Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases

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A wide differential diagnosis must be considered in a patient presenting with urticarial plaques. Although acute and chronic urticaria are the commonest diagnoses, other differential diagnoses include polymorphous eruption of pregnancy, mast cell disorders, hypereosinophilic syndrome, urticarial vasculitis, pemphigoid, systemic lupus erythematosus, and autoinflammatory disease. This review will specifically address urticarial vasculitis and autoinflammatory syndromes. These entities represent contrasting examples of urticarial-like lesions resulting from either an adaptive immune complex–mediated mechanism (urticarial vasculitis) or an innate immune–mediated mechanism (autoinflammatory disorders), with differing therapeutic implications. In patients presenting with painful, persistent plaques that last more than 24 hours and resolve with bruising of the skin, consideration should be given to a diagnosis of urticarial vasculitis. A biopsy should be obtained to ascertain this diagnosis. In patients presenting with a persistent history of recurrent urticarial plaques associated with signs of systemic inflammation including fevers and elevated inflammatory markers (C-reactive protein [CRP]/serum amyloid A, leukocytosis, and negative connective tissue serologies), consideration should be given to autoinflammatory disorders: the 3 cryopyrin-associated periodic syndromes, Schnitzler syndrome, and familial cold autoinflammatory syndrome 2. Serum protein electrophoresis should be checked to rule out an underlying monoclonal gammopathy. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1162-70)**

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A wide differential diagnosis is entertained in a patient presenting with urticarial plaques. Although acute and chronic urticaria are the commonest diagnoses, other differential diagnoses include polymorphous eruption of pregnancy, mast cell disorders, hypereosinophilic syndrome, urticarial vasculitis (UV), systemic lupus erythematosus (SLE), and autoinflammatory disease. This review will specifically describe UV and autoinflammatory syndromes. These entities represent contrasting examples of urticarial-like lesions resulting from either an adaptive immune complex–mediated mechanism (UV) or an innate immune–mediated mechanism (autoinflammatory disorders), with differing therapeutic implications.

When urticarial plaques are persistent and associated with signs of vasculitis such as bruising and with systemic disease, a diagnosis of UV should be considered.[1] The clinical presentation of UV is an example of adaptive immune complex activation; in response to a number of etiologic factors, immune complexes become activated, leading to complement activation and the generation of C3a and C5a, which as anaphylatoxins can activate mast cells (and basophils) to degranulate with the release of preformed histamine with resultant clinical manifestations of urticaria and UV.

In patients with recurrent or persistent fever accompanied by an array of inflammatory symptoms, the possibility that autoinflammatory diseases result from inappropriate activation of the innate immunity (with the absence of significant levels of autoantibodies and autoreactive T cells) needs to be considered. Urticarial rash is a differentiating characteristic in 5 of the autoinflammatory syndromes: the 3 cryopyrin-associated periodic syndromes (CAPS), Schnitzler syndrome, and familial cold autoinflammatory syndrome 2 (FCAS2).

Table I summarizes clinical, histologic, laboratory, and management findings that differentiate chronic urticaria, UV, and autoinflammatory diseases.

CASE 1: URTICARIAL VASCULITIS

A 54-year-old female Native-American ancestry presents for further evaluation of a 2-year history of an urticarial skin eruption lasting for up to a week at a time and resolving leaving either bruising or brown pigmentation on the skin; occasionally she develops blisters on the palms. This rash is generally extremely uncomfortable for her—it is associated with both itching and burning sensations, self-rated as approximately 10/10 in severity, and associated with disruption of her sleep, work, and social life. She cannot swim or teach water aerobics because of them. She missed work because of the symptoms. She additionally has alopecia, inflammatory polyarthritis, pleurisy, and strongly positive serologies including antinuclear antibody (ANA), Sjögren syndrome antigen A (SSA), ribonucleoprotein (RNP), and anti-Smith antibody; urinalysis was normal. Her complement levels are markedly decreased (total, C3 and C4 in addition to C1q) consistent with hypocomplementemia.

