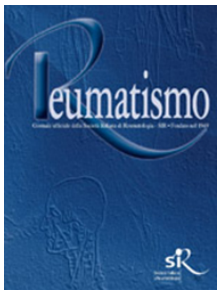

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Hypocomplementemic urticarial vasculitis: a rare presentation revealing systemic lupus erythematosus and Sjögren's disease

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Summary
Hypocomplementemic urticarial vasculitis (HUV) is a rare small-vessel vasculitis that may occur as a primary form or secondary to systemic disease. Its concurrent association with systemic lupus erythematosus (SLE) and Sjögren's disease (SD) remains exceptional. Diagnosis is particularly challenging due to overlapping clinical and immunological features among these entities. We report the case of a 46-year-old woman with no significant medical history, presenting with recurrent chronic urticaria resistant to antihistamines. Clinical, biological, and histological investigations led to the diagnosis of HUV associated with SLE and SD without severe organ involvement. Treatment with colchicine and hydroxychloroquine resulted in complete remission of symptoms. This case highlights the importance of considering HUV in any patient with chronic or refractory urticaria and of systematically screening for associated autoimmune diseases, particularly SLE and SD.

Introduction

Hypocomplementemic urticarial vasculitis (HUV) is a rare systemic small-vessel vasculitis with an incompletely understood pathophysiology (1). It is characterized by recurrent urticarial eruptions, marked hypocomplementemia, and systemic involvement primarily affecting joints and eyes, but it may also involve the gastrointestinal tract, lungs, or kidneys. A key distinguishing feature of the disease is the significant reduction in serum C1q levels, often associated with anti-C1q antibodies, found in about half of patients (2). HUV may occur as a primary (isolated) form in approximately 75% of cases or as secondary to an underlying autoimmune disease in about 25% (3).

Diagnostic criteria were established by Schwartz et al. in 1982 (4). Diagnosis relies on chronic urticaria lasting more than 6 months, hypocomplementemia, and at least two additional criteria among the following: arthralgia or arthritis, angioedema, glomerulonephritis, ocular inflammation, gastrointestinal involvement, leukocytoclastic vasculitis, or the presence of anti-C1q antibodies (4). The term “hypocomplementemic urticarial vasculitis” was confirmed in the revised 2012 Chapel Hill consensus conference classification (1), solidifying its nosological status among systemic vasculitides.

The coexistence of HUV with systemic lupus erythematosus (SLE) and Sjögren’s disease (SD) is exceptional and has been reported only in a few cases. This triple association poses a true diagnostic and therapeutic challenge due to clinical, immunological, and histopathological overlap. We report an illustrative case highlighting the importance of investigating autoimmune diseases in patients with HUV to ensure optimal management.

Case Report

A 46-year-old woman, with no notable medical history, was referred for investigation of chronic recurrent urticaria resistant to antihistamines. Symptoms began 1 year earlier with mildly pruritic urticarial lesions initially located on the palms, progressively spreading to the arms and legs (Figures 1 and 2). These lesions were associated with angioedema, particularly palpebral swelling, as well as fatigue and low-grade fever. For the past month, the patient had experienced inflammatory polyarthralgia affecting both small and large joints, myalgia, ocular pain with redness, and xerostomia without xerophthalmia. At admission, she was febrile (38.5°C), normotensive (blood pressure 100/70 mmHg), with a heart rate of 78 bpm, respiratory rate of 14 cycles/min, and body mass index of 25 kg/m². Clinical examination revealed a maculo-erythematous urticarial rash, mildly pruritic, located on the legs, thighs, and arms, persisting for more than 24 hours. No other cutaneous signs were noted. There was left eye redness and inflammatory arthralgia of elbows, wrists, knees, and ankles, without objective arthritis, and the patient reported xerostomia. Ophthalmologic examination revealed episcleritis and conjunctivitis of the left eye with a negative Schirmer test.

Biological tests revealed chronic inflammation, with an erythrocyte sedimentation rate of 100 mm/h and a protein C-reactive level of 12 mg/L, along with polyclonal hypergammaglobulinemia (24 g/L). The complete blood count showed microcytic hypochromic anemia due to iron deficiency: hemoglobin at 10 g/dL, mean corpuscular volume at 71 fl, and mean corpuscular hemoglobin concentration at 32 g/dL. The white blood cell count was 7600/mm³, and platelets were 207.000/mm³. The reticulocyte count was 60.300/mm³. Iron studies showed a ferritin level of 109 µg/L and serum iron of 17 µg/dL. The Coombs test was negative. Renal function was normal (urea = 0.17 g/L; creatinine = 7 mg/L; creatinine clearance = 103 mL/min). Two 24-hour proteinuria tests were negative (145 mg/24 h; 72 mg/24 h). Urine cytology showed 50 red blood cell/mm³ and one urinary cast; urine culture was sterile. Viral serologies for hepatitis B virus, hepatitis C virus, HIV, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19 were all negative.

