

Inflammatory myositis complicating hypocomplementemic urticarial vasculitis despite on-going immunosuppression

Gary Y. J. Chew · Paul A. Gatenby

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Abstract We present a patient with previously diagnosed hypocomplementemic urticarial vasculitis syndrome, with skin, lung, and renal involvement, who presented with congestive cardiac failure. During the course of her hospitalization, she was also found to have profound proximal muscle weakness in both upper and lower limbs associated with raised creatinine kinase levels. A muscle biopsy was performed, which demonstrated evidence of an inflammatory myositis with vasculitis, which had returned despite on-going immunosuppression. This occurrence of a new autoimmune disease may well be an example of the “waste disposal” hypothesis.

Keywords C1q · Complement · Hypocomplementemic urticarial vasculitis · Myositis

Introduction

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare vasculitic disorder, which was first described by McDuffie et al. [1]. It has a female to male ratio of 8:1 [2], similar to systemic lupus erythematosus (SLE).

HUVS can be distinguished by the presence of angioedema, urticaria, uveitis, and chronic obstructive pulmonary disease, which are rare in SLE. With renal involvement, although histological appearance may resemble those seen in SLE, progression to chronic renal failure is unusual. In addition, antibodies specific to SLE, namely those to double-stranded DNA and Sm antigen, are not found in patients with HUVS.

The pathogenesis of HUVS is complex and not fully understood but is thought to involve immune complexes as components of the classical complement pathway are usually reduced, particularly C1q. [1, 3] This may be due to the production of IgG autoantibodies to C1q found in most cases [3].

Case report

This 55-year-old woman was initially diagnosed with HUVS 7 years ago after investigations for recurrent unexplained angioedema and biopsy-proven urticarial vasculitis revealed elevated C1q antibody levels; low C1q; normal C1r and C1s; and persistently low C2, C4, and C3. C1 inhibitor both quantitative and functional was normal. Antinuclear antibodies have only been intermittently detected in low titers throughout the course of the illness. DNA antibodies measured by ELISA and Crithidia assay have been consistently negative. Her course has been complicated by diffuse membranoproliferative glomerulonephritis with heavy proteinuria, which is responsive to prednisolone and pulse cyclophosphamide but did not progress to end-stage renal failure, pulmonary vasculitis or a thrombotic cerebrovascular event, and recurrent pulmonary emboli associated with low-titer anticardiolipin antibody.

G. Y. J. Chew (✉) · P. A. Gatenby
Department of Immunology, The Canberra Hospital,
Woden, Australian Capital Territory, Australia
e-mail: gary.chew2@act.gov.au

P. A. Gatenby
Australian National University Medical School,
Canberra, Australia

She presented with a 3-day history of increasing shortness of breath that commenced immediately after a cyclophosphamide infusion (for persisting pulmonary involvement), at which time she received prehydration in addition to urosemide. Her medications on presentation included omeprazole, prednisolone, and warfarin. There was no associated cough, chest pain, or systemic symptoms.

On examination, she was hemodynamically stable. She had signs of congestive cardiac failure. An ECG did not reveal any ischemic changes, while a chest X-ray revealed a left-sided pleural effusion but no features of pulmonary edema. Troponin was undetectable. Her creatinine was stable at 67 $\mu\text{mol/l}$. Complement levels were reduced as they have consistently been with $\text{C3}=0.42 \text{ g/l}$ and $\text{C4}=0.07 \text{ g/l}$. Inflammatory markers, erythrocyte sedimentation rate and C-reactive protein, were both raised to 86 mm/h and 269 mg/l, respectively. Albumin decreased to 16 g/l, but a 24-h urine collection revealed only 0.76 g of protein, much less than the peak loss of 2.25 g/24 h months before. She responded well to fluid restriction and aggressive diuretic therapy.

The patient was also noted to have pain in her abdomen and in the right gluteal region. Ultrasound confirmed an intra-abdominal wall hematoma and a larger one in the right gluteus maximus muscle. Her creatine kinase (CK) level was 4260 U/l. Initially, the elevated muscle enzyme was attributed to the two intramuscular hematomas and warfarin was ceased. However, the patient subsequently complained of not being able to use her upper limbs. Examination revealed proximal muscle weakness in both her upper and lower limbs with power being 2/5. Power in the rest of her muscle groups was graded as 4/5. She had normal tone, reflexes, and sensation in all her four limbs. There was also weakness of neck flexion. As she had been on steroids for many years, a provisional diagnosis of steroid-induced myopathy was made, and her dose of prednisolone was weaned gradually. Review of her CK results indicated that, although there was a significant fall that occurred in parallel with resolution of the hematomas, her CK level remained elevated. Consequently, a muscle biopsy was performed, which confirmed an inflammatory myositis with vasculitis with moderate mononuclear inflammation in between the fascicles and muscle fibers. Type I and II fibers were equally distributed and affected.

As myositis arose while she was being treated with pulsed cyclophosphamide, she was commenced on 15 mg oral methotrexate weekly and maintained on 7.5 mg prednisolone daily. The proximal muscle weakness initially progressed but the escalation of methotrexate to 20 mg weekly and prednisolone to 75 mg daily has resulted in the normalization of CK levels and progressive improvement of her proximal limb weakness. After rehabilitation, she is

currently able to walk unaided on the flat, although she has some problems on the stairs. Her upper limbs are still weak, but much improved. She is now maintained on 25 mg oral methotrexate weekly with folic acid supplements.

Discussion

The patient we described clearly has HUVS with a number of typical clinical and serological findings.

Feig et al. [4] reported a case of a 31-year-old woman with urticarial vasculitis, hypocomplementemia, and arthralgias in whom myositis, glomerulonephritis, and pseudotumor cerebri were present. Two muscle biopsies were performed in the absence of muscle weakness or tenderness and normal creatine phosphokinase level. They revealed focal interstitial and septal infiltration of lymphocytes without vasculitis. Callen and Dubin [5] described a case of urticarial vasculitis and polymyositis, but the patient had normal total hemolytic complement levels making HUVS unlikely.

Myositis can be autoimmune as evidenced by its association with other autoimmune diseases (such as autoimmune thyroid diseases, type I diabetes mellitus, primary biliary cirrhosis, and connective tissue diseases) and the presence of autoantibodies. Consequently, an association with HUVS is not surprising. It is interesting that the histological appearance of the muscle biopsy in our patient showed histological features of both polymyositis and dermatomyositis. This would suggest that both cytotoxic cell-mediated and humoral mechanisms are involved in the pathogenesis.

The occurrence of an additional autoimmune manifestation while on immunosuppressive therapy is of interest. Despite therapy, the patient constantly had low levels of complement of the classical complement pathway. These complements are potentially protective against autoimmunity—the “waste disposal” hypothesis [6]. Conceivably, the hematomas were associated with the release of important muscle autoantigens that could not be cleared because of the relative complement deficiency.

In our patient, the diagnosis of inflammatory myositis was not apparent initially as she had been on long-term steroids, and we were distracted by two large intramuscular hematomas. It is also interesting to note that the myositis developed despite the patient being treated with monthly cyclophosphamide. It has, however, responded in a typical manner to methotrexate.

Adding to the case reported by Feig et al. [4], this case emphasizes that myositis should be included as a manifestation of HUVS and it can be successfully treated with methotrexate.

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