Physical examination is significant for discrete and confluent urticarial appearing plaques involving approximately 20% to 30% of the skin (Figure 1, *A*). They measure from 2 to 4 cm

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Abbreviations used
AA- Amyloid A
ANA- Antinuclear antibody
ANCA- Antineutrophil cytoplasmic antibody
CAPS- Cryopyrin-associated periodic syndromes
CINCA- Chronic infantile neurologic, cutaneous, and articular
CRP- C-reactive protein
FCAS2- Familial cold autoinflammatory syndrome 2
GI- Gastrointestinal
HUV- Hypocomplementemic urticarial vasculitis
HUVS- Hypocomplementemic urticarial vasculitis syndrome
MWS- Muckle-Wells syndrome
NUV- Normocomplementemic urticarial vasculitis
RNP- Ribonucleoprotein
SLE- Systemic lupus erythematosus
SSA- Sjögren syndrome antigen A
UV- Urticarial vasculitis

diameter. No bruising is associated with these current urticarial plaques.

Biopsies were consistent with UV, showing superficial and deep perivascular and interstitial polymorphonuclear infiltrate with nuclear dust, leukocytoclasis, and red blood cell extravasation. Direct immunofluorescence studies of skin biopsy specimens showed IgM, IgA, and C3 involving the blood vessels; discontinuous weak IgM and IgA and C3 staining along the basement membrane zone was also noted.

A final diagnosis of SLE with hypocomplementemic UV (HUV) was made. The diagnosis of UV was based on the clinical manifestations of painful urticarial plaques lasting for more than 24 hours, occasionally associated with bruising by history and resolving with postinflammatory hyperpigmentation, the laboratory finding of hypocomplementemia, and the histology demonstrating changes of UV. The diagnosis of SLE was made based on the wide range of clinical and serological manifestations of alopecia, inflammatory polyarthritis, pleurisy, and strongly positive serologies including ANA, SSA, RNP, and anti-Smith antibody.

She was started on oral antihistamines (loratadine), oral prednisone 30 mg daily (weaning as tolerated to zero over months), and antimalarial medication hydroxychloroquine (because smoking can hasten the clearance of hydroxychloroquine from the system and reduce its efficacy, she was additionally advised to stop smoking). Nonsteroidal anti-inflammatory drugs in moderation were recommended. If refractory, methotrexate, mycophenolate mofetil, or azathioprine was recommended as consideration.

Urticarial vasculitis

General aspects

Introduction. UV is a diagnosis that requires clinicopathologic correlation. It is characterized in the skin by an inflammatory injury of dermal capillaries and postcapillary venules, with clinical signs varying from urticaria to signs of frank vasculitis. The diagnosis requires clinical manifestations of urticaria and the objective finding of vasculitis.

As with any vasculitis, many organs can be affected. Although clinical presentation generally involves skin, additional involvement of almost any other organ may be present, including musculoskeletal, pulmonary, renal, gastrointestinal (GI), and cardiac and ophthalmologic. The term "urticarial vasculitis" encompasses a wide spectrum of disease, varying from mild and limited disease to life-threatening organ involvement.

Precipitating factors may be similar to those associated with any vasculitis: infection, medication reactions, autoimmune reactions, and underlying malignancies are all possible underlying etiologies and should be sought. Frequently, the UV is idiopathic (of unknown cause).

The syndrome is thought to be driven by deposition of immune complexes in the skin predominantly, which activates the complement cascade, and therefore low complement levels are often noted. Low complement levels denote a more severe form of the disease; therefore, when UV is observed with hypocomplementemia, there is likely to be more organs involved.

Nosology/classification. Currently, the following classification of UV is generally accepted:

- normocomplementemic urticarial vasculitis (NUV),
- hypocomplementemic urticarial vasculitis (HUV),

and "urticarial vasculitis" is a term used for patients who have urticarial plaques and the skin pathology findings of leukocytoclastic vasculitis. UV generally can be divided into 2 groups according to complement levels, that is, NUV and HUV.[2]

The nomenclature and classification of HUV have been debated. HUV represents a continuum of the same disease, ranging from isolated urticarial lesions to a more systemic disease associating vasculitis. Although a specific syndrome called hypocomplementemic urticarial vasculitis syndrome (HUVS) has been described, it is not well delineated and is on the spectrum of HUV.[2]

A classification of UV is outlined in Table II. Table III presents a summary of identified etiologies,[3-8] Table IV summarizes systemic involvement,[9-13] Table V describes the suggested workup,[14] and Table VI provides an approach to management.[15]

Epidemiology. Although UV is rare, there are no epidemiologic studies that are population based describing the incidence and prevalence of this disorder. Most reports detail that women are more often affected (comprise 60% to 80% of reported patients). UV can occur at any age but is commonly reported in the fourth decade of life.

