Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare disorder characterized clinically by recurrent urticaria and a variety of systemic manifestations. HUVS was first described by McDuffie in 1973. In 1982, Schwartz et al established the diagnostic criteria (Table 1). Two major criteria (recurrent urticaria for > 6 months and hypocomplementemia) and at least 2 minor criteria (venulitis on skin biopsy, arthralgias or arthritis, glomerulonephritis, ocular inflammation, abdominal pain, and positive C1q antibodies) are required for a diagnosis of HUVS. Exclusion criteria are cryoglobulinemia, high levels of antinuclear antibody, positivity of anti–double-stranded DNA antibody, hepatitis B virus antigenemia, and deficiency of complement factors.

Renal involvement in HUVS occurs in up to 50% of cases; the majority manifest in a benign manner. In a 1994 literature review, Kobayashi et al described 78 patients with HUVS reported from 1973 to 1990. Eighteen biopsies had been performed in this group. The various histopathologic types reported by these investigators were mesangial proliferative (8 cases), focal proliferative (3 cases), membranoproliferative (3 cases), membranous (2 cases), minimal change (1 case), and severe sclerosing proliferative glomerulonephritis (1 case). In 1995, Wisnieski et al reported another 18 patients with HUVS, of whom 50% had renal involvement. The investigators described renal manifestations ranging from minimal proteinuria to nephrotic syndrome with variable degrees of hematuria. Glomerular involvement included mesangial and membranoproliferative glomerulonephritis.

Crescentic glomerulonephritis in patients with HUVS is very rare. Since the original description in 1973, only 2 adults and 2 pediatric patients with crescentic glomerulonephritis complicating the course of HUVS have been reported in the world literature (Table 2). We describe a young woman with crescentic glomerulonephritis associated with HUVS who rapidly progressed to end-stage renal disease.

**CASE REPORT**

**Clinical History**

A 23-year-old Hispanic woman was seen as an emergency department consultation. She had been well until 6 months earlier, when she developed a skin rash over her trunk and extremities soon after she changed the carpet in her apartment. The rash was diffuse, erythematous, and wheal-like; varying in size; pruritic; and painful. It resolved on its own and the patient did not seek medical attention at that time. During the next 5 months, the rash appeared intermittently, lasting for 24 to 48 hours at a time. She then saw her primary care physician, who treated her with an antihistamine and topical steroid cream for a possible urticarial allergic reaction. There was no improvement. One week later, she developed increased urinary frequency, dysuria, abdominal pain, dark orange urine, and a 5-pound weight gain. She returned to the physician, who obtained laboratory tests. Urinalysis showed 3+ protein and 3+ blood, and microscopy showed more than 30 red blood cells and more than 30 white blood cells/high-power field. Blood urea nitrogen level was 18 mg/dL (6.426 mmol/L), and creatinine level was 1 mg/dL (88.4 mol/L). She was treated with oral antibiotics for a presumed urinary tract infection. Three days later, the patient presented to our emergency department because of worsening skin rash, suprapubic and flank pain, arthralgias of the joints of the hands and knees, and a 20-pound weight gain with total-body swelling. The patient denied respiratory symptoms, chest pain, fever, morning
undetectable complement C1q fraction (C1q), increased normal range, 19.7 to 57.0 mg/dL [0.20 to 0.57 g/L]), low complement C4 fraction (C4) of 10.4 mg/dL (0.10 g/L; normal range, 86.3 to 184.1 mg/dL [0.86 to 1.84 g/L]), and low complement C3 fraction (C3) of 41.8 mg/dL (0.42 mmol/L), blood urea nitrogen level of 43 mg/dL, and creatinin level of 2.3 mg/dL. Complement analysis showed hypocomplementemia with low total hemolytic component level of 2.3 mg/dL. Cultivation results showed 3+ protein and 3+ blood, and microscopy showed 50 to 100 red blood cells/high-power field, 2 to 5 white blood cells/high-power field, and a few granular casts. Twenty-four–hour urine protein was 3.9 g. The patient had hypocomplementemia, blood urea nitrogen level, and creatinin level, which are all below the normal range, indicating hypocomplementemia.

