

Urticarial vasculitis and associated disorders

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ARTICLE INFO

Article history:

Received for publication November 11, 2016.

Received in revised form January 15, 2017.

Accepted for publication January 18, 2017.

Patients often present to allergists with urticarial eruption symptoms. In many instances, these lesions represent chronic idiopathic or spontaneous urticaria.¹ Some of these patients may have a condition referred to as urticarial vasculitis (UV), including its variants normocomplementemic urticarial vasculitis (NUV), hypocomplementemic urticarial vasculitis (HUV), and hypocomplementemic urticarial vasculitis syndrome (HUVS) or Schnitzler syndrome.^{2,3} There are some features that set this condition apart, and in some instances, the disease may be severe enough to require systemic immunosuppressive therapies. UV, Schnitzler syndrome, and related disorders are discussed in this review.

Urticarial Vasculitis

UV is a form of cutaneous leukocytoclastic vasculitis that presents with urticarial eruption in combination with other clinical, histologic, and immunologic characteristics.^{2,4} The disease tends to occur in young to middle-aged women and can be a heterogeneous disorder, characterized by varying severity from mild lesions to severe disease with systemic, organ-specific manifestations.

Case Report

A 37-year-old white woman presented with recurrent episodes of fever and pruritic rash of 6 months' duration. The rash was in the form of urticarial plaques and papules that started from her torso then spread later to her extremities (Fig 1A). It was extremely pruritic and burning in nature. It usually lasted for 3 to 4 days before it completely resolved, leaving behind a dusky pigment on healing, then recurred again every 3 to 4 weeks. Palm involvement from the rash occasionally led to blistering (Fig 1D). Leukocytosis, elevated sedimentation rates, and very low C4 levels were observed. A skin biopsy of a lesion revealed superficial and deep

perivascular and interstitial polymorphonuclear infiltrate with leukocytoclasia, nuclear dust, and red blood cell extravasation (Fig 1B and C). She was diagnosed with HUVS, and immunosuppressive therapy was initiated with resolution of disease.

The most common clinical manifestation in UV is cutaneous (Fig 1).^{5,6} Patients with UV are more likely to describe urticarial lesions as burning or painful, although most will describe it as also pruritic.⁶ Lesions may last more than 24 hours, leaving bruising on the skin.⁶ In one series of 72 patients with UV, only 32% reported burning or painful sensation, and 35% had residual purpura or hyperpigmentation, and absence of these skin manifestations does not rule out UV.⁵ In the same group, angioedema is reported in approximately 42% of cases. Figure 1 shows the clinical and pathologic characteristics of UV, chronic urticaria, and angioedema complicating these disorders. More severe forms of UV include musculoskeletal, pulmonary, renal, and gastrointestinal complications. Musculoskeletal manifestations are among the most common (arthralgia) presentations with pulmonary involvement being the leading cause of morbidity and mortality in patients with UV.^{2,4,5,7} Less frequently ophthalmologic, cardiovascular, and neurologic symptoms may predominate. Some patients may present with erythema multiforme-like lesions. Other cutaneous presentations include bullae, livedoid changes, Raynaud phenomenon, and palpable purpura. The diagnostic criteria for HUVS are given in Table 1.

Three variants of UV may be seen clinically as mentioned earlier (Table 2): NUV, HUV, and HUVS.

NUV

Patients with NUV present with skin lesions consistent with UV and confirmed by biopsy.⁴ However, complement levels, including C1q and C4, are normal, and there is little extracutaneous disease. This disease could be managed with antihistamines, nonsteroidal anti-inflammatory drugs, colchicine, or a short pulse of systemic glucocorticoids. On occasion, patients may require simple reassurance, and no treatment may be necessary.^{2,4}

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<http://dx.doi.org/10.1016/j.anai.2017.01.017>

1081-1206/Published by Elsevier Inc on behalf of the American College of Allergy, Asthma & Immunology.