Etiologies and associated conditions. Like other forms of vasculitis, identified etiologies include medications, infections, autoimmune disease and malignancies, and other miscellaneous causes and often remain unidentified (idiopathic). Described etiologies are outlined in Table III.[3-8] Most instances of NUV are idiopathic.

Pathophysiology. It is thought that immune complexes (antigen antibody complexes secondary to antigens above) in the blood are deposited in vessel walls. These antigen antibody complexes activate the classic complement pathway such as C3A and C5A, leading to mast cell degranulation that leads to urticarial plaques, by increasing vessel permeability and chemotaxis of neutrophils. IL-1 is also thought to play a role.

Complement antibodies against their components cause conformational changes leading to pathological activation or inhibition of complement with organ damage and/or limited capacity of the immune system to clear immune complexes and apoptotic debris.[16]

TABLE I. Key differentiating features of classical urticaria, urticarial vasculitis, Schnitzler syndrome, cryopyrin associated periodic syndromes (CAPS), and familial cold autoinflammatory syndrome 2 (FCAS2)

	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 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, leukocytoclasis, 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, leukocytoclastic vasculitis in 25% of patients	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
FCAS2	Recurrent urticarial rash lasting 5 to 10 d. Triggered by exposure to cold	Fever, headache, arthralgia, sensorineural hearing loss	Increased inflammatory parameters during attacks	Not reported	Response to antihistamines and low-dose corticosteroids in some, rapid response to anti-IL-1 therapy

AA, Amyloid A.

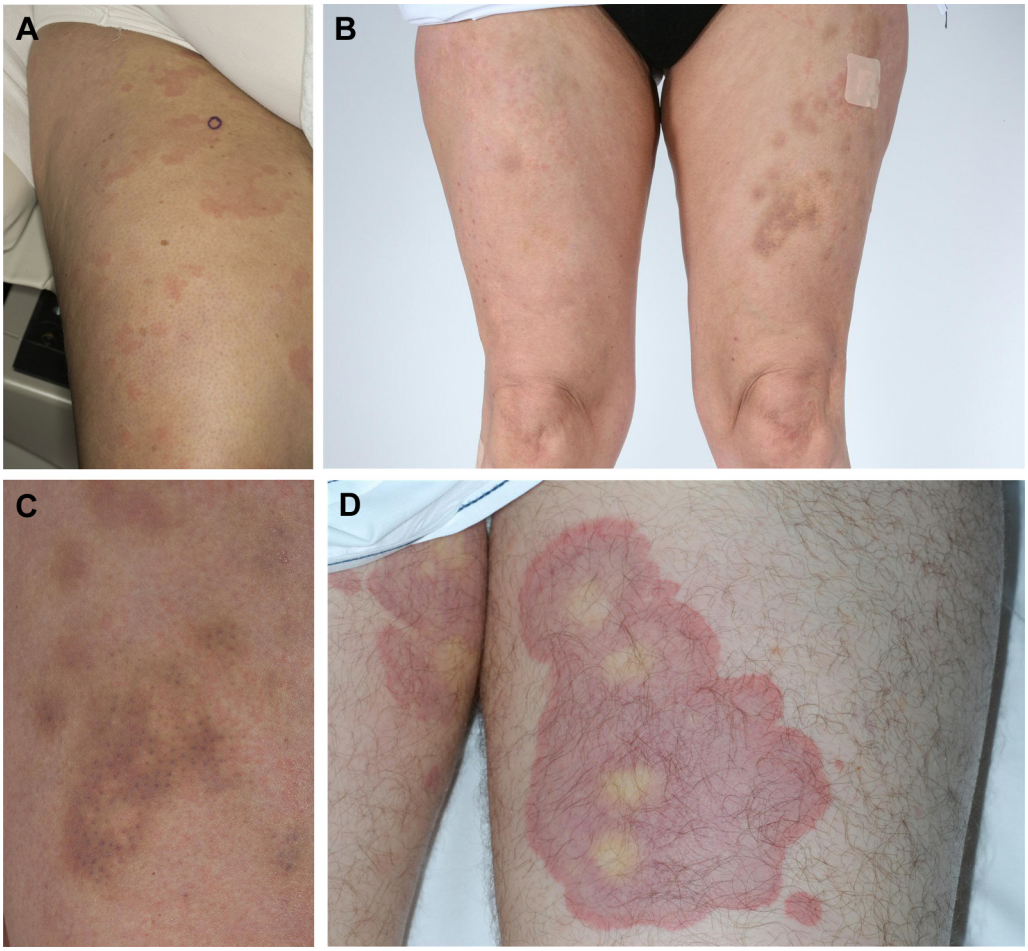

FIGURE 1. **A**, Urticarial plaques alone may be observed. **B** and **C**, Dusky pigmentation may be present after resolution of urticarial plaques. **D**, Clinical signs of urticarial vasculitis—purpuric patches at sites of urticarial vasculitis.

