Hypocomplementemic urticarial vasculitis: a rare presentation of systemic lupus erythematosus

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Abstract

Background Urticarial vasculitis is a small-vessel vasculitis, presenting clinically as persistent urticarial skin lesions and microscopically as leucocytoclastic vasculitis. Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a distinct type of urticarial vasculitis with multiorgan involvement, whose etiology and link with other diseases are still unknown. Some authors have suggested that HUVS can be accompanied by systemic lupus erythematosus (SLE), and others believe that it is a rare subtype of SLE. Urticarial vasculitis is seen in 7–8% of SLE, while 50% of HUVS patients are diagnosed with SLE.

Observations and results We report a case of HUVS associated with SLE with fatal outcome unresponsive to the combination of systemic corticosteroids and azathioprine.

Conclusions SLE and HUVS share both clinical and laboratory features and are probably not separate entities. It is mostly likely that HUVS and SLE fall into the same spectrum of autoimmune diseases. HUVS is probably a subset of SLE. As both diseases can fatally, it should be kept in mind that the overlap of SLE and HUVS may exhibit a relatively rapid progression and poor prognosis.

Introduction

Urticarial vasculitis is one of the small-vessel vasculitides, characterized clinically by urticarial skin lesions and microscopically by leukocytoclastic vasculitis (LCV). It is classified as an immune complex-mediated or type III hypersensitivity reaction. Urticarial papules and plaques of greater than 24–48 h duration and causing pain and/or burning are most commonly localized on the lower extremities with a tendency to heal with pigmentation or purpura. Urticarial vasculitis has been associated with connective tissue diseases, such as systemic lupus erythematosus (SLE) and Sjögren’s syndrome, immunoglobulin M (IgM) paraproteinemia (Schnitzler’s syndrome), serum sickness, infections (hepatitis B, infectious mononucleosis), and drug sensitivity. Patients with urticarial vasculitis can be subgrouped as those with normal complement levels and those with depressed complement: hypocomplementemic urticarial vasculitis syndrome (HUVS). Normocomplementemic urticarial vasculitis has a milder course than HUVS. HUVS is a rare form of urticarial vasculitis with organ involvement. HUVS resembles SLE both clinically and immunologically, and is also accepted as a SLE-associated syndrome.

We report a case of HUVS associated with SLE with fatal outcome that was unresponsive to the combination of systemic corticosteroids and azathioprine.

Case Report

A 55-year-old woman was seen at our clinic for pruritic wheals of 4 months’ duration that initially emerged on the face and trunk and disseminated to the upper and lower extremities within a few weeks. The pruritic wheals lasted for 48 h and healed with pigmentation. Physical examination was normal except for symmetric arthralgia, fever, and episcleritis. There was no family history of connective tissue disease. Central malar eruption and angiedema were present on the face (Fig. 1a). The dermatologic examination revealed multiple, annular, edematous, and pruritic, violet-colored plaques (Fig. 2a). Palmar, periungual erythema and Raynaud’s phenomenon were also observed. Punch biopsy of a facial lesion was compatible with lupus erythematosus (LE) (Fig. 1b). Punch biopsies of lesions from the leg and arm were compatible with LCV (Fig. 2b). Biochemical analysis of the serum and urine were within normal limits. Persistent anemia and leukopenia were detected. The erythrocyte sedimentation rate was 52 mm/h and the C-reactive protein was positive. Antinuclear antibody (ANA), and anti-RNP, anti-Sm, anti-SS-A(Ro), and anti-SS-B(La) antibodies were all positive; LE cell, lupus band test, antibodies for perinuclear- and cytoplasmic-antineutrophil cytoplasmic antibody (p-ANCA and c-ANCA), antithyroglobulin, anticardiolipin antibody, cryoglobulin, and Venereal Disease
Research Laboratory (VDRL) test were negative. Serum immunoglobulins were within normal limits. The levels of complement C3c (45 mg/dL; normal, 90–180 mg/dL) and C4 (4.2 mg/dL; normal, 10–40 mg/dL) were low. Viral serologic
investigations [hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), rubella, cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes virus, and human parvovirus B19] were negative. Direct immunofluorescence study of a lesional skin biopsy was negative.

The case fulfilled the American Rheumatism Association (ARA) criteria for SLE with malar eruption, photosensitivity, ANA and anti-Sm antibody positivity, hematologic features of persistent anemia, and leukopenia. In addition, hypocomplementemia, positivity of anti-SS-A and anti-SS-B antibodies, and ocular inflammation supported the diagnosis. The case also fulfilled the two major (urticarial vasculitic skin lesions, low complement level) and three minor (dermal venulitis, episcleritis, arthralgia) criteria of McDuffie et al. (Table 1) as HUVS. Therefore, the complete picture was that of HUVS associated with SLE.