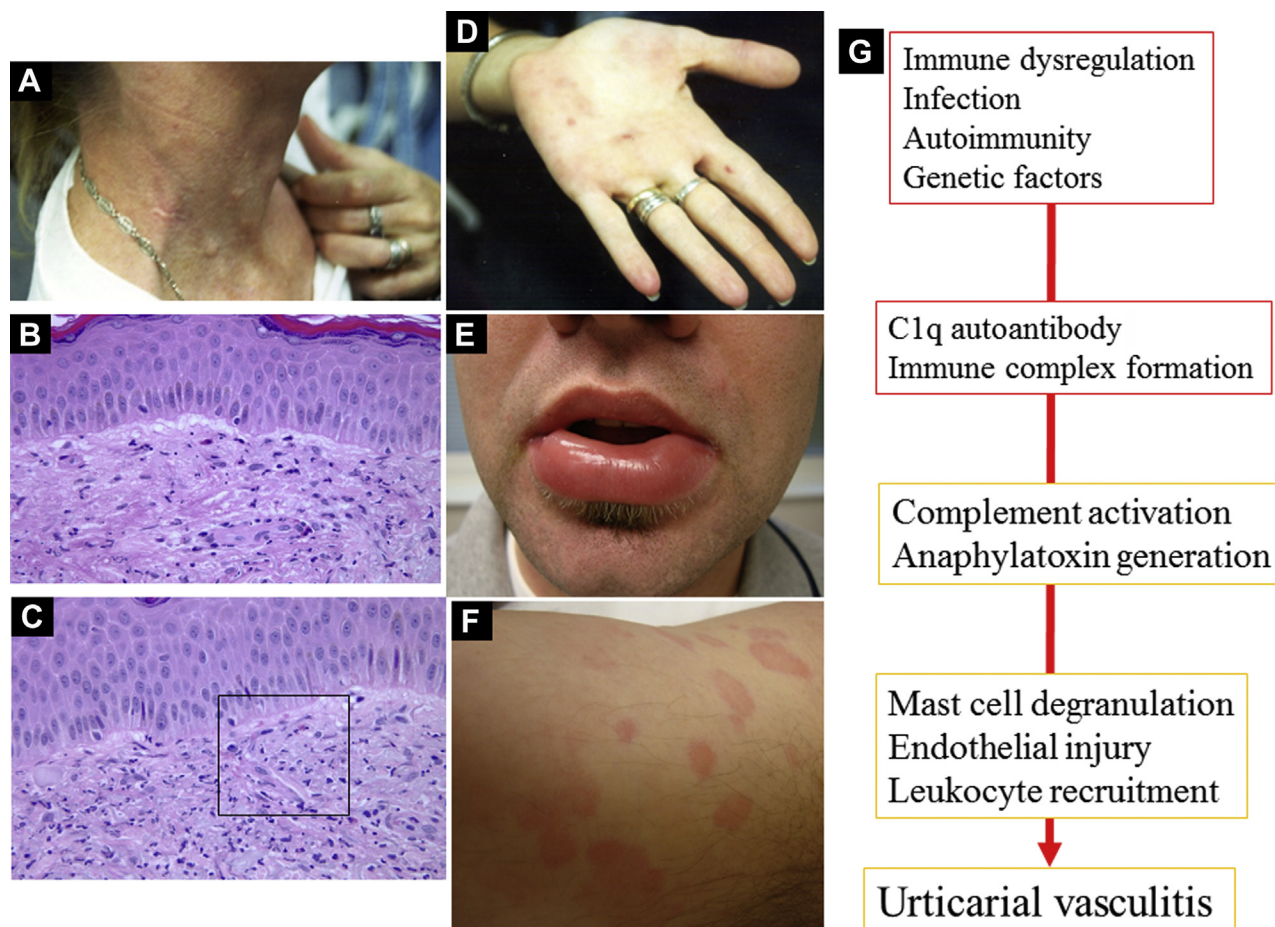


Figure 1. Clinical and pathologic manifestations of urticaria and urticarial vasculitis. A, Urticarial vasculitic lesions on the head and neck of a patient. The lesions were erythematous, were raised above the skin, and had a purplish discoloration. B, Microscopic examination (courtesy of George Youngberg, MD) reveals the presence of a moderate amount of perivascular and interstitial neutrophilic, eosinophilic inflammatory infiltrate, and leucocytoclasia. C, Red blood cell extravasation (box) is present in the upper dermis. Fibrinoid necrosis of the vessel walls is not clearly identified. D, Urticarial vasculitis involving the palms, with necrosis and ulceration. E, Angioedema as a manifestation of urticarial vasculitis and chronic urticaria. F, Chronic idiopathic urticaria with positive autoantibodies to FcεR1 and no evidence of vasculitis. G, Presumed mechanisms underlying hypocomplementemic urticarial vasculitis syndrome.

Hypocomplementemic UV

Patients with hypocomplementemic UV have a typical vasculitic eruption and low levels of complement components and elevated C1q autoantibodies. Arthritis or arthralgia, abdominal pain, and asthmatic symptoms may be extracutaneous manifestations. They can overlap with or be mistaken for systemic lupus erythematosus (SLE), but antinuclear antibodies are less likely to be detected. In a French study of 57 patients with HUV, angioedema (51%), purpura (35%), and livedo reticularis (14%) were seen. Musculoskeletal disease, ocular complications, and pulmonary, gastrointestinal, and renal disease were seen in 82%, 56%, 19%, 18%, and 14%, respectively.⁸ A total of 55% of patients had detectable C1q autoantibodies, and hydroxychloroquine or colchicine were effective as first-line therapies.⁸ In more severe or relapsing disease, a variety of options often used for systemic vasculitis or HUVS was effective, with a rituximab-based approach tending to be more effective.

