

Urticarial vasculitis

Suyoung Chang, M.D., and Warner Carr, M.D.

ABSTRACT

A case of urticarial vasculitis (UV) is presented. The pathogenesis, clinical characteristics, diagnosis, and management of this disease are reviewed, followed by clinical pearls and pitfalls for the practicing allergist (Venzor J, et al., *Urticarial vasculitis, Clin Rev Allergy Immunol* 23:201–216, 2002). The lesions in UV typically lasts >24 hours in a fixed location, resolves with residual hyperpigmentation, and may or may not be pruritic. In contrast, standard urticaria lesions persist <24 hours, leave no trace, and is always pruritic (Black AK, *Urticarial vasculitis, Clin Dermatol* 17:565–569, 1999). Since urticarial vasculitis is characterized by a variety of cutaneous, systemic, and serological features, different names of this disorder exist in the literature (Wisniewski JJ, *Urticarial vasculitis, Curr Opin Rheumatol* 12:24–31, 2000). A biopsy of an active lesion remains the gold standard for the diagnosis of urticarial vasculitis.

(Allergy Asthma Proc 28:97–100, 2007; doi: 10.2500/aap.2007.28.2972)

Key words: Cutaneous, hypocomplementemic, leukocytoclastic, urticaria, vasculitis

Question:

A 50-year-old woman presented to the clinic for evaluation of her rash. She described a diffuse eruption of erythematous raised lesions, which started 10 months ago. A given lesion would last 24–48 hours and had left residual pigmentation on occasion. The lesions were pruritic and painful only on her upper extremities. She denied any other systemic symptoms. On examination, she had a urticarial-like eruption, distributed around her face, neck, axillae, abdomen, arms, and lower legs. Laboratory investigation revealed an erythrocyte sedimentation rate of 39 mm/hour; complement component C3, 74.9 mg/dL (normal range, 90–180 mg/dL); and C4, 8.9 mg/dL (normal range, 10–40 mg/dL). Screening for rheumatoid factor and autoantibody to C1q was negative. Skin biopsy of her left upper arm showed a superficial perivascular and interstitial neutrophilic infiltrate with leukocytoclasia consistent with urticarial vasculitis. Which of the following statements are correct?

- A. This patient has C1 esterase deficiency associated angioedema.
- B. These symptoms are most likely caused by an immediate IgE hypersensitivity reaction.

- C. In this disease, prednisone is the treatment of choice.
- D. This patient most likely has urticarial vasculitis.
- E. Antihistamines are not used regularly to treat this disease.

INTRODUCTION

Urticarial vasculitis (UV) is a clinicopathological entity. It manifests itself as an eruption of erythematous wheals that clinically resemble urticaria, but the lesions of UV last longer, may leave residual hyperpigmentation, and may or may not be pruritic (Figs. 1 and 2). UV can be the presenting manifestation of a systemic disease or a local process unassociated with an underlying disease. Because UV is characterized by a variety of cutaneous, systemic, and serological features, different names of this disorder exist in the literature. Based on complement levels and presence of systemic findings, some of the terms that appear in the literature include hypocomplementemic urticarial vasculitis syndrome (HUVS), hypocomplementemic urticarial vasculitis (HUV), and normocomplementemic urticarial vasculitis (NUV).

PATHOPHYSIOLOGY AND CLINICAL CHARACTERISTICS

UV is believed to result from the formation of immune complexes that deposit in blood vessel walls. Immune complexes have been found in the circulation of 30–75% of patients with UV.¹ The antigens eliciting the formation of antibodies are not known. In some patients with UV, a collagen-like region on C1q has

From the Walter Reed Army Medical Center, Washington, D.C.
Address correspondence and reprint requests to Suyoung T. Chang, M.D., Walter Reed Army Medical Center, 6900 Georgia Avenue, Washington, D.C. 20307
E-mail-address: stinachang@verizon.net
Copyright © 2007, OceanSide Publications, Inc., U.S.A.



Figure 1. Right forearm.