Prednisolone therapy (50 mg/day) was started but, as a result of the rapid progression of the disease and the recurrence of lesions, the dose was increased to 80 mg/day and azathioprine (100 mg/day) was added. Fever, dyspnea, and chest pain developed on the 10th day of therapy. On physical examination, cough, sputum, shortness of breath, rales, and rhonchi were absent. The chest X-ray revealed interstitial pulmonary edema and pulmonary function tests showed moderate restrictive impairment. Despite therapy, the consolidations in the lung progressed rapidly and the patient died of acute respiratory distress.

**Discussion**

Urticarial vasculitis is a form of leukocytoclastic vasculitis involving the postcapillary venules; urticarial vasculitis is classified as a type III hypersensitivity reaction and has been associated with connective tissue disease. It usually affects young women and the diagnosis is confirmed by histologic examination. Histopathologic examination of the persistent urticarial lesions shows a predominantly polymorphonuclear cell infiltrate with fibrinoid necrosis, leukocytoclasia, and perivascular hemorrhage. Direct immunofluorescence study of HUVS lesions shows immunoglobulin and complement deposition in a granular pattern in and around blood vessels of the upper dermis and at the basement membrane zone. In patients with urticarial vasculitis, the associations and outcome of the disorder are related to the complement levels. Familial partial deficiency of complement without true SLE has also been described in patients with HUVS.

HUVS was first defined by McDuffie et al. in 1973 and various features were stated as major and minor criteria for diagnosis. The course of HUVS tends to be more severe than that of the normocomplementemic form. Angiokeratoma is common and sometimes laryngeal edema may be observed. The respiratory, gastrointestinal, renal, and central nervous systems may be involved, as well as ocular (conjunctivitis, uveitis, episcleritis) and arthritic signs or symptoms. Restrictive-type pulmonary disease occurs in as many as 25–30% of SLE patients. Chronic obstructive pulmonary disease (COPD), which is a common manifestation of HUVS, is no different from that in the normal population in SLE patients. COPD is progressive in HUVS and is the major reason for death. Patients with HUVS are predisposed to pyogenic infections, including pneumonia. The lung disease is progressive, and the clinical course is markedly accelerated by cigarette smoking. As many as 30% of patients have ocular inflammation, particularly of the uveal tract, but also conjunctivitis and episcleritis (as in our case).

The identity of HUVS as a collagen tissue disease, such as SLE, is still debatable. The clinicopathologic features of the disease are similar to those of SLE. Indeed, HUVS is present in 7–8% of SLE patients and 54% of HUVS patients are diagnosed with SLE in the follow-up period. The normocomplementemic form of urticarial vasculitis is not strongly associated with SLE (2%). Some authors emphasize the possible progression from HUVS to SLE, whereas others state that HUVS is the precursor lesion of SLE. Davis et al. defined HUVS as a subtype of SLE. There are rare case reports of the coexistence of HUVS and SLE in the literature which underlies the difficulties of treatment in these cases. Many common clinical, laboratory, and immunologic features of SLE and HUVS are summarized in Tables 2 and 3. By definition, serum complement levels in HUVS are decreased. Another consistent laboratory abnormality in HUVS is the elevated erythrocyte sedimentation rate. The serum ANA is positive in 50–60% of patients, although anti-double-stranded DNA is rarely detected. Although the serologic results at admission were negative, our patient had a history of positive ANA and anti-double-stranded DNA previously. Clinically and serologically, our patient had most of the characteristics of HUVS; the exception was the restrictive pulmonary component.
There is no specific treatment for HUVS. Multiple therapies have been attempted with no consensus on an effective therapeutic regimen. Skin lesions rarely respond to antihistaminic therapy. Nonsteroidal anti-inflammatory agents for symptomatic relief of joint pain may be helpful. Moderate to high doses of oral steroids have been demonstrated as being the most effective treatment. Cytotoxic agents, including azathioprine, methotrexate, and cyclophosphamide, alone or in combination with prednisolone, control the disease if used long term. Other treatment options, including antimalarial agents, dapsone, colchicine, and rituximab, may be considered if lesions are refractory. Unfortunately, pulmonary involvement is difficult to treat and may be fatal, as in our patient.\(^{4,13,16}\)

In conclusion, SLE and HUVS share both clinical and laboratory features and are probably not separate entities. Clinical progression and treatment are also similar. It is most likely that HUVS and SLE fall into the same spectrum of autoimmune diseases. Our case represented HUVS as an exacerbation of acute SLE. Therefore, all patients diagnosed as HUVS should also be examined for SLE. As both diseases can end fatally, it should be kept in mind that the overlap of SLE and HUVS may exhibit a relatively rapid progression and poor prognosis.

**References**