HUVS

As indicated in Table 2, HUVS is a severe systemic form of UV. Serositis, renal disease, neurologic disease, and cardiopulmonary complications ensue. The disorder is more commonly seen in women.^{2,4}

The following disorders may sometimes complicate HUVS: arthritis, cardiopathy, and IgG4-related disease. Pericarditis,

tamponade, and valvular disease in association with Jaccoud arthropathy have been previously described. C1q and C1q autoantibodies may play pathologic roles.⁹ An association with tracheal

Table 1
Criteria for Diagnosis of Schnitzler Syndrome and Urticarial Vasculitis

Syndrome	Major criteria	Minor criteria
Schnitzler syndrome^{a,b}	Chronic urticarial eruption Monoclonal IgG or IgM	Recurrent fever Bone remodeling with or without bone pain Neutrophilic infiltrate on skin biopsy Acute-phase response
Hypocomplementemic urticarial vasculitis	Chronic urticarial eruption Hypocomplementemia	Leukocytoclastic vasculitis Arthralgia or frank arthritis Ocular disease (uveitis or episcleritis) Renal disease (glomerulonephritis) Abdominal pain Anti-C1q autoantibodies

^aStrasbourg criteria: acute-phase response (leukocytosis [$>10,000$ cells/mm³] or elevated C-reactive protein level [>30 mg/L]).

^bDefinitive diagnosis is the presence of 2 obligate or major criteria and at least 2 minor criteria if IgM or 3 minor criteria if IgG. Probable diagnosis is the presence of 2 obligate criteria and at least 1 minor criteria if IgM or 2 minor criteria if IgG. Chronic eruption indicates eruption lasting 6 months or longer.

Table 2
Clinicopathologic Variables Differentiating Urticaria and Urticarial Vasculitis Syndromes