Immunology testing revealed positive antinuclear antibodies (ANA) at 1:1000 with a speckled pattern (*via* HEp-2-IF), anti-Sjögren's syndrome-related antigen A (SSA)/Ro60 positive, and anti-double-stranded deoxyribonucleic acid (dsDNA) positive (244 IU/L; normal <40). Complement testing revealed low C3 (0.66 g/L; N=0.9-1.8), low C4 (0.03 g/L; N=0.1-0.4), and decreased C1q (<51 mg/L;

N=190-344) with strongly positive anti-C1q antibodies (>100 U/mL; N<10). C1 esterase inhibitor levels and activity were normal.
Skin biopsy showed leukocytoclastic vasculitis with granular deposits of C1q (+), immunoglobulin G (+), immunoglobulin M (+), and immunoglobulin A (+) along the dermo-epidermal junction and around small vessels. Neck ultrasound revealed heterogeneous parotid glands with bilateral inflammatory lymphadenopathy, confirmed by cytology. Abdominal ultrasound was normal. Echocardiography showed a moderate pericardial effusion. Chest X-ray and pulmonary function tests were normal.
Given xerostomia, a labial salivary gland biopsy was performed, showing focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm² (Chisholm and Mason classification).
The diagnosis of HUV was established based on chronic urticaria, hypocomplementemia, inflammatory arthralgia, ocular involvement, presence of anti-C1q antibodies, and leukocytoclastic vasculitis with C1q deposits.
The patient also met the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for SLE (fever, inflammatory arthralgia, high ANA titer, positive anti-dsDNA, and hypocomplementemia).
The diagnosis of associated SD was based on xerostomia, positive anti-SSA/Ro60 antibodies, focal sialadenitis (focus score ≥ 1/4 mm²), and ultrasound evidence of heterogeneous parotid glands with inflammatory lymphadenopathy.
The patient was treated with hydroxychloroquine (400 mg/day) and colchicine (1 mg/day). Clinical improvement was observed within days, with resolution of skin lesions, systemic symptoms, arthralgia, and ocular signs. Ophthalmologic follow-up was normal. After one year of follow-up, no relapse or new organ involvement was noted.

Discussion

HUV is an uncommon clinicopathological entity characterized by a type III hypersensitivity reaction with immune complex deposition in small vessels (1). It can be primary, known as HUV syndrome or McDuffie syndrome (first described by McDuffie in 1973), or secondary when associated with other disorders (5).
These include autoimmune diseases (SLE, SD, rheumatoid arthritis), viral infections (hepatitis B, mononucleosis), or drug exposure (cimetidine, diltiazem, potassium iodide, fluoxetine, nonsteroidal anti-inflammatory drugs, methotrexate, telmisartan, enalapril, levetiracetam) (6). HUV predominantly affects women. Its diagnosis is based on Schwartz's criteria (4). Systemic involvement is more frequent in HUV than in normocomplementemic urticarial vasculitis (7), with its prevalence varying across studies (8).
The association of HUV with SLE and SD is rare but likely non-random. Our patient had osteoarticular and ocular involvement (episcleritis), angioedema, low C1q level, and anti-C1q antibodies, but no renal involvement. Angioedema occurs in approximately half of all patients with HUV (8), although fatal forms are rare (9).
Anti-C1q antibodies are strongly associated with HUV, but they are not specific to this condition; for example, they are found in approximately 35% of patients with SLE (9). Some authors suggest that HUV and SLE represent a continuum of the same disease rather than distinct entities.
The patient fulfilled the diagnostic criteria for HUV, presenting with chronic urticarial lesions persisting more than 24 hours and hypocomplementemia (two major criteria), and arthralgia, episcleritis, anti-C1q antibodies, and leukocytoclastic vasculitis on histology with granular deposits on immunofluorescence (four minor criteria). However, such deposits are also seen in lupus and Sjögren's (7).
The combination of fever, arthralgia, hypocomplementemia, high anti-dsDNA, and ANA titers supported the diagnosis of SLE (ACR/EULAR 2019). In Davis *et al.*'s cohort of 24 hypocomplementemic patients (19 with leukocytoclastic vasculitis), SLE association or progression occurred in 54% (10).

