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# Urticaria and Episcleritis in a Woman With Chronic Cough

Christina Dai, BA; David Weinstein, MD

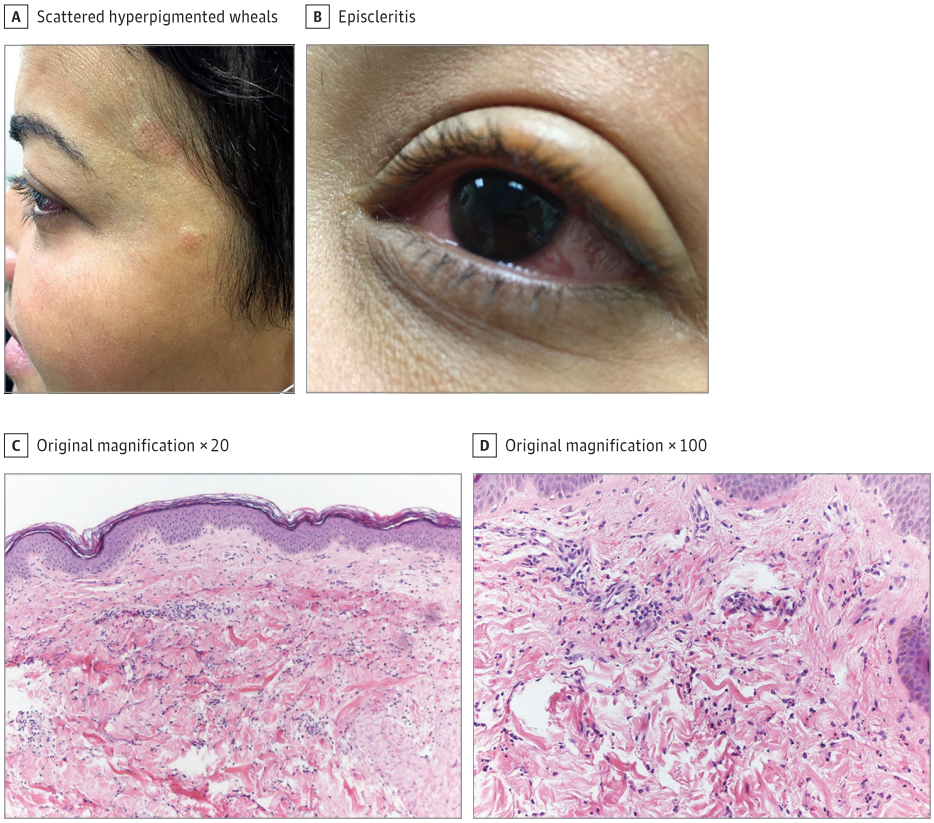


**Figure.** A, Physical examination revealed multiple scattered wheals distributed over head, trunks, and extremities. B, Scleral injection of the left eye suggesting episcleritis. C and D, Hematoxylin-eosin.

**A woman in her 30s** presented with a 10-month history of painful pruritic eruption and painful red eyes. The eruption was exacerbated by stress but unrelated to time of day, ambient temperature, or sunlight exposure. Additionally, she reported edema of the dorsal hands and proximal fingers lasting approximately 8 hours during flares without any joint swelling. She also reported recent worsening of a chronic cough. She had an otherwise negative review of systems including denial of any other type of eruption, oral or nasal ulcers, seizures, chest pain, or arthritis. She had no notable medical or family history.

A physical examination revealed scattered wheals distributed on her head, trunk, and extremities (**Figure**, A), with hyperpigmentation and petechiae. Eye examination revealed mild episcerlitis (Figure, B). A punch biopsy was performed (Figure, C and D). Blood work revealed negative results for her antinuclear antibodies (ANA) panel and low levels of C1q, C2, and C3 complement. She also had an elevated C-reactive protein and elevated levels of anti-C1q antibodies (38; normal, <20). Results of urinalysis, complete blood count, and comprehensive metabolic panel were unremarkable; C1-inhibitor levels, anti–double-stranded DNA, hepatitis B virus surface antigen, cryoglobulins, anti–neutrophil cytoplasmic antibodies, and serum protein electrophoresis were within normal limits.

**WHAT IS YOUR DIAGNOSIS?**

- **A.** Systemic lupus erythematosus
- **B.** Hypocomplementemic urticarial vasculitis syndrome
- **C.** Neutrophilic urticaria
- **D.** Familial cold autoinflammatory syndrome

## Diagnosis

**B.** Hypocomplementemic urticarial vasculitis syndrome

## Microscopic Findings and Clinical Course

Biopsy revealed fibrin and neutrophils within blood vessel walls surrounded by leukocytoclastic debris, extravasated erythrocytes, and a mixed cellular infiltrate consistent with leukocytoclastic vasculitis (LCV).

Owing to the duration of urticaria for over 6 months, hypocomplementemia, episcleritis, LCV on biopsy, and anti-C1q antibodies in the absence of positive exclusion criteria, a diagnosis of hypocomplementemic urticarial vasculitis syndrome (HUVS) was established.

The patient began treatment with dapsone, indomethacin, desonide cream, and diclofenac eye solution and responded rapidly. Owing to her chronic cough and smoking history, she was referred to a pulmonologist for evaluation of pulmonary involvement of HUVS.