Figure 2. Left forearm.

been implicated as the antigenic target, and the auto-antibody is referred to as C1q precipitin.^{2,3} The histology of urticaria is edema of the collagen bundles in the upper dermis, with no cellular infiltrate or a minimal diffuse infiltrate of lymphocytes and eosinophils.³ The histology of UV lesions include most of the features of leukocytoclastic vasculitis and include the following: injury and swelling of endothelial cells, extravasation of red blood cells, fragmentation of leukocytes with nuclear debris, fibrin deposition in and around vessels, and perivascular infiltrate composed mostly of neutrophils. Immunofluorescence reveals deposits of immunoglobulins, complement, or fibrin around blood vessels in most patients with UV.^{2,4} Active urticarial lesions stain positive for immunoglobulin and complement deposits ~80% of the time.⁵ These findings are not specific to UV and are frequently seen in patients with systemic lupus erythematosus.⁶

Classically, an individual UV lesion typically persists for 24 hours and often resolves with faint residual

hyperpigmentation.³ These lesions can be pruritic but are more commonly asymptomatic or painful, accompanied by a stinging or burning sensation. In contrast, true urticaria persists for 2–8 hours and leaves no trace, and the sensory hallmark of true urticaria is pruritus.³ Patients with UV may or may not have systemic findings and complement levels can be low or normal. Several groups of investigators have indicated that patients with UV and complement activation are much more likely to have systemic disease than are UV patients with normal serum complement levels.^{4,7–9} Based on complement levels and the presence of specific systemic findings, different terms have been used in the literature to describe UV. HUVS is the term used to describe patients with hypocomplementemia, UV, and various systemic findings. HUV is the term used to describe patients with hypocomplementemia, UV, and few or no systemic manifestations. NUV is the term used to describe patients that are more likely to have mild disease, normal complement levels, and UV. It has been proposed that UV likely presents a continuum of disease progressing from NUV through HUV to HUVS. In contrast, Wisnieski's retrospective and prospective observations in >50 idiopathic NUV, HUV, and HUVS patient for >20 years support the hypothesis that there is no transition among these UV subtypes.³

Systemic manifestations may include constitutional symptoms (fever, malaise, and fatigue); arthralgia, arthritis, and, very rarely, Jaccoud's arthropathy; angioedema and dermal ulceration; iritis, uveitis, and episcleritis; pericarditis and cardiac valve disease; pseudotumor cerebri and peripheral neuropathy; pleuritis and obstructive lung disease; glomerulonephritis and interstitial nephritis; and digital infarction and Raynaud's phenomenon.³ Arthralgia and arthritis are the most commonly encountered systemic symptoms, with roughly 50% of patients reporting arthralgias.^{4,5} Renal involvement has been found to occur in 20–30% of patients with hypocomplementemia.^{4,10} COPD and asthma can be present in ~17–20%^{5,11} of hypocomplementemic patients and 5% of normocomplementemic patients.¹¹ Gastrointestinal symptoms include substernal and abdominal pain, nausea, vomiting, diarrhea, or a general feeling of gastrointestinal distress and are noted between 17 and 30% of the time.⁴ Ophthalmologic complications, including episcleritis, uveitis, or conjunctivitis, may occur in up to 10% of patients with UV.¹ UV is more common among women and adults. The average age at presentation has been found to be 48 years.⁵ However, a few pediatric cases have been reported.^{12,13} The duration of UV tends to be limited. However, the maximum reported duration is 23 years.^{14,15}

Although most cases of UV are idiopathic, there are a variety of conditions associated with UV such as

infections, hematologic diseases, connective tissue diseases, immune complex diseases, and malignancy. Connective tissue diseases are the most commonly associated conditions, particularly systemic lupus erythematosus and Sjogrens syndrome.^{16,17} The causal role of these conditions still has not been well established.

DIAGNOSIS

To confirm the diagnose of UV, the first step is to obtain a biopsy specimen of the lesion for histological examination. Early lesions are preferred and multiple biopsies are needed to accurately make the diagnosis. There should be evidence of leukocytoclasia and vessel wall destruction, which may be accompanied by fibrinoid deposits. After establishing the diagnosis, the physician must be aware of systemic disease as a complication. A careful history and physical exam will aid in identifying any clues of systemic disease. Chest radiographs and pulmonary function tests are appropriate when respiratory symptoms are present.

The most common findings when testing for UV is an increased erythrocyte sedimentation rate, hypocomplementemia (usually C3 and C4), circulating immune complexes, and a positive ANA.^{11,18} The level of the erythrocyte sedimentation rate is not related to the severity of UV or to the presence of systemic involvement.