Patients with HUV typically presented with low C1q levels and normal C1 inhibitor levels, in association with anti-C1q antibodies in 55% of patients.[2]

Anti-C1q antibodies are not specific. They may be observed in patients with both primary and secondary vasculitis.[17]

Diagnosis

Clinical presentation. Generally, urticarial plaques persist for more than 24 hours, but they may resolve sooner than that in up to one-third of patients. They are often itchy (pruritic), but can also be painful (reported by up to one-third of patients) (Figure 1). Angioedema, purpura, and livedo reticularis have also been reported. In one series of 57 patients, angioedema was present in 51%, purpura in 35%, and livedo reticularis in 14%.

Histology/findings on biopsies. UV is defined by the pathologic finding of leukocytoclastic vasculitis as manifested by signs of vessel damage involving postcapillary venules: leukocytoclasis (fragmentation of leukocytes with nuclear debris), fibrinoid deposits (fibrin deposition in and around the vessels), perivascular infiltrates composed of neutrophils, extravasation of red blood cells, and injury and swelling of the endothelial cells. More severe findings, typically with a diffuse neutrophilic infiltrate in the dermis, are seen in patients with HUVS.

Direct immunofluorescence of skin biopsy specimens reveals immunoglobulin and complement deposition in or around blood vessels of the upper dermis and/or at the dermal-epidermal junction in 31 of 53 patients (58%).[2]

Systemic involvement. As mentioned above, systemic vasculitis associated with UV may occur in almost any organ. Table IV summarizes systemic involvement.[9-13]

Physical examination. Urticarial plaques, dusky pigmentation at the site of plaques, and frank signs of vasculitis/purpura may be observed (Figure 1).

Skin biopsy. It is recommended that a skin biopsy be obtained. Direct immunofluorescence should be performed. Generally, this is a 5-mm punch biopsy of an affected area. Alternatively, two 3-mm or 4-mm punch biopsies may be obtained.

Lab and radiologic studies. Suggested laboratory studies include complete blood count, blood biochemistries, serum creatinine, sedimentation rate, hepatitis studies, urinalysis, and complement studies (total complement, C3, C4), C1q levels and/or anti-C1q antibody assays. Additional studies may include

TABLE II. Classification of urticarial vasculitis

"Normocomplementemic urticarial vasculitis" is a term used for urticarial vasculitis in the presence of normal complement levels. Other organs are generally not involved
"Hypocomplementemic urticarial vasculitis" (also being called anti-C1q vasculitis in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides) is the term used to describe patients with urticarial vasculitis and hypocomplementemia; there is a spectrum of disease from the absence of systemic involvement to multisystem involvement

TABLE III. Urticarial vasculitis: identified etiologies

1. Medications: multiple medications have been described to be associated with urticarial vasculitis including over-the-counter diet pills, deferasirox,[3] etanercept[4]
2. Infections: multiple infections have been described to be associated, including infectious mononucleosis, Lyme disease, hepatitis B and C, Epstein-Barr virus,[5] meningococcal serogroup B vaccine,[6] and neurocysticercosis[7]
3. Autoimmune disease, including Sjögren syndrome and systemic lupus erythematosus: many patients with hypocomplementemic urticarial vasculitis fulfill criteria for systemic lupus erythematosus, and it can be difficult to distinguish the disorders. Features common to urticarial vasculitis include uveitis, angioedema, and chronic obstructive pulmonary disease that are less common in systemic lupus erythematosus
4. Malignancy: multiple malignancies, including lymphomas, myelomas, solid organ tumors, leukemias, myelodysplasias, and myeloproliferative diseases, have been associated with urticarial vasculitis, in addition to monoclonal gammopathies
5. Complement disorders: inherited complement deficiencies of C3 and C4 have been associated with the development of urticarial vasculitis
6. Immunologic-IgG4 disease[8]
7. Idiopathic

