Hypocomplementemic urticarial vasculitis complicated with diffuse alveolar hemorrhage: a case report and review of literature

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ABSTRACT

Urticarial vasculitis is a small-vessel vasculitis characterized clinically by urticaria and microscopically by leukocytoclastic vasculitis. Hypocomplementemic urticarial vasculitis syndrome is a rare subtype of urticarial vasculitis with organ involvement and persistent, acquired hypocomplementemia. Pulmonary involvement, usually seen as diffuse alveolar damage, is an uncommon complication and a significant cause of morbidity and mortality. Here we present a rare case of hypocomplementemic urticarial vasculitis syndrome complicated by diffuse alveolar damage and describe the beneficial effect of cyclophosphamide-dexamethasone.

Introduction

Urticarial vasculitis (UV) is an immune complex-mediated vasculitis characterized by recurrent episodes of urticaria with evidence of leukocytoclastic vasculitis.[1] The lesions typically persist for more than 24 h and resolve with residual hyperpigmentation. Hypocomplementemic urticarial vasculitis syndrome (HUVS) is an uncommon, distinct subtype of urticarial vasculitis with multiorgan involvement.[2] To make a diagnosis of HUVS, the typical cutaneous efflorescences must be accompanied by decreased complement levels. All HUVS patients exhibit extremely low levels of C1q.[3] The etiology and link with other conditions such as infection, malignancy, certain drugs and connective tissue diseases, including systemic lupus erythematosus (SLE), are still unknown.[4] The exact incidence and prevalence of HUVS are also unknown, as this is a rare and severe systemic form of UV. HUVS is present in 7 to 8% of patients with SLE and 54% of patients with HUVS are diagnosed as having SLE in their follow-up period.[4] Patients with HUVS may have significant morbidity and mortality, most commonly caused by chronic obstructive pulmonary disease and acute laryngeal edema.[2] One of the worst pulmonary complications is acute lung injury with a clinical presentation of acute respiratory distress syndrome.[5] The classic histological manifestation of acute lung injury/acute respiratory distress syndrome is diffuse alveolar damage (DAH). DAH is a clinical entity characterized by hemoptysis, dyspnea, anemia and diffuse pulmonary infiltrations on chest radiography.[5] Most cases of DAH have a pulmonary capillaritis usually seen in systemic autoimmune diseases, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, systemic lupus erythematosus, rheumatoid arthritis and other systemic rheumatic diseases.[6] Here we present a rare case of HUVS complicated by DAH and describe the excellent response to treatment with cyclophospamide and glucocorticoids.[7] To the best of our knowledge, no previous cases of HUVS complicated by DAH have been published in the literature (Table 1).[7-28]

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Case Report

A 58-year old female was referred to our department in March 2008 for persistent urticarial skin lesions which had started 11 months previously. She also reported suffering from arthralgia, deteriorating general health and recurrent conjunctivitis. She had a past history of a state of hypercoagulability (episodes of post-operative thrombosis in the upper legs). Physical

Table 1. Hypocomplementemic urticarial vasculitis syndrome case reports.