The patient denied a significant medical and surgical history. There was no history of food, drug, or dust allergy. She denied using any medicine, including over-the-counter or herbal remedies, other than those prescribed by her physician. She denied a family history of autoimmune or kidney diseases. She did not smoke, drink alcohol, or use recreational drugs. The patient was married and had a monogamous relationship with her husband. She worked as a house cleaner.

Physical examination showed a young woman in no distress. Blood pressure was 140/93 mm Hg, with a regular heart rate of 74 beats/min. She was febrile and had urticarial lesions all over her body, except for her face, and anasarca was noted. No oral ulcers were seen. The rest of the physical examination findings were unremarkable.

Laboratory tests showed the following values. Urinalysis showed 3+ protein and 3+ blood, and microscopy showed 50 to 100 red blood cells/high-power field, 2 to 5 white blood cells/high-power field, and a few granular casts.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Manifestations</th>
<th>Required for Diagnosis</th>
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<tbody>
<tr>
<td>Major</td>
<td>Recurrent urticaria for &gt;6 mo</td>
<td>The patient must have both major criteria</td>
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<tr>
<td></td>
<td>Hypocomplementemia</td>
<td></td>
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<tr>
<td>Minor</td>
<td>Venulitis of the dermis (established by means of biopsy)</td>
<td>The patient must have at least 2 minor criteria</td>
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<td></td>
<td>Arthralgia or arthritis</td>
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<tr>
<td></td>
<td>Glomerulonephritis</td>
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<tr>
<td></td>
<td>Ocular inflammation (uveitis or episcleritis)</td>
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<td></td>
<td>Recurrent abdominal pain</td>
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<tr>
<td></td>
<td>Positive C1q precipitin test result by immunodiffusion with an associated suppressed C1q level</td>
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</table>

Kidney biopsy

Prior to the kidney biopsy, a skin biopsy had been performed. As shown in Fig. 1, an urticarial lesion was sampled and showed interstitial edema with acute venulitis. The kidney biopsy specimen is shown in Fig. 2. Light microscopy showed 19 glomeruli, all of which showed crescents (Fig 2A and B). Extensive tubular loss and interstitial inflammation were of note, and fibrosis was present even at the early stage of the patient’s course. Immunofluorescent studies showed a heavy granular epimembranous staining strongly positive with antisera directed against immunoglobulin G, immunoglobulin A, immunoglobulin M, C1q, C3, C4, and κ and λ light chains, with particularly heavy deposition of C1q (Fig 2C).

Electron microscopy showed abundant subendothelial deposits (Fig 2D). The pattern of renal changes was indistinguishable from that of severe lupus nephritis, except for the absence of tubuloreticular inclusions. A repeated biopsy 6 weeks later showed a decrease in both inflammation and immune deposits; however, all 11 glomeruli were almost totally sclerotic with extensive tubular loss and interstitial fibrosis.

Diagnosis

Our patient fulfilled the diagnostic criteria for HUVS.

Clinical follow-up

Three daily doses of methylprednisolone (each 500 mg) and 1 dose of 1 g of intravenous cyclophosphamide followed by oral prednisone, 1 mg/kg/d, were administered. The skin lesions resolved; however, proteinuria and hematuria persisted, with progressive worsening of kidney function and peak creatinine level of 4.7 mg/dL. Plasmapheresis was initiated 1 week after the first dose of intravenous steroids.
was administered. It was given every other day as 1 plasma exchange with albumin replacement. After 2 plasmapheresis treatments, creatinine level decreased to 3.4 mg/dL. However, 2 days later, the patient was transferred to the intensive care unit with gram-negative sepsis, pneumonia, and respiratory failure. Kidney function also deteriorated. The patient was treated with broad-spectrum antibiotics and respiratory support with mechanical ventilation. Cyclophosphamide and plasmapheresis therapy were discontinued. Hemodialysis therapy was initiated to treat volume overload and uremic symptoms. One month after hospitalization, repeated laboratory tests showed normal complement levels, but kidney function never improved. Repeated renal biopsy performed 6 weeks after the first biopsy showed sclerosis of all glomeruli. Oral steroid therapy was discontinued. Currently, the patient is on maintenance hemodialysis therapy.