TABLE IV. Urticarial vasculitis: systemic involvement

1. Musculoskeletal: arthralgias and arthritis are commonly reported in up to 50% of patients. Jaccoud arthropathy is described in hypocomplementemic urticarial vasculitis, and is characterized by clinical arthritis to rheumatoid arthritis
2. Renal disease: patients are noted to have proteinuria and hematuria, which may be due to many forms of glomerulonephritis (eg, crescentic glomerulonephritis,[9] membranous glomerulonephritis,[10] membranoproliferative glomerulonephritis,[11] focal necrotizing vasculitis, tubulointerstitial nephritis)
3. Pulmonary involvement: involvement is thought to result from vasculitis involving lung tissue, leading to the release of neutrophil elastase and the development of emphysematous lung disease. Smoking accelerates this process. Patients may present with cough, shortness of breath, dyspnea, hemoptysis, chronic obstructive pulmonary disease, pleuritis, pleural effusion, and asthma as well as tracheal stenosis and adult respiratory distress syndrome[9]
4. COPD and asthma have been reported to occur in up to 20% of patients with hypocomplementemic urticarial vasculitis syndrome and 5% of patients with normocomplementemic urticarial vasculitis. In the series reported, pulmonary involvement is a leading cause of morbidity and mortality in urticarial vasculitis
5. GI symptoms are observed in up to one-third of patients. Abdominal pain, nausea, vomiting, and diarrhea are reported. Intestinal ischemia has been described[12]
6. Hepatomegaly and splenomegaly have been reported
7. Eye involvement: ophthalmologic involvement is seen in approximately 10% of patients with urticarial vasculitis and may include inflammation, conjunctivitis, episcleritis, and uveitis
8. Cardiovascular disease: pericarditis, pericardial effusion, cardiac tamponade, and valvular disease have been reported particularly in the setting of hypocomplementemic urticarial vasculitis syndrome. More rarely, Jaccoud arthropathy has been described
9. Neurologic: aseptic meningitis, pseudotumor cerebri, cranial nerve palsies, transverse myelitis, and peripheral neuropathy have been reported
10. Endocrine: autoimmune thyroid disease[13]

COPD, Chronic obstructive pulmonary disease; *GI*, gastrointestinal.

connective tissue cascade including ANAs, anti−double-stranded deoxyribonucleic acid, anti-Ro, anti-La, anti-Smith, and RNP antibodies, antineutrophil cytoplasmic antibody (ANCA), rheumatoid factor, immunofixation electrophoresis, cryoglobulins, and cryofibrinogens.[2]

Chest x-ray and pulmonary function studies are recommended. An age-appropriate screen for malignancy should be performed.

Screening for cardiac involvement using transthoracic echocardiography or cardiac magnetic resonance imaging may be considered in the appropriate clinical setting where cardiac involvement is suspected.[18]

Differential diagnosis. The differential diagnosis includes all differential diagnoses for urticarial eruptions and also for vasculitis.

In the differential diagnosis for urticarial eruptions, entities to be considered include particularly acute and chronic urticaria, acquired angioedema, erythema multiforme minor, neutrophilic dermatosis, AHA syndrome (arthritis, hives, and angioedema), and autoinflammatory disorders.[14]

Management. Treatment may be challenging. There are no guidelines for management. Randomized controlled trials have not been performed. In a report of a series of 57 patients, Jachiet et al[2] reported that hydroxychloroquine or colchicine seemed to be as effective as corticosteroids as first-line therapy. Antihistamines were consistently ineffective for treating skin and extracutaneous manifestations, despite increases in dosage or use of different antihistamines.[2] In patients with relapsing and/or refractory disease, rates of cutaneous and immunologic response to therapy seemed to be higher with conventional immunosuppressive agents, in particular, azathioprine, mycophenolate mofetil, or cyclophosphamide, whereas a rituximab-based regimen tended to have higher efficacy.[2] An approach to management is outlined in Table VI.[15]

Prognosis. Generally, if the cause can be removed, UV will resolve. The average duration of disease has been reported to be 3 to 4 years, although there are reports of UV persisting beyond 20 years.

NUV is associated with a good prognosis. Although published data are few, HUV seems to have a good prognosis.[2]

CASE 2: AUTOINFLAMMATORY DISEASE

Case report

A 48-year-old Belgian man was admitted to our outpatient clinic for further evaluation of a persistent urticarial rash, arthralgia and low-grade fever.