	Study	Age (in years), sex and date	Case presentation	Treatment	Organ involvement
1	Current study	58, F (2007)	2013	Prednisone (variable dose), cyclophosphamide 100 mg/day and mycophenolate mofetil (2 g/day) No response to antihistamines, cyclosporine 200 mg/day, azathioprine 100 mg/day, dapsone 100 mg/day, methotrexate 7.5 mg/week	Eyes (conjunctivitis), kidneys (glomerular hematuria), lungs (DAH), joints (arthralgia)
2	Agnello *et al.*[8]	Not done	1973	Corticosteroids	Joints (arthralgia), angioneurotic edema
3	McDuffie *et al.*[9]	4 patients	1973	Corticosteroids	Not known
4	Oishi *et al.*[10]	33, F	1976	Prednisolone	Joints (arthralgia), kidneys (nephropathy), angioneurotic edema, eyes (conjunctival injection)
5	Zeiss *et al.*[11]	50, F (1975)	1980	Prednisone (up to 40 mg/day), hydroxyazine, azathioprine (50 to 150 mg/day)	Joints (arthralgia and arthritis), lungs (asthma), seizures
6	Zeiss *et al.*[11]	45, F (1974)	1980	Prednisone	Joints (arthralgia and arthritis)
7	Zeiss *et al.*[11]	36, F (1974)	1980	Prednisone	Joints (arthralgia), neurological (mononeuritis)
8	Zeiss *et al.*[11]	43, F (1976)	1976	Antihistamines	Joints (arthralgia and arthritis)
9	Zeiss *et al.*[11]	46, F (1974)	1980	Died of acute pneumonia	Joints (arthralgia and arthritis), lungs (asthma), neurological (depression)
10	Meyrier[12]	58, F	1984	Corticosteroids	Joints (arthralgia), kidneys (renal venulitis)
11	Sturgess *et al.*[13]	42, F	1988	Prednisolone (10-5 mg) plus azathioprine (100 mg/day)	Vasculitis affected the femoral, cystic and renal arteries Jaccoud's arthritis
12	Palazzo *et al.*[14]		1993	Valve replacement and later a heart transplant	Jaccoud's hand deformity and cardiac valve disease
13	Palazzo *et al.*[14]		1993	Not known	Jaccoud's hand deformity and cardiac valve disease
14	Palazzo *et al.*[14]		1993	Not known	Jaccoud's hand deformity and cardiac valve disease
15	Wisnieski *et al.*[15]	2 twins	1994	Not known	Kidneys (glomerulonephritis), lungs (obstructive lung disease), eyes (ocular inflammation), joints (arthralgia)
16	Mituiki *et al.*[16]	62, M	1994	No response to corticosteroid treatment. Died of acute respiratory distress syndromes	Kidneys (nephrotic syndrome), eyes (iritis)
17	Wisnieski *et al.*[17]	18 patients	1995		Angioedema, ocular inflammation, kidneys (glomerulonephritis), lungs (obstructive pulmonary disease)
18	Ishikawa *et al.*[18]	33, M	1997	Prednisolone (10-5 mg/day)	Joints (polyarthralgia) Jaccoud's syndrome
19	Worm *et al.*[7]	43, F	1998	No response to prednisolone, dapsone/pentoxifylline, prednisolone/azathioprine, cyclosporine, prednisolone/IVIG Responded to cyclophosphamide-dexamethasone pulse therapy	Joints (arthritis), eyes (episcleritis)

To be continued on next page

Table 1. Continued from previous page.

Study	Age (in years), sex and date	Case presentatiom	Treatment	Organ involvement
20 Worm *et al.*[7]	45, F	1998	No response to treatment with prednisolone, interferon-α, dapsone/ pentoxifylline, dapsone/pentoxifylline/ prednisolone, prednisolone/IVIG Responded to cyclophosphamide-dexamethasone pulse therapy	Joints (arthritis), eyes (conjunctivitis)
21 Trendelenburg *et al.*[4]	37, F	1999	No response to treatment with hydroxychloroquine, prednisone alone, plasmapheresis, IVIG (sandoglobulin 12 g/day for 5 doses) Responded to azathioprine (150 mg/day) plus prednisone (60-7.5 mg)	Kidney (nephritis), eyes (conjunctivitis). Patient subsequently developed SLE
22 Trendelenburg *et al.*[4]	43, F	1999	Azathioprine (50 mg/day) plus prednisone (50 mg/day)	Eyes (conjunctivitis and episcleritis), angioedema Patient subsequently developed SLE
23 Houser *et al.*[19]	34, M	2002	Valve replacement	Cardiac valve disease (aortic and mitral regurgitation)
24 Cadnapaphornchai *et al.*[20]	12, F	2000	Dapsone, corticosteroids	Kidneys (membrano-proliferative glomerulonephritis), joints (polyarthritis)
25 Grimbert *et al.*[21]	36, F	2001	Corticosteroids, hemodialysis	Kidneys (end-stage renal disease)
26 El Maghraoui *et al.*[22]	41, F	2001	Corticosteroids	Joints (polyarthritis)
27 El Maghraoui *et al.*[22]	39, F	2001	Corticosteroids and cyclophosphamide	Joints (polyarthritis), Lungs (cough and dyspnea)
28 Chen *et al.*[23]	29, F	2001	Prednisone, azathioprine and tolmetin. Valve replacement	Joints (polyarthritis and polyarthralgia) Valvular heart disease (stenosis and regurgitation of aortic and mitral valves)
29 Hunt *et al.*[24]	46, F	2006	Corticosteroids and cyclosporine, Lung transplantation	Lungs (obstructive airways disease)
30 Aydogan *et al.*[25]	44, F	2006	Prednisolone (50-80 mg/day) plus azathioprine (100 mg/day) Died of acute respiratory distress	Joints (polyarthritis), eyes (episcleritis). Patient fulfilled the ARA criteria fo SLE
31 Staubach-Renz *et al.*[26]	37, F	2007	No response to antihistamines and methotrexate/prednisolone Responded to herapy with IVIG (intraglobin F and intraglobin CP 2 g/kg)	Joints (polyarthralgia) Lung (obstructive lung disease) Eyes (irits)
32 Dincy *et al.*[27]	Prospective study of 68 patients from South India from 2003 to 2004	2008	Not known	Female preponderance among patients with HUVS. Systemic involvement was seen in 64.3% of of patients with HUVS. Fever, ANA positivity and SLE were significantly associated with HUVS
33 Buck *et al.*[28]	34, M	2012	Azathioprine (150 mg/day) and prednisone, followed by cyclophosphamide (250 mg) and prednisone	Myalgia and arthralgia

