Clinical Report

Overlap between dermatomyositis and ANCA vasculitides

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Abstract

We present the second report of the association between antineutrophil cytoplasm antibodies (ANCA)-associated vasculitis with dermatomyositis (DM). A 47-year-old woman suddenly developed rapidly progressive renal failure in the context of DM. The kidney biopsy showed focal and segmental necrotizing glomerulonephritis with crescent formation. Cyclophosphamide treatment was commenced resulting in a significant recovery of kidney function and maintenance of recovery at 6 months. Although the pathophysiology is unknown, we hypothesize that CD8-T-deficient cells and MPO+ neutrophils in the DM lesions play an important role in the disease process.

Keywords: ANCA vasculitis; dermatomyositis; focal and segmental necrotizing glomerulonephritis; microscopic polyangiitis; vasculitis

Introduction

Microscopic polyangiitis (MPA) is a pauci-immune necrotizing small-vessel vasculitis secondary to antineutrophil cytoplasm antibodies (ANCA). Dermatomyositis (DM) is the commonest subtype of idiopathic inflammatory myopathy (IIM). It is characterized by chronic muscle inflammation, progressive symmetrical proximal myopathy and classical cutaneous manifestations. Although both are systemic autoimmune diseases, to our knowledge, this is only the second report of this association [1].

Case report

A 47-year-old woman was referred to our renal outpatient clinic with rapidly progressive renal failure. In the past, she only reported a spontaneous miscarriage at 39 years of age. Five months before the referral, she developed a rash on her arms, trunk and legs and a few spots on the face. The rash was erythematous, made of round patches with slight elevation. The initial diagnosis by dermatologists was one of urticarial rash. She was treated with antihistamines achieving a slight improvement.

Two months later, she began to have speech difficulties, weakness and pain in her legs along with diminished knee reflexes. The laboratory values showed C-reactive protein (CRP) 43 mg/L, erythrocyte sedimentation rate (ESR) 40 mm/L, white cell count (WBC) 12.1 \times 10^9/L, platelets 389 \times 10^9/L, ESR 112 mm/h, CRP 237 mg/L, creatinine 365 µmol/L, urea 18 mmol/L, potassium 5.1 mmol/L, creatinine kinase 22 µ/L and urine albumin:creatinine ratio (UACR) 19.8 mg/mmol. The repeat ANCA screen was positive with a peri-nuclear pattern, MPO-ANCA 37.61 U/mL and PR3-ANCA negative. C3 and C4 levels were 73 mg/dL (normal range 65–135) and 24 (normal range 13–35), respectively. The urinalysis showed red cells 5–10 \times 10^6 cells/mL with occasional dysmorphic erythrocytes. The urine culture, chest X-ray, anti-glomerular basement membrane (GBM) antibodies, anti-nuclear antibody (ANA), extractable nuclear antibody (ENA), anti-smooth muscle antibody (anti-SMA), myeloma screen, hepatitis B and C serology and human immunodeficiency virus (HIV) serology were all negative. On examination, the rash was slightly improved but persisted on the arms and trunk. The weakness and speech difficulties disappeared but she complained of arthralgia in the small joints. There was no evidence of pulmonary involvement.

The kidney biopsy yielded 19 glomeruli, 4 of which were globally sclerosed, while the remainder showed focal segmental necrotizing glomerulonephritis with a wide variability in severity (some were almost normal whereas others showed extensive necrosis with crescent formation). Figures 2 and 3 the residual segments of the non-necrotic glomeruli tufts showed non-specific mesangial thickening and Bowman’s capsule was also focally daily. Chest and abdominal computed tomography (CT) did not reveal any malignancy.