TABLE V. Suggested workup of a patient with urticarial vasculitis

History
• History of present illness: history of onset of the urticarial lesions, persistence for more than 24 h, residual purpura, and the presence of angioedema
• Past medical history: history of infections and malignancies
• Medications: medications started before the onset of disease are possible culprits
• Review of systems: may be helpful in establishing whether there is systemic involvement
• Physical examination: urticarial plaques may be noted with residual purpura[14]
• Photographs may be helpful if the lesions are not active at the time of physical examination

TABLE VI. Approach to management of urticarial vasculitis

1. Symptomatic management: antihistamines, nonsedating and sedating, may be used if urticaria is prominent. Frequently, this is not effective for urticarial vasculitis, however
2. Nonsteroidal anti-inflammatory drugs: this has been reported to be very helpful in patients with urticarial vasculitis. Naproxen, indomethacin, and ibuprofen may be used
3. In recalcitrant cases, consider dapsone, colchicine, and hydroxychloroquine
4. If the disease is recalcitrant to the above management, and/or there is more systemic involvement, consider systemic corticosteroids 0 to 1 mg/kg per day, and other immunosuppressive medications including methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine; more rarely used is cyclophosphamide. Recent reports of rituximab, anakinra, canakinumab, and omalizumab[15] may all be used

He suffered from an urticarial rash and arthralgia for 2 years; in the last 6 months, he also notes a low-grade fever up to 38.0°C. The urticarial rash involves the trunk and both upper and lower extremities. The rash was not painful but was accompanied by mild pruritus. There is a diurnal pattern with limited signs and symptoms in the morning, gradually increasing in the afternoon and a peak around 8:00 AM. There are periods of a few days that the rash is more intense, which is sometimes provoked by exposure to cold. His past medical history is uneventful except for an appendectomy at the age of 22. He has no history of allergy or asthma. The family history is negative for urticarial symptoms, autoimmune, and autoinflammatory diseases. Antihistamines were started shortly after first symptoms appeared but had no effect on the rash. Subsequently, the patient was treated—with methylprednisolone 16 mg QD. This was initially associated with improvement in his symptoms, but the effect subsided within 1 month. The corticosteroids were tapered without aggravating his symptoms. At presentation to our clinic, he did not use any medications except for an antihistamine. On physical examination, discrete urticarial plaques involving the thorax, axillae, and upper legs were noted.

His laboratory findings demonstrated an increased C-reactive protein (CRP) (67 mg/L), leukocytosis (14.1×10^9/L), and normal IgE 17 IU/mL (0-100 IU/mL). Liver and renal functions were in the normal range. Blood and urine cultures were negative. ANA, ANCA, rheumatoid factor, and cryoglobulin were also negative.

TABLE VII. Diagnostic criteria of CAPS

Obligatory criterion: elevated inflammatory markers during episodes (CRP/SAA)
At least 2 of 6 minor criteria:
• Urticaria-like rash
• Episodes are triggered by cold and/or stress
• Sensorineural hearing loss
• Arthritis and/or arthralgia and/or myalgia
• Chronic aseptic meningitis
• Typical bone lesions

Applying these criteria has a sensitivity of 81% and a specificity of 94%.
CAPS, Cryopyrin-associated periodic syndromes; *CRP*, C-reactive protein; *SAA*, serum amyloid A.
Adapted with permission from Kuemmerle-Deschner et al.[29]

Genetic testing showed no mutations in the coding regions of mevalonate kinase (MVK), TNF receptor superfamily member 1A (TNFRSF1A), and NACHT, LRR and PYD domains-containing protein 3 (NLRP3/NALP3), cold-induced autoinflammatory syndrome 1 (CIAS1) making the diagnoses of hyper-IgD syndrome, TNF receptor–associated periodic syndrome, and Muckle-Wells syndrome (MWS)/familial cold urticaria all unlikely.

Additional protein electrophoresis showed an IgM kappa paraprotein in the serum. Bone marrow biopsy showed a mild increase in plasma cells, which were positively stained immunohistochemically for IgM kappa. A diagnosis of Schnitzler syndrome was reached.

The patient started with IL-1 blocking drugs (anakinra, 100 mg sc QD), and within a day all of his symptoms disappeared. One week after the start of treatment his inflammatory parameters were normal. After 14 months of treatment he remains free of symptoms.