DAH, diffuse alveolar damage; IVIG, intravenous immunoglobulin; SLE, systemic lupus erythematosus; ARA, American College of Rheumatology; HUVS, hypocomplementemic urticarial vasculitis syndrome; ANA, antinuclear antibodies.

examination showed a diffuse eruption of raised, erythematous lesions which persisted >24 h with residual hyperpigmentation (Figures 1-3). Extensive oncohematological, cardiological, dermatological, gastroenterological, infectious and radiological investigations failed to revealed the diagnosis. Laboratory studies showed an increased erythrocyte sedimentation rate, raised level of C-reactive protein, anemia, slight elevation of antinuclear antibodies to 1:80 - without demonstration of double-stranded DNA antibodies - complement deficiency and positivity for autoantibodies to C1q. ANCA and immune complexes were not detected. The patient showed resistance to activated protein C (factor V Leiden). Examination of the urinary sediment revealed isolated glomerular hematuria in the absence of cylinders or proteinuria. Two skin biopsies were performed, at a distance of about 4 months. In both biopsies we observed an intense neutrophilic and eosinophilic inflammatory perivascular infiltrate (Figure 4) with capillaritis (Figure 5). There was edema in the dermis with dilated blood vessels and focal nuclear dust. The overall appearance suggested perivascular and interstitial dermatitis with prominent neutrophils. This pattern is consistent with leukocytoclastic vasculitis. The diagnostic criteria for SLE were not fulfilled and a diagnosis of HUVS was made (Table 2).[1] The patient was treated unsuccessfully for up to 1 year with several immunosuppressive drugs (cyclosporine 200 mg/day p.o., cyclophosphamide 100 mg/day p.o., azathioprine 100 mg/day p.o.), immunomodulatory drugs (dapsone 100 mg/day p.o., methotrexate 7.5 mg/week) and antihistamines (anti-H1 and anti-H2 receptors) associated with variable doses of prednisolone (10-50 mg/day). During treatment with dapsone (100 mg/day), prednisolone (12.5 mg/day) and cinarazine the patient was admitted to our hospital with severe dyspnea. Arterial blood-gas analysis showed hypoxia. Laboratory studies revealed a reduction of hemoglobin (Hb 7.8 mg/dL; normal range 12-14 mg/dL). Computed tomography of the chest evidenced the bilateral diffuse basal alveolar filling (Figure 6).The diagnosis of DAH was suggested by the clinical symptoms (dyspnea), the decrease in hemoglobin concentration as well as infiltrates on chest X-ray films and was confirmed by the progressively bloody aspiration and the increase of hemosiderin-laden macrophages in the bronchoalveolar

Table 2. Typical laboratory findings in hypocomplementemic urticarial vasculitis syndrome.

