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Clinical Report

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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 mmL/h ANCA positive with PR3 < 1.23 U/mL and MPO Abs 46.21 U/mL, serum creatinine 75 µmol/L. An electromyogram suggested widespread myopathy (Figure 1). Urinary dipstick was positive for protein (++), blood (++) and nitrites (+). At this point, DM was suspected and she was treated with prednisolone 40 mg and azathioprine 50 mg 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) 12.1×10^9/L, platelets 389×10^9/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

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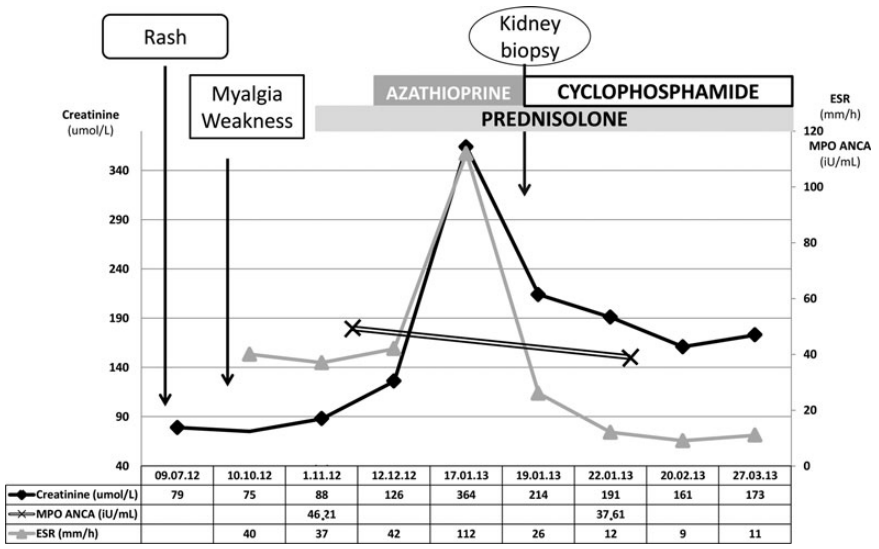

Fig. 1. Evolution of the patient during 6 months. In the graph, we represent the timing of the events: the rash developed in September 2012, myalgia and weakness in October 2012 and the kidney biopsy was performed in January 2013. We also represent the treatment timeline: prednisolone was introduced in November 2012 and continued until the end of the follow-up, Azathioprine was given between November 2012 and January 2013, and cyclophosphamide between January 2013 until the end of the follow-up. ESR, erythrocyte sedimentation rate; MPO-ANCA, myeloperoxidase–anti-neutrophil cytoplasmic antibody.

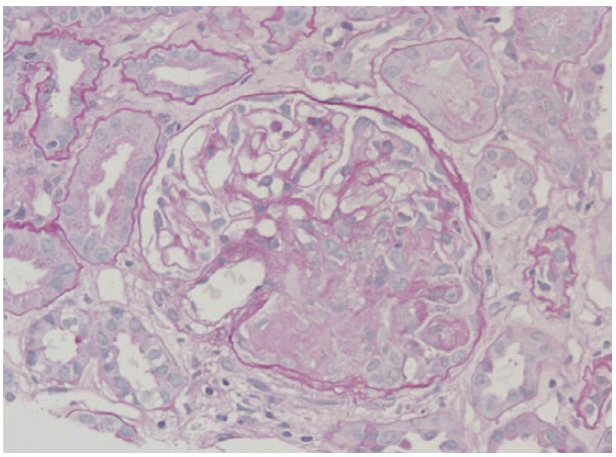

Fig. 2. Light microscopic examination of a kidney biopsy specimen. Segmental glomerular necrosis. Periodic acid Schiff base ×400 magnification.

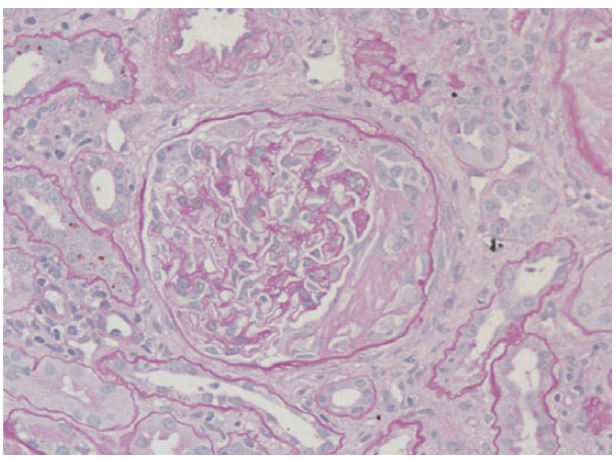

Fig. 3. Light microscopic examination of a kidney biopsy specimen, showing crescentic formation. Periodic acid Schiff base ×400 magnification.