Autoinflammatory diseases associated with urticarial rash

Introduction. Schnitzler syndrome is a member of the expending family of the autoinflammatory syndromes. This is a group of rare disorders that are characterized by recurrent or persistent fever accompanied by an array of inflammatory symptoms. Although autoimmune diseases are caused by dysregulation of the acquired immune system, the autoinflammatory diseases result from inappropriate activation of the innate immunity, with the absence of significant levels of autoantibodies and autoreactive T cells.[19,20] Each of the autoinflammatory syndromes has its own typical inflammatory characteristics. For example, in familial Mediterranean fever, attacks of fever are accompanied by signs of serositis (peritonitis, pleuritis, and/or pericarditis).[21] Skin manifestations can be an important clinical clue for diagnosis,[22,23] and urticarial rash is a differentiating characteristic in 5 of the autoinflammatory syndromes: the 3 CAPS, Schnitzler syndrome, and FCAS2.

Cryopyrin-associated periodic syndromes. General aspects of CAPS were originally described as 3 separate clinical syndromes with distinct clinical features: FCAS, MWS, and neonatal onset multisystem inflammatory disease, which is also known as chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome. With the discovery of NLRP3 mutations in all 3 diseases, it has become clear that the clinical phenotype of

CAPS is a continuous spectrum of severity instead of 3 distinct diseases.[24] CAPS is an orphan disease, affecting an estimated 1 to 3 in a million children and adults worldwide; there is no sex or ethnic predilection.[25] CAPS often becomes clinically manifest directly after birth or in early childhood. It is characterized by episodes with urticaria-like rash, arthralgia, myalgia, headache, and fever. Ocular symptoms including conjunctivitis and uveitis are common.[26] Some patients develop sensorineural hearing loss during adolescence or adulthood. Duration of attacks is variable and ranges from hours to days.[24] At the severe end of the spectrum, patients have continuous inflammation.[27] Attacks may be triggered by exposure to cold, minor trauma, or emotional stress. At the severe end of the clinical spectrum central there is continuous inflammation accompanied by central nervous symptoms, including chronic aseptic meningitis, characterized by chronic headache, increased intracranial pressure, hydrocephalus, mental retardation, and seizures. Papilledema with optic nerve atrophy may lead to loss of vision.[28] In patients with CINCA, there is a severe arthropathy with premature patellar and epiphyseal long bone ossification, and osseous overgrowth develops in early childhood. When patients are not treated, the arthropathy leads to severe joint contractures and persisting disability.

Diagnosis. The diagnosis can be made by a set of clinical criteria (Table VII). The diagnosis of CAPS can be confirmed by the genetic analysis of the *NLRP3* gene. However, in approximately 40% of patients with a typical phenotype of a cryopyrinopathy, no known mutations are found.[29,30] In those with a positive genetic test, there is no genotype-phenotype association, suggesting a role for other yet undiscovered disease-modifying factors.

Management. The common feature of most autoinflammatory diseases is overproduction of the proinflammatory cytokine IL-1β.[31,32] This protein is produced as an inactive proform (pro-IL-1β) that has to be cleaved by the enzyme caspase-1 to be activated. Caspase-1 is transcripted as an inactive proform (procaspase-1), and has to be cleaved by a multiprotein complex called the inflammasome.[32,33] In CAPS, a gain of function mutation leads to an inappropriate activation of the NLRP3-inflammasome. On activation of the inflammasome, procaspase-1 is converted into mature caspase-1, which is able to cleave inactive pro-IL-1β to its active form.

The clinical manifestations are the result from the overproduction of IL-1β.[34] It is therefore not surprising that blocking IL-1 is very effective in treating CAPS. Currently, 3 anti-IL-1 drugs are available.[35] Anakinra is a recombinant homolog of the human IL-1 receptor that competitively inhibits binding of IL-1α and β to its receptor. It is administered as a daily subcutaneous injection. Canakinumab is a human IgG antibody directed against IL-1β. It is administered subcutaneously every 4 to 8 weeks. Rilonacept is a dimeric fusion protein consisting of the extracellular portions of the human IL-1 receptor and the Fc region of human IgG1 that binds and neutralizes IL-1. All 3 drugs have been shown efficacious in treating patients with CAPS.[36-38]