Accelerated ESR
Hpocomplementemia with low C1q, C3, C4
C1q antibodies
ANA without anti-double-stranded DNA

ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies.

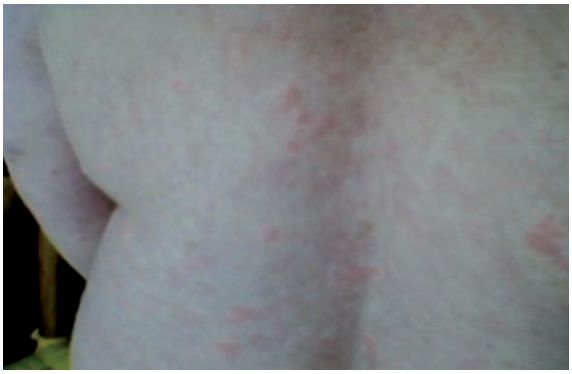

Figure 1. Urticarial vasculitis skin lesions over the patient's back.

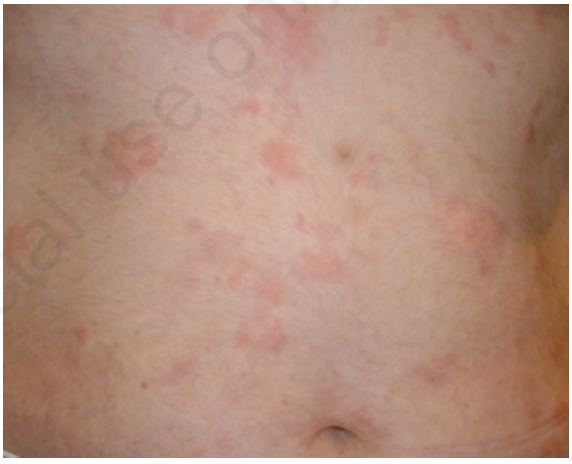

Figure 2. Urticarial vasculitis skin lesions on the patient's abdomen.

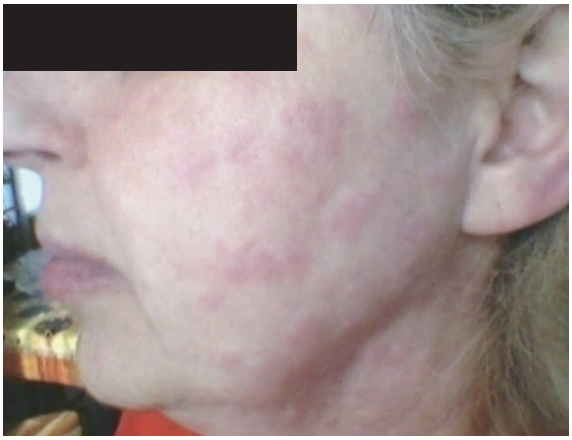

Figure 3. Urticarial vasculitis skin lesions on the patient's face.

lavage fluid in the absence of macroscopic airway lesions. Cultures for common microbes, *Pneumocystis carinii*, Aspergillus and Koch's bacillus from the same samples were negative. The intradermal reaction to tuberculosis was negative. The patient was then treated with corticosteroids combined with cyclophosphamide.

Methylprednisolone pulse (1 g/day for 3 consecutive days) was given as the initial therapy, followed by cyclophosphamide (100 mg/day) associated with prednisolone (1 mg/kg bw/day p.o.). The patient's health improved progressively and the pulmonary probles resolved completely. The patient is currently receiving 2 g mycophenolate mofetil combined with 5 mg prednisolone and has been in complete remission for more than 24 months.

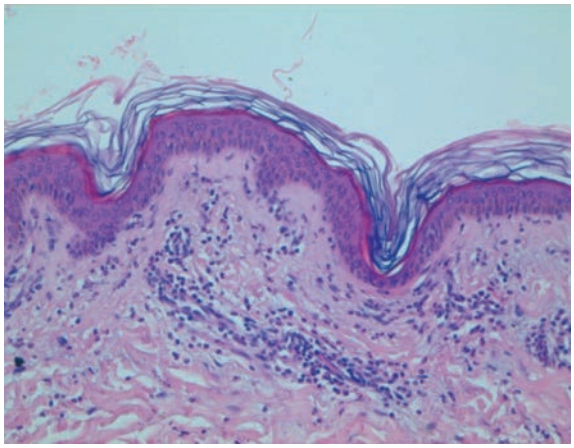

Figure 4. Skin biopsy: perivascular dermatitis with capillaritis and edema (H&E 10X).