Variable	Chronic urticaria	NUV	HUV	HUVS	Schnitzler syndrome
Urticarial lesions	Last few hours, pruritic	Last >24 hours, burning or pruritic, induration, pigmentation	Last >24 hours, burning or pruritic, induration, pigmentation	Last >24 hours, burning or pruritic, induration, pigmentation	Last >24 hours, burning or pruritic, induration, pigmentation
Fever and acute-phase response	No	No	Positive or negative	Positive or negative	Fever, CRP >30 mg/L, or WBC count >10,000/mm ³
Joint	None	None	Arthralgia or arthritis	Arthralgia or arthritis	Arthralgia or arthritis
Asthma or lung disease	None	None	Asthma-like disease	None	None
Bone pain or bone remodeling	Negative	Negative	Negative	Negative	Changes on MRI or bone scan
Lymphadenopathy	Negative	Negative	Nausea, vomiting, diarrhea, abdominal pain	Positive or negative	Yes
Gastrointestinal disease	Negative	Negative	Negative	Ischemic heart disease, serositis, tamponade, and valvular disease	Hepatosplenomegaly
Heart disease	Negative	Negative	Angioedema	Episcleritis	Negative
Ocular disease	Angioedema	Angioedema	Negative	Myopathy, seizures, transverse myelitis, mononeuritis, pseudotumor cerebri	Negative
Neurologic disease	Negative	Negative	Negative	Glomerulonephritis, hematuria, proteinuria	Negative
Renal disease	Negative	Negative	Low C1q, low C3/C4, anti-C1q antibody	Low C1q, low C3/C4/CH50, anti-C1q antibody	Negative
Complement abnormalities	Negative	Negative	Polyclonal	Polyclonal	IgG or IgM paraprotein
Serum protein electrophoresis	Normal	Normal	Pathologic findings include fibrinoid changes in blood vessel, eosinophilic infiltration, and dermal edema. Neutrophilic infiltrate typifies Schnitzler syndrome.	Polyclonal	IgG or IgM paraprotein
Skin biopsy	Typical urticaria changes	Vasculitis is seen: neutrophilic infiltration, and dermal edema.			

Abbreviations: CRP, C-reactive protein; HUV, hypocomplementemic urticarial vasculitis; HUVS, hypocomplementemic urticarial vasculitis syndrome; MRI, magnetic resonance imaging; NUV, normocomplementemic urticarial vasculitis; WBC, white blood cell.

stenosis and cardiopathy has been described in a patient monitored for 3 decades. Prednisone, azathioprine, and nonsteroidal drugs in various combinations have been used to treat this disease.

In addition, IgG4-related disease is a new and evolving multi-system disease associated with high IgG4 levels.^{10,11} A patient described in the literature had recurrent abdominal pain, purpuric urticarial lesions, hypocomplementemia, and leukocytoclastic vasculitis on skin biopsy.¹² She had an IgG4 level greater than 1,000 mg/dL and IgG4 deposits in skin biopsy. IgG4-positive cells were detected infiltrating her lymph nodes, suggesting an overlap between IgG4-related disease and HUVS. The extent and prevalence of this condition are unknown but have raised some interest in the association because rituximab is an effective treatment for both disorders.¹¹ This disorder is rare, and if suspected, the assistance of a physician skilled in management of this disease may need to be sought.

Mechanisms

In a genetically predisposed individual exposed to a certain environmental antigen or self-antigen, immune complex formation and deposition in vessel walls followed by activation of the complement system underline the pathophysiologic features of UV.^{2,4} C1q autoantibodies may be instrumental in immune complex formation (Fig 1G). Complement activation generates C3a and C5a, which activate mast cells degranulation, resulting in urticarial lesions seen in the skin. Therefore, UV is categorized as a type 3 hypersensitivity reaction. Why lesions are limited to skin in some patients or cause severe systemic disease in others is not entirely understood.¹³ DNAS1L3 mutations have been reported in one study of HUVS.¹⁴

Skin Biopsy

Skin biopsy is essential for diagnosis and may reveal various combinations of fibrinoid changes in blood vessel walls, eosinophil infiltration, leukocytoclastic vasculitis, erythrocyte extravasation, edema of the dermis, and neutrophil infiltration.^{2–4} Immunofluorescence studies are likely to find deposition of immunoglobulins or complement components (C1q, C3, or C4) and fibrinogen. Direct immunofluorescence may reveal perivascular and/or basement membrane zone deposits of immunoglobulins, complement, or fibrin. If the results do not show leukocytoclastic vasculitis but the clinical suspicion for HUVS is high, a subsequent biopsy of a new lesion is likely needed to establish the diagnosis.