One month later, her laboratory results showed that she had rapidly progressive renal failure. As a result, she was admitted to the Renal Department for further investigations including kidney biopsy. The laboratory results were haemoglobin 91 g/L, white cell count (WBC) 12.1 \times 10^9/L, platelets 389 \times 10^9/L, ESR 112 mm/h, CRP 237 mg/L, creatinine 365 µmol/L, urea 18 mmol/L, potassium 5.1 mmol/L, creatinine kinase 22 µ/L and urine albumin:creatinine ratio (UACR) 19.8 mg/mmol. The repeat ANCA screen was positive with a peri-nuclear pattern, MPO-ANCA 37.61 U/mL and PR3-ANCA negative. C3 and C4 levels were 73 mg/dL (normal range 65–135) and 24 (normal range 13–35), respectively. The urinalysis showed red cells 5–10 \times 10^6 cells/mL with occasional dysmorphic erythrocytes. The urine culture, chest X-ray, anti-glomerular basement membrane (GBM) antibodies, anti-nuclear antibody (ANA), extractable nuclear antibody (ENA), anti-smooth muscle antibody (anti-SMA), myeloma screen, hepatitis B and C serology and human immunodeficiency virus (HIV) serology were all negative. On examination, the rash was slightly improved but persisted on the arms and trunk. The weakness and speech difficulties disappeared but she complained of arthralgia in the small joints. There was no evidence of pulmonary involvement.
thickened. The surrounding renal cortex showed focal acute-on-chronic inflammatory changes. Small- and medium-sized vessels showed no evidence of vasculitis. Immunofluorescence showed focal segmental deposition of IgG along with capsular C3 deposition. Based on these findings, a diagnosis of ANCA-associated focal and segmental necrotizing glomerulonephritis with crescent formation was made and cyclophosphamide 100 mg and prednisolone 60 mg per day were started. Three months later, measurement of thiopurine methyltransferase (TPMT) showed a low-activity, cyclophosphamide treatment was switched to mycophenolate mofetil 500 mg twice daily. Since then we have observed a progressive recovery in her renal function, which remains stable after 6 months with a creatinine of 134 µmol/L and UACR 10 mg/mmol (Figure 1). The prednisolone dose was tapered slowly to 5 mg/day.

Discussion

DM is an idiopathic acute inflammatory connective tissue disease characterized by inflammation of skeletal muscle and skin, with progressive symmetrical proximal myopathy. It is the commonest IIM [2] and affects women more frequently than men. Although the cause is not well known, it has been described to be associated with malignancies [3, 4], previous viral infections [5, 6] and autoimmune diseases [7], of which systemic lupus erythematosus (SLE) and Sjögren's syndrome are the most frequently observed. Renal involvement typically consists of acute tubular injury due to myoglobinuria secondary to rhabdomyolysis. Histologically, DM is a micro-angiopathy with an inflammatory infiltration of the muscles by B lymphocytes. The mechanism of injury is thought to be by activation and deposition of complement which causes lysis of endomysial capillaries and muscle ischaemia [2].

MPA is a subtype of primary systemic vasculitis associated with ANCA antibodies. The pathologic hallmark of ANCA-associated vasculitis is an intense necrotizing capillaritis.
Association between ANCA vasculitides and dermatomyositis

Although the histological expression is usually made of a destructive pauci-immune crescentic glomerulonephritis, focal and segmental sclerosis has been described as having an excellent prognosis with renal survival percentages of 93% at 5 years [8]. In our case, we should probably be chastised for not having biopsied earlier, particularly with the finding of the presence of blood and protein in the urine and positive pANCA with MPO specificity, although renal referral was made at the time of rapidly progressive renal failure 1 month later.

MPO-ANCA can also be positive in a subset of patients with collagen diseases such as MPA, SLE and progressive systemic sclerosis. No patients with polymyositis or DM have been previously reported to express MPO-ANCA [9, 10]. To our knowledge, this is the second case report of the pure association between these diseases. There is another finding of the presence of blood and protein in the urine and positive pANCA with MPO specificity, although renal referral was made at the time of rapidly progressive renal failure 1 month later.

Both diseases (MPO ANCA vasculitis and DM) have a very similar pathogenesis [12, 13]. CD8+ T-cell deficiency is a feature of many chronic auto-immune diseases, including DM [14] and MPA [15]. It has been proposed that CD8+ T-cell deficiency could be a predisposing factor with superimposed trigger stimuli (environmental factor [16], drugs [17] and viral [14] or bacterial [18] infections) acting on it. The result is an autoreactive B-cell accumulation in the target organ where they produce pathogenic auto-antibodies and provide co-stimulatory survival signals to autoreactive T cells which would otherwise die in the target organ by activation-induced apoptosis.

There is another, perhaps more plausible pathogenic pathway. Caproni et al. [19] reported a significant amount of MPO+ cells (neutrophil granulocytes) in Gottron's papules (pathognomonic lesions of DM). Given the timeline of events, the MPO ANCA antibodies formed in response to the presence of MPO+ neutrophils in DM lesions could subsequently have caused the renal disease. Furthermore, both diseases produce similar histological changes (i.e. a necrotizing micro-angiopathy with hyper-activation of B lymphocytes), but in different tissues.

Harpe et al. [20] reported that pulse cyclophosphamide regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen, and this at a reduced cumulative cyclophosphamide dose and with fewer cases of leukopaenia. However, in our case report, we used oral cyclophosphamide in accordance with the current standard of care.

The patient reported here developed signs of glomerulonephritis <2 months after being diagnosed with DM. This is the second case report of the association between MPA and DM. Although the overlap between these two diseases could be coincidental, we believe that some interactions between their pathways provide biological plausibility to this proposed overlap.

Conflict of interest statement. None declared.

References

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