, the full clinical picture may not be evident from the outset, often taking many years to become easily recognizable.

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