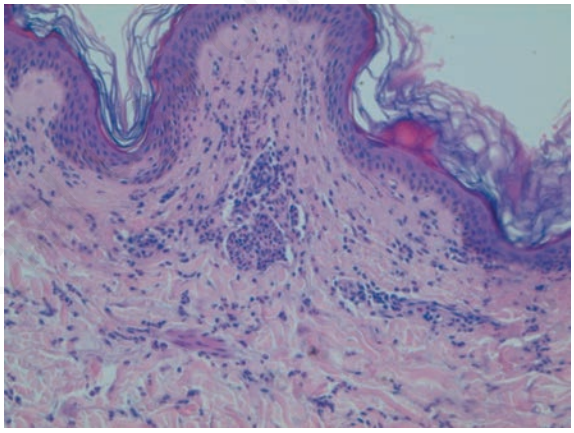

Figure 5. Skin biopsy: infiltrate of neutrophils and eosinophils around and within small vessels (H&E 25X).

Discussion

In 1971 Agnello *et al.*[8] and later McDuffie *et al.* (1975)[9] and Oishi (1976)[10] described some patients with erythema multiforme, C1q precipitins, hypocomplementemia and angioedema and considered that these patients could have a new immune complex syndrome, initially referred to as an unusual SLE-related syndrome. For the first time in 1980 Zeiss *et al.*[11] used the term *hypocomplementic vasculitic urticarial* to define the subgroup of patients who had characteristics similar to those reported by Agnello *et al*. Currently, HUVS is considered to be an independent immunological disease although differentiation from SLE is sometimes difficult because almost half of all patients with HUVS are positive for antinuclear antibodies and often fulfill the American College of Rheumatology's criteria for SLE.[1] This is why some authors defined HUVS as an SLE-associated syndrome.[25,29] Our pa-

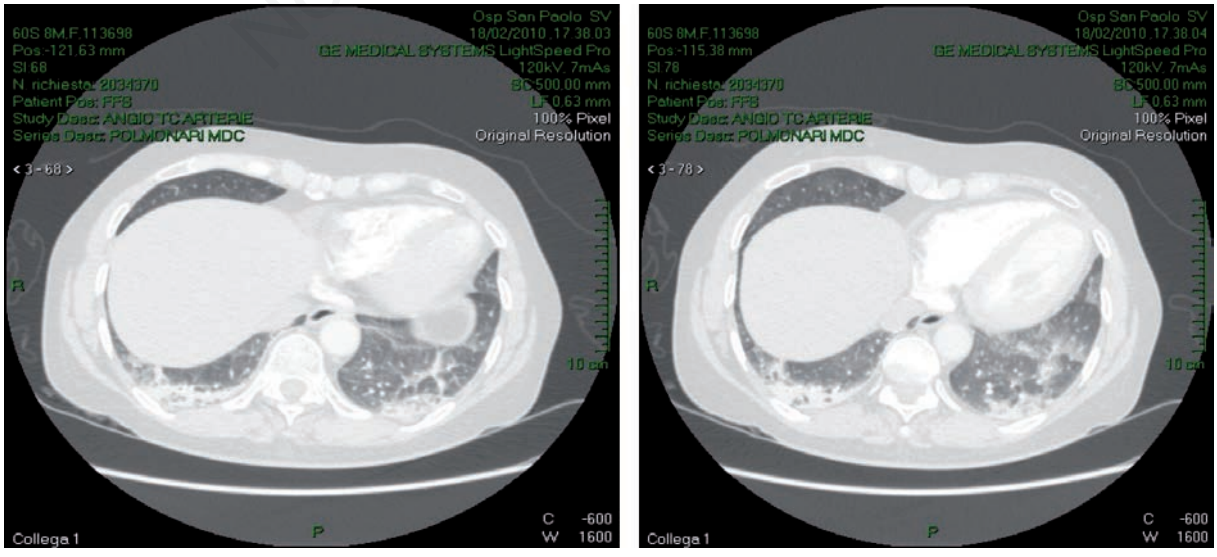

Figure 6. Computed tomography scans of chest showing basal bilateral non-specific alveolar infiltrates.

tient fulfilled the criteria for HUVS but not for SLE. In fact, he had only two of the 11 SLE criteria.