MANAGEMENT

If an underlying disease is identified, it should be the focus of initial treatment. In general, the more severe the systemic involvement is in patients with HUVS, the more challenging it is to treat the disease. Antihistamines may be started to help improve cutaneous disease and for symptomatic relief of itching. Additional therapies such as indomethacin, colchicine, dapsone, and hydroxychloroquine are most commonly used to help clear the skin lesions and minimize the use of corticosteroids and their associated side effects. Indomethacin has been reported to have good results in up to 50% of patients.^{5,14} The most common reason for discontinued use is upset stomach and gastrointestinal toxicity. Colchicine has been deemed effective in previous reports but has been shown to be ineffective in some patients. Colchicine is a teratogenic drug and must be used with caution. Side effects include gastrointestinal toxicity and cytopenias. Dapsone is a sulfone drug that has been associated with sustained remissions in patients with HUV. It has been viewed as the drug of choice for HUV because of its high therapeutic index, ease of administration, low cost, and persistent beneficial effects. Patients who have glucose-6-phosphate deficiency experience severe hemolysis when

treated with dapsone, and this serum enzyme level should be checked before initiating treatment.

Answer: D

Pearls

- When obtaining a history, key questions to ask are the time of onset of the lesions, duration of the lesions, whether the lesions are painful or burning, and if there is any hyperpigmentation on resolution of an individual lesion.
- UV lesions last >24 hours in a fixed location, often are painful or burning, and leave residual hyperpigmentation in contrast to urticaria, which resolves in minutes to hours, migrates continually, is mainly pruritic, and leaves no residual pigmentation.
- A biopsy specimen of an active lesion remains the gold standard for diagnosing UV.

Pitfalls

- Before starting dapsone for treatment of UV, patients should be screened for glucose-6-phosphate deficiency.
- UV is divided into hypocomplementemia and normocomplementemic categories and patients with hypocomplementemia are more likely to complain of systemic symptoms such as fever, arthralgia, abdominal pain, and angioedema.
- If the patient's complement levels are abnormal, patients should be followed for systemic complications related to the cause of their hypocomplementemia

REFERENCES

1. Venzor J, Lee WL, and Huston DP. Urticarial vasculitis. *Clin Rev Allergy Immunol* 23:201-216, 2002.
2. Black AK. Urticarial vasculitis. *Clin Dermatol* 17:565-569, 1999.
3. Wisniewski JJ. Urticarial vasculitis. *Curr Opin Rheumatol* 12:24-31, 2000.
4. Sanchez NP, Winkelmann RK, Schroeter AL, and Dicken CH. The clinical and histopathologic spectrums of urticarial vasculitis: study of forty cases. *J Am Acad Dermatol* 7:599-605, 1982.
5. Mehregan DR, Hall MJ, and Gibson LE. Urticarial vasculitis: A histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 26:441-448, 1992.
6. Monroe EW. Urticarial vasculitis: An updated review. *J Am Acad Dermatol* 5:88, 1981.
7. Wisniewski JJ, Baer AN, Chritensen J, et al. Hypocomplementemic urticarial vasculitis syndrome: Clinical and serologic findings in 18 patients. *Medicine* 74:24-41, 1995.
8. Beltrani VS. Urticaria and angioedema. *Dermatol Clin* 14:171-198, 1996.
9. Davis MD, Daoud MS, Kirby B, et al. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. *J Am Acad Dermatol* 38:899-905, 1998.
10. Callen JP, and Kalbfleisch S. Urticarial vasculitis: A report of nine cases and review of the literature. *Br J Dermatol* 107:87-94, 1982.

11. Davis MDP, Daoud MS, Kirby B, et al. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. [J Am Acad Dermatol 38:899–905, 1998.](#)
12. Soylyu A, Kavukcu S, Uzuner N, et al. Systemic lupus erythematosus presenting with normocomplementemic urticarial vasculitis in a 4-year-old girl. [Pediatr Int 43:420, 2001.](#)
13. Martini A, Ravelli A, Albani S, et al. Hypocomplementemic urticarial vasculitis syndrome with severe systemic manifestations. [J Pediatr 124:742–744, 1994.](#)
14. Aboobaker J, and Greaves MW. Urticarial vasculitis. [Clin Exp Dermatol 11:436–444, 1986.](#)
15. Asherson RA, D'Cruz D, Stephens CJ, et al. Urticarial vasculitis in a connective tissue disease clinic: Patterns, presentations, and treatment. [Semin Arthritis Rheum 20:285–296, 1991.](#)
16. Van der Horst JC, and Bronsveld W. Urticarial vasculitis in a patient with systemic lupus erythematosus: A case report. [Clin Exp Dermatol 6:489, 1981.](#)
17. O'Loughlin S, Schroeter AL, and Jordon RE. Chronic urticaria-like lesions in systemic lupus erythematosus. A review of 12 cases. [Arch Dermatol 114:879, 1978.](#)
18. Berg RE, Kantor GR, and Bergfeld WF. Urticarial vasculitis. [Int J Dermatol 27:468–472, 1988.](#) □

Property of



OceanSide Publications

IP: 84.220.139.234