Laboratory Testing

It is important to measure complement levels (C3, C4, or CH50) in this disease because this allows the clinician to categorize and prognosticate the illness, allowing changes in monitoring and management of this potentially serious disorder. Laboratory testing in patients suspected of having UV are not diagnostic and are performed usually to check for systemic disease. Such tests include a complete blood cell count with differential; renal function tests; liver enzyme tests; measurement of CH50, C3, C4, C1q, and anti-C1q antibody levels. Urinalysis needs to be evaluated for proteinuria, erythrocytes, or leukocytes indicating the presence of glomerulonephritis. Erythrocyte sedimentation rate is elevated in most patients with UV. Testing for hepatitis B surface antigen, hepatitis C, antinuclear antibody panel, double-stranded DNA, rheumatoid factor, and anti-cyclic citrullinated peptide needs to be considered to evaluate for secondary causes in selected patients.^{4,15}

Autoantibodies

Several autoantibodies may be detectable in patients with HUV or HUVS and include those directed against C1q, interleukin (IL) 1,

IgE, high-affinity IgE receptors, and thyroid microsomal antigens.^{2,4} The best characterized of these are the antibodies directed against C1q, which are commercially measurable in the United States. C1q is essential for the removal of apoptotic cells and cellular debris, and autoantibodies to C1q may be associated with other immune complex diseases, including proliferative lupus nephritis. These antibodies are highly associated with UV (100%) but may also be detectable in Felty syndrome, rheumatoid arthritis, Sjögren syndrome, IgA nephropathy, and membranoproliferative glomerulonephritis. As in the case of other autoantibodies, 5% of healthy individuals may express low titers of these antibodies. In a patient with UV, the discovery of C1q autoantibodies should strongly suggest the diagnosis of HUV or HUVS.

Differential Diagnosis

The differentiation of chronic urticaria from forms of UV and Schnitzler syndrome is indicated in Table 2. Many features of HUV overlap with SLE, and HUV can evolve into SLE. The findings of malar rash, photosensitivity, oral ulcers, and lung fibrosis suggest SLE, whereas symptoms of angioedema and asthma suggest HUV.⁴ The detection of antibodies to double-stranded DNA and leukopenia suggest SLE.⁴

Acquired angioedema attributable to autoantibody directed against C1 esterase inhibitor requires exclusion. In this condition, C3 levels are normal and C1 esterase inhibitors are very low, in association with very low or undetectable C1q component levels. Other disorders entering the differential diagnosis are discussed below.

Neutrophilic urticarial dermatosis

The group of disorders, referred to as neutrophilic urticarial dermatosis, need exclusion.^{16,17} These conditions are characterized by predominantly neutrophilic infiltration on biopsy and do not have typical vasculitis changes. Neutrophilic urticarial dermatosis is resistant to antihistaminic therapy, and severe cases with systemic inflammatory features have been found to respond, like Schnitzler syndrome, to anakinra, the IL-1 receptor antagonist.

Arthritis, hives, and angioedema syndrome

The arthritis, hives, and angioedema syndrome often complicates stress and excessive alcohol consumption and may be mistaken for HUV.

Muckle-Wells syndrome

Muckle-Wells syndrome is an autosomal dominant systemic inflammatory disorder associated with the development of UV, progressive sensorineural hearing loss, and a secondary amyloidosis with nephrotic syndrome.^{6,16} It is caused by mutations in a gene called *NLRP3*, which controls cryopyrin, a protein that regulates inflammation in the body, causing an overproduction of IL-1 β responsible for symptoms of inflammation. The disease often begins in infancy and hence can be readily differentiated from HUVS.

