Normocomplementemic Urticarial Vasculitis: An Unusual Presentation

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Abstract
Urticarial vasculitis (UV) is a form of cutaneous vasculitis which lasts for >24 h. Clinically, the patients present with erythema and wheals. The level of complement decides the type of UV. This is a case of a middle-aged lady, who developed vesiculobullous lesion over her leg after trekking. She was diagnosed to have normocomplementemic UV. Bullous presentation of UV is a rare scenario.

Key Words: Complement, cutaneous vasculitis, leukocytoclastic vasculitis, urticaria

Introduction
Urticarial vasculitis (UV) is a form of cutaneous vasculitis, characterized by inflammation of the small blood vessels. The condition is more common among women, and about 50% of the cases have an idiopathic etiology. Others may be triggered by or associated with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, hepatitis, cancers, hyperthyroidism or drugs, such as ACE inhibitors, penicillin, and nonsteroidal anti-inflammatory drugs (NSAIDs). It may also be precipitated by anxiety, emotional stress, exercise, and excessive alcohol consumption.[1-4]

Case Report
A 48-year-old female school teacher presented with complaints of blackish skin lesions over her right leg and multiple reddish spots over her body. She had gone for trekking in the morning at a rubber plantation 4 days ago. The same night she noticed grayish-black bullous lesions over her right leg with mild burning sensation. Over the next 2 days, she noticed multiple reddish spots over her body, mainly over limbs. She also had arthralgia and mild swelling of the fingers. On day 4, one of the bullous lesions over her leg had disappeared, leaving behind a hyperpigmented patch. She did not have fever and denied history of any unknown bite. She did not have any comorbidity and was not on any regular medications.

On examination, her vitals and systemic examinations were normal. She had a 12 cm × 6 cm vesiculobullous lesion over the lower part of her right leg along with an eschar [Figure 1], petechiae lesions over her legs and feet [Figure 2], and multiple erythematous and purpuric lesions over her body, mainly over the arms and legs [Figure 3].

Her complete hemogram, peripheral smear, renal and liver functions, electrolytes, calcium, uric acid, TSH, and HbA1c were normal. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 45 mm/h and 76 mg/dL, respectively. Urine routine was normal, with no hematuria or proteinuria. Rheumatoid factor, anticyclic citrullinated peptide, antinuclear antibodies profile, and antineutrophil cytoplasmic antibodies were negative. Blood and wound swab cultures were sterile. Weil–Felix, Scrub IgM, and viral markers (HIV, HBsAg, and anti-HCV) were negative. Chest X-ray, ultrasound abdomen, ECG, and echocardiography were normal. Skin biopsy was suggestive of leukocytoclastic vasculitis [Figure 4], with immunofluorescence being negative for anti-C1q, C3, IgG, IgM, and IgA. During her hospital stay, she had episodes of central chest pain and abdominal pain, angioedema, and left eye episcleritis. Serum complement...
levels of C1q, C3, C4, and C1q esterase inhibitor were normal.

On the basis of her history, clinical course, and investigational findings, a diagnosis of normocomplementemic UV (NUV) was made. She was initially started on oral cetirizine (10 mg twice daily), but there was no improvement. Later, pulse doses of intravenous methylprednisolone (500 mg once daily) were given for 3 days, followed by oral prednisone (1 mg/kg/day) along with oral hydroxychloroquine (200 mg once daily), to which she responded. Wound debridement was done for the vesiculobullous lesion over the right leg, along with regular dressing.

The patient was reviewed on weekly basis. By the beginning of 2nd week, her purpuric lesions started disappearing. Regular dressings were continued along with topical mupirocin, and the wound showed good healing. Prednisolone was tapered and stopped over 3 weeks. By the end of the month, her lesions showed complete resolution. On review after 1 month, she did not have any episode of UV.