**DISCUSSION**

This case illustrates several important points. First, although many may consider HUVS as a subset of lupus, the absence of classic serological test results and a different skin picture have led to this being regarded as a separate entity. Second, the case illustrates the importance of measuring C1q and anti-C1q antibodies in a patient with suspected HUVS. Third, it emphasizes the importance of complement as a prognostic indicator in patients with this disease. The low complement levels in patients with this syndrome herald a poor prognosis, and the diminution or absence of

### Table 2. Summary of All Reported Cases of Crescentic Glomerulonephritis and Hypocomplementemic Urticarial Vasculitis Syndrome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Age (y)/Sex</th>
<th>Clinical Presentation</th>
<th>Kidney Biopsy</th>
<th>Treatment</th>
<th>Clinical Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini et al²</td>
<td>12/Boy</td>
<td>Renal: hypertension, renal failure, microscopic hematuria, proteinuria Extrarenal: urticaria, angioedema, arthritis, conjunctival hyperemia</td>
<td>LM: mesangial proliferation with complete sclerosis and crescents in 50% of glomeruli IF: C3, C1q, C4, IgG, IgM EM: not available</td>
<td>CS, CyC</td>
<td>Maintenance hemodialysis initiated 5 mo after diagnosis</td>
</tr>
<tr>
<td>Messiaen et al⁴</td>
<td>27/Woman</td>
<td>Renal: renal failure, gross hematuria, proteinuria Extrarenal: urticaria, arthritis, episcleritis, hemoptysis with intrapulmonary hemorrhage</td>
<td>LM: membranoproliferative with crescents IF: C3, C1q (mesangium), IgM (vessel walls) EM: subepithelial and subendothelial deposits</td>
<td>CS, CyC</td>
<td>Maintenance hemodialysis initiated 3 y after diagnosis, subsequently received renal transplant</td>
</tr>
<tr>
<td>Enriquez et al³</td>
<td>39/Woman</td>
<td>Renal: renal failure, hypertension, microscopic hematuria, nephrotic syndrome Extrarenal: urticaria, arthralgias, xerophthalmia</td>
<td>LM: mesangial proliferation, membranoproliferative with crescents IF: C3, C4, C1q, IgG, IgM (capillary walls) EM: not available</td>
<td>CS, CyC, MMF</td>
<td>Mild renal insufficiency and nephrotic syndrome 42 mo after diagnosis</td>
</tr>
<tr>
<td>Present study</td>
<td>23/Woman</td>
<td>Renal: gross hematuria, nephrotic syndrome, acute renal failure Extrarenal: urticaria, arthralgias, abdominal pain</td>
<td>LM: crescents with extensive tubular loss and interstitial inflammation IF: heavy granular epimembranous staining strongly positive with antisera directed against IgG, IgA, IgM, C1q, C3, C4, k and l light chains with particularly heavy deposition of C1q EM: subendothelial deposits</td>
<td>CS, CyC, PPH</td>
<td>Maintenance hemodialysis initiated 3 wk after diagnosis</td>
</tr>
</tbody>
</table>