## Discussion

First described in 1973 by McDuffie et al,[1] HUVS is an uncommon autoimmune disorder that disproportionally affects women in their 40s. The diagnostic criteria for HUVS requires the presence of 2 major criteria—a chronic urticarial exanthema and hypocomplementemia—and at least 2 minor criteria—LCV, arthralgias or arthritis, ocular inflammation, glomerulonephritis, abdominal pain, or anti-C1q antibody positivity.[2] Exclusion criteria include symptoms and markers of cryoglobulinemia, high titers of double-stranded DNA antibody, hepatitis B virus antigenemia, decreased C1 esterase inhibitor levels, and congenital complement defects.[3,4] A positive diagnosis can be established solely by clinical presentation and laboratory tests, but a biopsy showing the presence of LCV should be pursued to assist with diagnosis.[4] However, it is important to note that these histological features can be subtle and often require repeat biopsies.

The urticaria are characteristically painful, pruritic, violaceous, and resolve with residual hyperpigmentation.[5] Common signs of systemic involvement are angioedema, ocular inflammation, glomerulonephritis, and obstructive pulmonary disease.[6] Cigarette smoking is a strong risk factor for developing chronic obstructive pulmonary disease, the major cause of mortality in the HUVS population.[7]

Similar to an immune complex disease, the pathophysiology behind HUVS is thought to involve circulating C1q–anti-C1q immune complexes. The associated chronic obstructive pulmonary disease–like changes are due to cross-reactions between C1q antibodies with a C1q collagen-like binding region on pulmonary surfactant.[2]

Autoimmune diseases such as systemic lupus erythematous (SLE) or systemic sclerosis are associated with a quarter of HUVS cases.[8] Owing to similar clinical and laboratory features such as hypocomplementemia and systemic organ involvement, the relationship between HUV and SLE has been debated. Half of patients with HUVS present with a positive ANA panel and fulfill the classification criteria for SLE set forth by the American College of Rheumatology.[3] Conversely, some patients with SLE have anti-C1q and can present with urticarial vasculitis. These overlaps have prompted a discussion over whether HUVS should be classified as a subset of SLE or considered an independent immunological entity because it can occur without positive ANA test results.[4,7,9] Further research is required to better understand the relationship between these diseases.

There remains no definitive guideline to manage HUVS. Some patients have responded to low-dose corticosteroids, hydroxychloroquine, or dapsone while others required stronger immunosuppressive treatments.[10] Patients often require initial glucocorticoid therapy with an aim to taper the medication. A recent retrospective study[8] found hydroxychloroquine and colchicine to be effective as first line therapies and antihistamines to be ineffective.[10] One case report[10] found omalizumab to be ineffective in treating the urticarial component of HUVS. Treatments with corticosteroids plus a conventional immunosuppressive agent such as azathioprine, mycophenolate mofetil, or cyclophosphamide have resulted in an overall positive cutaneous and immunological response while rituximab-based regimens seemed to provide higher response rates and were associated with increased time to treatment failure compared with corticosteroids and conventional immunosuppressive agents.[10]


### ARTICLE INFORMATION

**Author Affiliations:** University of Central Florida College of Medicine, Orlando (Dai); Department of Internal Medicine, University of Central Florida College of Medicine, Orlando (Weinstein).

**Corresponding Author:** Christina Dai, BA, University of Central Florida College of Medicine, PO Box 160116, Orlando, FL 32816 (cd1246@knights.ucf.edu).

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### REFERENCES

1. McDuffie FC, Sams WM Jr, Maldonado JE, Andreini PH, Conn DL, Samayoa EA. Hypocomplementemia with cutaneous vasculitis and arthritis: possible immune complex syndrome. *Mayo Clin Proc*. 1973;48(5):340-348.

2. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. *Immunol Allergy Clin North Am*. 2004;24(2):183-213, vi. vi.

3. Grotz W, Baba HA, Becker JU, Baumgärtel MW. Hypocomplementemic urticarial vasculitis syndrome: an interdisciplinary challenge. *Dtsch Arztebl Int*. 2009;106(46):756-763.

4. Buck A, Christensen J, McCarty M. Hypocomplementemic urticarial vasculitis syndrome: a case report and literature review. *J Clin Aesthet Dermatol*. 2012;5(1):36-46.

5. Khasnis A, Langford CA. Update on vasculitis. *J Allergy Clin Immunol*. 2009;123(6):1226-1236.

6. Wisnieski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serologic findings in 18 patients. *Medicine (Baltimore)*. 1995;74(1):24-41.

7. Davis MD, Daoud MS, Kirby B, Gibson LE, Rogers RS III. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. *J Am Acad Dermatol*. 1998;38(6 Pt 1):899-905.

8. Jachiet M, Flageul B, Deroux A, et al; French Vasculitis Study Group. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. *Arthritis Rheumatol*. 2015;67(2):527-534.

9. Aydogan K, Karadogan SK, Adim SB, Tunali S. Hypocomplementemic urticarial vasculitis: a rare presentation of systemic lupus erythematosus. *Int J Dermatol*. 2006;45(9):1057-1061.

10. Aurich S, Simon JC, Treudler R. Omalizumab does not improve skin lesions in a patient with hypocomplementemic urticarial vasculitis syndrome. *J Eur Acad Dermatol Venereol*. 2017;31(9):e395-e397.