Cogan syndrome

Cogan syndrome is a rare inflammatory disorder that most commonly affects young adults. It is defined by nonsyphilitic interstitial keratitis and audiovestibular impairment and sometime associated with systemic vasculitis, UV, inflammatory bowel disease, and rheumatoid arthritis.^{18,19}

Treatment

In mild cases, observation or nonsteroidal agents and antihistamines may suffice. The medications used in the management of

Table 3
Treatment Guidelines for Urticarial Vasculitis

Disease severity	Treatment options	Suggested doses
Mild disease	Antihistamines	Cetirizine, 10 mg once or twice per day
	NSAIDs	Indomethacin, 25 mg once to thrice per day
Moderate disease	Prednisone	1 mg/kg body weight
	Colchicine	0.6 mg once or twice per day
	Dapsone	50–100 mg/d
	Hydroxychloroquine	200–400 mg/d
Severe disease	Mycophenolate mofetil	500–1,000 mg twice per day
	Methotrexate	15 mg weekly
	Azathioprine	1 mg/kg per day up to 2.5 mg/kg per day
	Cyclosporin A	2.5–5.0 mg/kg per day
Biological agents (experimental therapy for resistant disease or as adjunctive therapy)		
IgE pathway drug	Omalizumab	150–300 mg monthly subcutaneously
B-cell depletion	Rituximab	375 mg/m ² intravenously
IL-1 pathway drug	Anakinra	100 mg/d subcutaneously
	Canakinumab	150 mg every 8 weeks subcutaneously

Abbreviations: IL, interleukin; NSAIDs, nonsteroidal anti-inflammatory drugs.

UV, HUVS, and more severe forms of UV are listed in Table 3. The duration of therapy is based on response and likelihood of relapse.

Schnitzler Syndrome

Schnitzler syndrome was described more than 4 decades ago by Liliane Schnitzler, a French dermatologist. Subsequent descriptions of a case cluster and the creation of an interest group (Schnitzler Syndrome Study Group) led to advances in pathogenesis, diagnostic criteria, and classification of the disease (Table 1). The syndrome occurs in middle age and is characterized by fever associated with an urticarial eruption (present in 100%) that demonstrates neutrophils on biopsy. Pruritus is not universal and might be a symptom in less than 50% of patients.^{2,20} Associated symptoms of an acute or relapsing inflammatory illness are often present, which might include intermittent fever (93% of cases); myalgia, arthralgia, or frank arthritis (77%); bone pain (68%); and generalized lymphadenopathy (74%). Laboratory evaluation usually reveals an IgM or IgG paraprotein or elevated κ light chains (89%), a finding that sets this apart from the other urticarial syndromes, including autoimmune urticarial and UV. Leukocytosis (>70%) and elevated acute-phase response markers (such as C-reactive protein and erythrocyte sedimentation rate) are present, with the erythrocyte sedimentation rate often elevated (>95%).^{2,20,21} Enhanced production of IL-1 β and the enhanced secretion of this monokine from mononuclear cells in this disease have opened up several therapeutic possibilities.^{22,23} Increased long-term risks of lymphoproliferative diseases, nephropathy, and amyloidosis have been described.^{2,20,24,25}

Management

The adequate management of this inflammatory syndrome consisted of careful monitoring (of the inflammatory response and paraprotein levels, evaluating periodically for complications, including amyloidosis, nephropathy, and lymphoproliferative disorders) and intervention with biological agents that interrupt the IL-1 pathway.²⁰ The disorder is resistant to traditional therapies,

such as antihistamines and nonsteroidal anti-inflammatory agents. Hydroxychloroquine (400 mg/d) or colchicine (1–2 mg/d) may be effective in some patients. In others, anakinra (a recombinant form of the IL-1 receptor antagonist protein) or toziclumab (anti-IL-6 receptor) may be required, with the former having consistent and sometimes remarkable efficacy. Canakinumab (monoclonal antibody against IL-1 β), rituximab (monoclonal antagonist directed against the CD20 molecule on B lymphocytes), and rilonacept (a dimeric fusion protein that functions as a decoy IL-1 receptor binding up IL-1) have also been reported to be of benefit.

Conclusion

UV and Schnitzler syndrome are rare disorders that may be seen in the allergy practice. Insight into these disorders, the differential diagnosis, and skillful use of immunosuppressive therapies or cytokine antagonism may allow improved outcomes of these systemic inflammatory disorders.

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