Abbreviations: Aza, azathioprine; CS, corticosteroids; CyA, cyclosporine; CyC, cyclophosphamide; EM, electron microscopy; IF, immunofluorescence; IgG, immunoglobulin G; LM, light microscopy; MMF, mycophenolate mofetil; PPH, plasmapheresis.
C1, C2, and C4 tend to favor the development of autoimmune disease. Fourth, the case is important in illuminating a pathogenetic mechanism. C1q antibody can be detected in 100% of patients with HUVS. However, only approximately half the patients with HUVS develop renal manifestations; severe renal involvement is uncommon. Animal studies have shown that injection of anti-C1q antibodies, either monoclonal or polyclonal, did not result in overt renal disease, although glomerular deposition of C1q and anti-C1q antibodies, as well as a significant influx of leukocytes, could be observed. Anti-C1q autoantibodies were pathogenic only in combination with glomerular C1q-containing immune complexes. The investigators concluded that anti-C1q autoantibodies by themselves do not seem to be able to induce overt renal inflammatory disease. However, in the presence of immune complex deposition that is recognized by C1q, C1q and subsequently C1q antibodies bind to the immune complexes. This results in full activation of the classical pathway of the complement system, leading to tissue injury mediated by the membrane attack complex and the influx of inflammatory cells. This mechanism may explain why certain patients with HUVS (those with immune complex deposition) develop renal disease, whereas others are spared, although all patients have detectable C1q antibody. Finally, the case highlights the prognosis and treatment of patients with HUVS and crescentic glomerulonephritis; the potential for rapid deterioration in kidney function and a possible role for plasmapheresis.

The 4 known patients with HUVS and crescentic glomerulonephritis were treated with combinations of immunosuppressive therapy, including steroids, cyclophosphamide, cyclosporine A, azathioprine, and mycophenolate mofetil, but not plasmapheresis. Enriquez et al described a 39-year-old woman with crescentic membranoproliferative glomerulonephritis in the setting of HUVS who was treated with pulse doses of steroids and cyclophosphamide, with improvement in kidney function in a 42-month follow-up period. Messiaen et al described a 27-year-old woman with a clinical course complicated by crescentic glomerulonephritis 6 years after the initial diagnosis of HUVS, with partial response to steroids and cyclophosphamide initially. However, the patient eventually developed end-stage renal disease requiring hemodialysis therapy 3 years after the diagnosis of glomerulonephritis. Martini et al and Renard et al described 2 pediatric patients with crescentic glomerulonephritis associated with HUVS. One responded to steroid and immunosuppressive therapy with normalization of kidney function, but persistent mild proteinuria, and the other did not respond and developed end-stage renal disease within 5 months after diagnosis. The kidney function of our patient did not respond to steroid and cyclophosphamide therapy, but may have had some improvement with plasmapheresis. Unfortunately, because of sepsis, treatment could not be continued and she developed end-stage renal disease within 3 weeks after the diagnosis of HUVS.

In conclusion, hypocomplementemic urticarial vasculitis is a separate disease from lupus, based on the absence of classic serological test results and different skin lesions and pathologi-
Low C1q levels in serum caused by circulating anti-C1q are crucial to making the diagnosis. Because of the limited number of cases, it is difficult to determine the effect of immunosuppressive therapy on patients with severe kidney disease associated with HUVS. However, it was suggested that steroids and cyclophosphamide are the drugs of choice. Cyclosporine A, azathioprine, mycophenolate mofetil, and plasmapheresis could be other valuable alternatives. Our case together with the 4 other reported cases of crescentic glomerulonephritis associated with HUVS support that this disease is potentially aggressive and should be considered in the differential diagnosis of small-vessel vasculitis with renal involvement.

Figure 2. (A) Renal biopsy specimen (hematoxylin and eosin stain; original magnification ×40). Three glomeruli show crescents that are cellular. The interstitium is severely inflamed, and there is obvious tubular loss and fibrosis. (B) A glomerulus (hematoxylin and eosin stain; original magnification ×400) shows a typical lesion. There is proliferation of all elements with relatively little acute inflammation. (C) Glomeruli (immunofluorescence with anti-C1q; original magnification ×400) all showed staining for immunoglobulin G (IgG), IgA, IgM, C1q, C3, C4, k, l, and fibrin. The pattern was granular and subendothelial. (D) Electron microscopy shows many large subendothelial electron-dense deposits. No tubuloreticular inclusions are seen.

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