HUV and SLE share many clinical and biological features, but at differing frequencies (Table 1). The presence of angioedema, episcleritis, and anti-C1q antibodies (found in 90-100% of HUV *vs.* 35% of SLE) supports an overlap between the two diseases (11). Unlike our case, SLE usually develops after HUV onset, suggesting a progressive immunological continuum (12, 13).
The presence of xerostomia, focal lymphocytic sialadenitis (focus score ≥1/4 mm^2), and anti-SSA/Ro60 positivity met the 2016 ACR/EULAR SD criteria.
The prognosis of HUV mainly depends on the occurrence of pulmonary or renal involvement (8); their absence in our patient may be due to early diagnosis and management.
Treatment combining colchicine (1 mg per day) and hydroxychloroquine (400 mg per day) achieved excellent disease control, with sustained remission after 12 months.
Recently, an "Urticarial Vasculitis Activity Score assessed over 7 days (UVAS7)" was proposed to guide treatment (14). However, no standardized therapeutic consensus exists. Management should be multidisciplinary, considering associated autoimmune diseases (8).
First-line options for cutaneous symptoms include dapsone, colchicine, hydroxychloroquine, or omalizumab following the failure of second-generation antihistamines. In refractory or systemic cases, corticosteroids and immunosuppressants such as azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, rituximab, or anti-IL1 agents are recommended (8, 14). This case illustrates the diagnostic and pathophysiological complexity of HUV when associated with SLE and SS, emphasizing the need for comprehensive immunologic assessment and early targeted management to prevent severe organ damage.

Conclusions

The coexistence of HUV, SLE, and SD represents a rare but genuine clinical entity, likely reflecting an immunopathological continuum between these disorders. The overlap of their cutaneous, articular, and immunological features makes diagnosis particularly challenging.
From a pathophysiological perspective, anti-C1q antibodies and complement consumption suggest persistent activation of the classical complement pathway—a mechanism common to both SLE and HUV, supporting the concept of immunologic interconnection rather than distinct diseases.
Therapeutic management should be individualized, guided by systemic activity and organ involvement. Synthetic antimalarials (hydroxychloroquine) and colchicine are effective for mild cutaneous and articular forms, whereas severe disease may require corticosteroids with immunosuppressants or targeted biologic agents. Finally, this observation underscores the importance of systematic screening for autoimmune diseases in any case of persistent or recurrent HUV to enable early management and prevent systemic complications.

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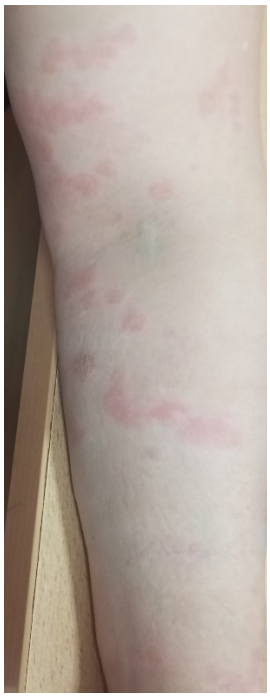

Figure 1. Urticarial lesions on the upper limb.

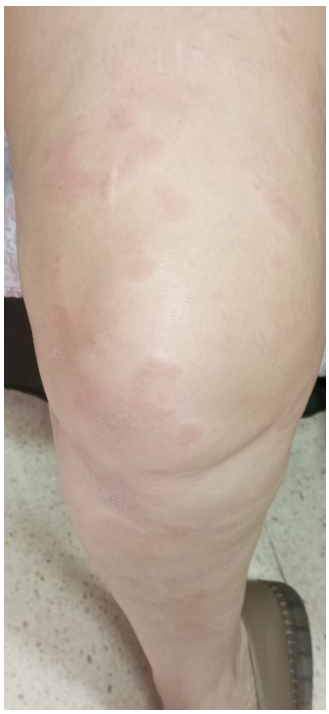

Figure 2. Urticarial lesions on the lower limb.

Table 1. Symptoms of hypocomplementemic urticarial vasculitis syndrome compared with systemic lupus erythematosus. Modified from: Buck *et al.* (2012) (15).

	HUV syndrome		SLE	
Clinical	Symptoms	Frequency (%)	Symptoms	Frequency (%)
	Urticarial-like skin lesion with biopsy consistent with LCV	100	Cutaneous symptoms (malar rash, oral ulcer photosensitivity *etc*.	80 (Urticaria<10%)
	Angioedema	72	Angioedema	<5
	Arthralgia and/or arthritis	100	Arthralgia and/or arthritis	95
	Chronic obstructive pulmonary disease	65	Restrictive pulmonary disease	30
	Eye involvement	61	Eye involvement	15
	Renal involvement	50	Renal involvement	50
	Pericardial effusion	17	Pericarditis	30
Laboratory	Investigation	Frequency (%)	Investigation	Frequency (%)
	Hematologic abnormalities	11	Hematologic abnormalities	85
	ANA	61	ANA	95
	dsDNA Ab (transient)	17	dsDNA Ab (transient)	≥70
	SSA-A/Ro Ab	17	SSA-A/Ro Ab	30
	Anti C1q autoAb	100	Anti C1q autoAb	35
	Low C1q	100	Hypocomplementemia	45

HUV, hypocomplementemic urticarial vasculitis; SLE, systemic lupus erymatosus; LCV, leukocytoclastic vasculitis; Anti C1q auto AB, autoantibodies C1q; ANA, antinuclear antibodies; dsDNA Ab, antibodies to native DNA; SSA-A/Ro Ab, antibodies to SSA/Ro.