Prognosis. Before the introduction of anti-IL therapy, the prognosis of CAPS was strongly dependent on the severity of disease. Because of the chronic inflammation with continuous elevation of serum amyloid A (AA), up to a quarter of patients developed type AA amyloidosis.[21,39] Patients with CINCA phenotype also had a grave prognosis. However, the introduction of anti-IL-1 therapy has dramatically improved quality of life and life expectancy in CAPS.[40]

Schnitzler syndrome

General aspects. Schnitzler syndrome is a rare condition that usually arises in the fifth decade of life.[41] Patients often present with chronic recurrent and mostly nonpruritic discrete and confluent plaques, typically 0.5 to 3 cm diameter. The urticarial plaques may persist for up to 24 hours, and generally resolve without residual pigmentation. This can be accompanied by fever, arthralgia, or arthritis and bone pain, lymphadenopathy, hepatosplenomegaly, leukocytosis, and acute phase protein elevation. Symptoms progress over years.[42] Characteristic for Schnitzler syndrome is the presence of monoclonal paraproteinemia, typically IgM. The presence of monoclonal IgG is less common and is sometimes referred to as variant Schnitzler syndrome. Symptom severity is unrelated to the level and type of paraproteinemia. The frequency of exacerbations is variable, although symptoms are daily in most patients.[41] Typically, the urticarial rash does not respond to antihistamines, and corticosteroids are, at best, moderately effective in controlling symptoms.

Diagnosis. Physicians need to have a high sense of alertness to diagnose Schnitzler syndrome. In our experience, there is a delay in diagnosis of years in most patients. There is no definite genetic test for Schnitzler syndrome. A set of diagnostic criteria have been developed[42] and validated in real-life patients.[43] Most importantly, a protein electrophoresis should be performed in all patients with chronic urticarial rash and elevated inflammatory parameters.

Management. The pathophysiology of Schnitzler syndrome remains unclear, but mechanisms of autoinflammation seem to play an important role because IL-1 antagonists induce a swift and often complete clinical response in the patients.[44-48] This rapid clinical effect of anti-IL-1 therapy is restricted to autoinflammatory disease and can even be used as a diagnostic test, to differentiate from other causes of inflammation.[49] The notion that Schnitzler syndrome is truly an autoinflammatory disease is further supported by a recent report that found mutations in NLRP3. Using next-generation sequencing technologies, de Koning et al[50] found a mosaicism in the *NLRP3* gene in myeloid cell lines in 2 patients with Schnitzler syndrome. One mutation had been described in 2 patients with severe CAPS.[50]

Prognosis. An important long-term complication of Schnitzler syndrome is Waldenström macroglobulinemia, which in a single study had an incidence of 15% 10 years after diagnosis. Whether anti-IL-1 therapy can prevent the progression to Waldenström macroglobulinemia is unknown, but there seems to be an inhibitory effect on disease progression in smoldering myeloma.[34]

Familial cold autoinflammatory syndrome type 2 or NLRP12-associated hereditary periodic fever syndrome

In 2008, Jeru et al[51] reported 2 unrelated families from Guadeloupe with a periodic fever syndrome. Inheritance was autosomal dominant. Since then, several families have been described.[52] The first symptoms in affected patients appear in the

first days of life and consists of episodic fever, arthralgia, and myalgia. The majority of patients have an urticarial rash. Similar to CAPS, exposure to cold can exacerbate the rash. In affected individuals, mutation in NLRP12 has been identified. NLRP12 shares structural similarities with NLRP3, although the exact mechanism of inflammation in FCAS2 remains to be elucidated.[53] IL-1β plays a crucial role in inflammation and anakinra has been shown successful although resistance has been described.[54]

GENERAL CONCLUSIONS

A wide differential diagnosis may be entertained in a patient presenting with urticarial plaques.

In patients presenting with painful, persistent plaques that last more than 24 hours and resolve with bruising of the skin, consideration should be given to a diagnosis of UV. A biopsy should be obtained to ascertain this diagnosis.

In patients presenting with a persistent history of recurrent urticarial plaques associated with signs of systemic inflammation including fevers and elevated inflammatory markers (CRP/SSA, leukocytosis, and negative connective tissue serologies), consideration should be given to autoinflammatory disorders: the 3 CAPS, Schnitzler syndrome, and FCAS2. Serum protein electrophoresis should be checked to rule out an underlying monoclonal gammopathy.

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