**Discussion**

As mentioned earlier, UV is a form of cutaneous vasculitis. In contrast to common urticaria, the lesions last for >24 h. They may be in the form of erythema or wheals, and sometimes accompanied by erythema multiforme, purpura, or bullous lesions; leaving behind residual hyperpigmentation on resolution. Patients may also experience burning sensation over the lesions. The noncutaneous manifestations include the following: angioedema, arthralgia/arthritis, chest or abdominal pain, fever, pulmonary or renal disease, uveitis, episcleritis, and Raynaud phenomenon. The pathogenesis is believed to be a Type III hypersensitivity reaction with antigen-antibody complexes being deposited in the vascular lumen. The complement is activated by the classical pathway, and these anaphylatoxins stimulate the release of mast cells, which in turn promote neutrophil chemotaxis and increase vascular permeability. The neutrophils take up a phagocytic role on arrival at the inflammatory site, and thereby aggravate tissue destruction and edema. Skin and renal biopsies show...
leukocytoclastic vasculitis. Blood investigations show elevated ESR and CRP levels. There are variants of UV based on complement levels. NUV is the less severe and self-limiting form with normal complement levels. Hypocomplementemic UV (HUV) is more severe with low C1q complements and elevated anti-C1q antibodies. It may be associated with systemic inflammatory disease. When HUV is associated with multiorgan involvement, it is called HUV syndrome (HUVS). Complement levels for C1q, C3 and C4, and anti-C1q antibodies are tested to determine the type of UV. Histologically, nuclear debris or fibrin deposits, with or without extravasated red blood cells are seen. Dermal eosinophils are more common in NUV, while diffuse neutrophilic infiltrates are frequently found in HUV. Treatment is with antihistamines and steroids, and in more severe cases immunosuppression with azathioprine, cyclophosphamide or mycophenolate mofetil may be required.\[6-9\]

Hydroxychloroquine, dapsone, colchicine, and NSAIDs such as naproxen or indomethacin may also be effective.\[6-9\] In unresponsive cases, intravenous immunoglobulin, anti-cytokine monoclonal antibodies, rituximab, and plasmapheresis may have a role.\[10,11\]

The diagnosis of HUVS requires the presence of two major criteria: chronic urticarial exanthema and hypocomplementemia with at least two minor criteria: leukocytoclastic vasculitis, arthralgia and arthritis, uveitis or episcleritis (or conjunctivitis), glomerulonephritis, abdominal pain, and positive C1q antibody. Angioedema, obstructive lung disease, and neurological findings such as peripheral neuropathy may also be present. The differential diagnosis for UV includes common urticaria, systemic lupus erythematosus, and mixed cryoglobulinemia. The special forms of UV include the following: AHA syndrome (arthritis, hives, and angioedema), Schnitzler syndrome (hyperostosis, lymphadenopathy, intermittent fever, and monoclonal IgM gammopathy), Cogan syndrome (interstitial keratitis and hypacusis), and Muckle–Wells syndrome (deafness and renal amyloidosis).\[3\]

Our patient developed bullous lesion with burning sensation over her lower limb with multiple erythematous and purpuric lesions over her body, following trekking (stress). The bullous lesion had a residual hyperpigmentation. The lesions lasted for >24 h. She also had symptoms of arthralgia, chest pain and abdominal pain, angioedema, and episcleritis. Her blood investigations showed normal complement levels with other autoimmune workup being negative. Skin biopsy had features of leukocytoclastic vasculitis. The diagnosis of NUV was made on the basis of diagnostic criteria of HUVS, with complement levels being normal and no systemic involvement.

**Conclusion**

UV rarely presents as bullous lesions, apart from the typical erythematous and wheal-like lesions. The lesions last for >24 h, thereby distinguishing it from common urticaria. These patients can have noncutaneous manifestations such as angioedema, arthralgia, and eye lesions. Histological examination of skin biopsy shows leukocytoclastic vasculitis. The measurement of complement levels will aid in determining the type of UV. The diagnosis is made on the basis of clinical, laboratory, and histological examinations.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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