HUVS is a rare syndrome; its exact incidence and the mechanism(s) underlying the pathogenesis are unknown.[2] Because of the rarity of this entity the treatment recommendations are based exclusively on reports of single cases or small series. A major problem in treating this disease is the frequent resistance to various therapies including immunosuppressive and immunomodulatory drugs.[30] For these reasons, the appropriate treatment of HUVS is determined by the severity of the disease and no single therapy is recognized as being highly effective, reliable, safe, convenient and inexpensive.[2]

Table 3. Etiology and histology of diffuse alveolar hemorrhage.

Pulmonary capillaritis
ANCA-associated granulomatous vasculitis
Microscopic polyangitis
Isolated pulmonary capillaritis
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disorder
Scleroderma
Polymyositis
Primary antiphospholipid antibody syndrome
Henoch-Schonlein purpura
Behcet's syndrome
IgA nephropathy
Idiopathic glomerulonephritis
Acute lung transplant rejection
Idiopathic pulmonary fibrosis
Diphenylhydantoin
Autologous bone marrow transplantation
Myasthenia gravis
Cryoglobulinemia
Ulcerative colitis
Propyl thiouracil
Bland pulmonary hemorrhage
Idiopathic pulmonary hemosiderosis
Goodpasture's syndrome
Systemic lupus erythematosus
Coagulation disorders
Trimellitic anhydride
Isocyanate exposure
Penicillamine
Amiodarone
Nitrofurantoin
Mitral stenosis
Subacute bacterial endocarditis
Polyglandular autoimmune syndrome
Multiple myeloma
Diffuse alveolar damage
Bone marrow transplantation
Crack cocaine inhalation
Cytotoxic drug therapy
Systemic lupus erythematosus
Radiation therapy
Acute respiratory distress syndrome

ANCA, anti-neutrophil cytoplasmic antibodies; IgA, immunoglobulin A.

Multiple therapies have been attempted and then is no consensus on a specific treatment for HUVS. Moderate doses of steroids are certainly effective in controlling symptoms, but the adverse effects associated with the long-term use of these drugs make it necessary to evaluate new therapeutic strategies and in particular the use of oral medications to prevent organ allograft rejection and biologics. Cyclosporine has been studied but reports have also suggested that tacrolimus and mycophenolate mofetil are promising therapies.[30-32] Cyclophosphamide-dexamethasone pulse therapy was initially described for the treatment of SLE but has also proven to be effective in Wegener's granulomatosis and in bullous autoimmune dermatoses. Worm *et al.* reported the beneficial effect of cyclophosphamide-dexamethasone pulse therapy followed by mycophenolate mofetil for the maintenance,[33] although the published results on this strategy are conflicting.

The fact that the prognosis of HUVS is worse than that of other forms of UV is due to the presence of multi-organ involvement. In particular, lung involvement is associated with shortness of breath, coughing, hemoptysis, pleural effusion, and chronic obstructive pulmonary disease and is the most frequent cause of death among HUVS patients.[6] In contrast and apparently uniquely, our patient presented with clinicopathological signs of DAH as a manifestation of lung involvement. DAH is usually acute in onset and is generally a condition with high morbidity and mortality. It requires prompt diagnosis and aggressive treatment to improve the survival. A review of the literature shows only a small number of cases of vasculitis associated with DAH and especially with ANCA, Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis (Table 3).[5] The treatment generally includes corticosteroids combined with cyclophosphamide.[7] To the best of our knowledge, there have been no published cases of HUVS complicated by DAH. In the light of this, the treatment of our patient was largely empirical and her prognosis is unknown. We have reported our clinical experience and views on a possible therapeutic strategy for this previously undescribed combination of conditions. At present, our patient has been in complete remission for more than 24 months.

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