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.

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 case report about this association [11]. However, this patient had other comorbidities (connective tissue disease including SLE, DM and systemic sclerosis), which may have played a more convincing role in the pathogenesis.

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) act. 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 also 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 hyperactivation 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

1. Kawai H, Kitagawa W, Suzuki N *et al*. Myeloperoxidase-antineutrophil cytoplasmic antibody-related crescentic glomerulonephritis after treatment for clinically amyopathic dermatomyositis: a coincidental combination or not? *Clin Exp Nephrol* 2011; 15: 577–581
2. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet* 2003; 362: 971–982
3. Hill CL, Zhang Y, Sigurgeirsson B *et al*. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 2001; 357: 96–100
4. Buchbinder R, Forbes A, Hall S *et al*. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. *Ann Intern Med* 2001; 134: 1087–1095
5. Ogoina D, Umar A, Obiako OR. Dermatomyositis associated with HIV-1 infection in a Nigerian adult female: a case report. *Afr Health Sci* 2012; 12: 74–76
6. Hoshino K, Shibata D, Miyagi T *et al*. Cytomegalovirus-associated gastric ulcers in a patient with dermatomyositis treated with steroid and cyclophosphamide pulse therapy. *Endoscopy* 2011; 43: E277–E278
7. Ng KP, Ramos F, Sultan SM *et al*. Concomitant diseases in a cohort of patients with idiopathic myositis during long-term follow-up. *Clin Rheumatol* 2009; 28: 947–953
8. Berden AE, Ferrario F, Hagen EC *et al*. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 2010; 21: 1628–1636
9. Merkel PA, Polisson RP, Chang Y *et al*. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. *Ann Intern Med* 1997; 126: 866–873
10. Chikazawa H, Nishiya K, Matsumori A *et al*. Immunoglobulin isotypes of anti-myeloperoxidase and anti-lactoferrin antibodies in patients with collagen diseases. *J Clin Immunol* 2000; 20: 279–286
11. Inada Y, Tanaka Y, Saito K *et al*. A case of mixed connective tissue disease with microscopic polyarteritis nodosa associated with perinuclear-antineutrophil cytoplasmic antibody and anti-glomerular basement membrane. *Nihon Rinsho Meneki Gakkai Kaishi* 1999; 22: 342–347
12. Chiricozzi A, Zhang S, Dattola A *et al*. New insights into the pathogenesis of cutaneous autoimmune disorders. *J Biol Regul Homeost Agents* 2012; 26: 165–170
13. Savage C. Pathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. *Clin Exp Immunol* 2011; 164(Suppl 1): 23–26
14. Pender MP. CD8+ T-cell deficiency, Epstein-Barr virus infection, vitamin D deficiency, and steps to autoimmunity: a unifying hypothesis. *Autoimmune Dis* 2012; 2012: 189096
15. Seta N, Kobayashi S, Hashimoto H *et al*. Characterization of autoreactive T-cell clones to myeloperoxidase in patients with microscopic polyangiitis and healthy individuals. *Clin Exp Rheumatol* 2009; 27: 826–829
16. Franchi L, Eigenbrod T, Nunez G. Cutting edge: TNF-alpha mediates sensitization to ATP and silica via the NLRP3 inflammasome in the absence of microbial stimulation. *J Immunol* 2009; 183: 792–796
17. Bonaci-Nikolic B, Nikolic MM, Andrejevic S *et al*. Antineutrophil cytoplasmic antibody (ANCA)-associated autoimmune diseases induced by antithyroid drugs: comparison with idiopathic ANCA vasculitides. *Arthritis Res Ther* 2005; 7: 1072–1081
18. Kallenberg CG. Pathophysiology of ANCA-associated small vessel vasculitis. *Curr Rheumatol Rep* 2010; 12: 399–405
19. Caproni M, Torchia D, Cardinali C *et al*. Infiltrating cells, related cytokines and chemokine receptors in lesional skin of patients with dermatomyositis. *Br J Dermatol* 2004; 151: 784–791
20. Harper L, Morgan MD, Walsh M *et al*. EUVAS investigators. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012; 71: 955–960

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