CASE REPORT

Antineutrophil cytoplasm antibody-positive pulmonary-renal syndrome in a patient with diffuse cutaneous systemic sclerosis

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SUMMARY

A 72-year-old male patient with known diffuse cutaneous systemic sclerosis (SSc) presented with severe haemoptysis and blood and protein in the urine. In light of his known interstitial lung disease, he had been repeatedly treated for recurrent community-acquired pneumonia. Immunological testing demonstrated a strongly positive perinuclear antineutrophil cytoplasm antibody with a high titre antimyeloperoxidase antibody. The patient was diagnosed with pulmonary-renal syndrome as a consequence of antineutrophil cytoplasm antibody-associated vasculitis. He started immediate plasmapheresis in combination with methylprednisolone, followed by cyclophosphamide and rituximab, with good clinical outcome.

BACKGROUND

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterised by fibrosis involving the skin and various internal organs including the lungs and the heart.¹ Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are multisystem autoimmune diseases characterised by necrotising inflammation of small vessels. They include granulomatosis with polyangiitis, (GPA), (formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis, (EGPA), (formerly Churg-Strauss syndrome).² There is a varying degree of organ involvement with frequent involvement of renal and respiratory systems.

Both AAV and SSc are uncommon with an incidence of approximately 10–20 per million population.^{3–4} The occurrence of a new diagnosis of AAV in patients with known SSc is thus extremely rare. Owing to the multisystem nature and presentation of SSc, it is possible that new symptoms of another multisystem disease such as vasculitis are attributed to SSc. This could lead to delayed or missed diagnosis of AAV, resulting in severe morbidity.

CASE PRESENTATION

A 72-year-old male patient of South Asian origin was transferred to our centre in January 2012 from a peripheral hospital with non-resolving severe haemoptysis and a new strongly positive perinuclear-ANCA (P-ANCA). He had been started on pulsed methylprednisolone at the referring hospital for a presumed diagnosis of MPA. His medical history included a diagnosis of diffuse cutaneous SSc (dcSSc) in 2002. Manifestations of this

included symptoms consistent with Raynaud's phenomenon and the findings of sclerodactyly and perioral restriction, in addition to oesophageal dysmotility for which he was treated with oesophageal dilatation in 2011. He was also diagnosed with SSc-associated interstitial lung disease (ILD). ILD was reported to be stable and he was under regular follow-up for this, but on no medication. He had a positive antiscleroderma 70 (Scl-70) antibody at presentation in 2002, and ANCA was negative. Repeat ANCA testing in 2008 remained negative. He had previously been diagnosed with monoclonal gammopathy of undetermined significance (of unknown duration) and had a coronary artery bypass graft in 2006.

In the history of the presenting complaint, the patient described a progressive cough productive of fresh blood of 10 days duration, on the background of shortness of breath and fevers for the preceding 2 months. In light of his ILD, he had been repeatedly treated for a recurrent community-acquired pneumonia and was on antibiotic treatment at the time of admission, in addition to irbesartan 75 mg and aspirin 75 mg once daily. He also reported marked weight loss of 10 kg, a productive cough and fatigue in the last year. He had experienced no upper airway symptoms, joint pain, abdominal symptoms or rashes. On examination, he had no fever, hypertensive (blood pressure 170/90 mm Hg) and had physical signs consistent with dcSSc. On auscultation of the chest there were bilateral posterior end-inspiratory crepitations. There was mild peripheral oedema, but he was clinically euvoelaemic. He underwent investigation including bronchoscopy at the referring hospital, but then experienced severe haemoptysis and was transferred to our centre.

INVESTIGATIONS

Investigations revealed haemoglobin 9.3 g/dL, mean corpuscular volume 87.7 fL, white cell count $7.9 \times 10^9/L$, platelets $345 \times 10^9/L$, erythrocyte sedimentation rate (ESR) 128 mm/h and C reactive protein 22.0 mg/L. The electrolytes were normal with creatinine 67 $\mu\text{mol/L}$ giving him an estimated glomerular filtration rate (GFR) of $>59 \text{ mL/min}$. Urine dipstick was positive for both blood and protein, with a urinary protein:creatinine ratio (PCR) of 114 mg/mmol (normal $<20 \text{ mg/mmol}$) and equating to approximately 1.1 g/24 h. Immunology testing was repeated and revealed a strongly positive P-ANCA with antimyeloperoxidase (MPO)

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antibody of 545 AU/mL (normal 0–25 AU/mL). There was no evidence of hypocomplementaemia (C3 1.20 g/L, C4 0.17 g/L) and antiglomerular basement membrane (GBM) antibody was negative. High-resolution CT (HRCT) in the referring hospital demonstrated new ground glass shadowing in both lower lobes consistent with either infection or haemorrhage (figure 1). Lung function tests revealed raised carbon monoxide transfer coefficient (KCO) suggestive of alveolar haemorrhage. Bronchoscopy had demonstrated no overt signs of bleeding, and cultures were reported as negative. Sputum culture for mycobacterium tuberculosis and an interferon- γ release assay were reported as negative. The patient was transferred to our centre on aspirin and irbesartan, and on arrival he was hypertensive. In view of this and his underlying Ssc, the risk of bleeding following renal biopsy was deemed too great to carry out this procedure. He was unstable from a respiratory perspective, with a low haemoglobin, abnormal chest radiograph and raised KCO. Bronchoscopy was thus not repeated at our centre and he was started on therapy without delay.

DIFFERENTIAL DIAGNOSIS

The patient was diagnosed with pulmonary-renal syndrome (PRS) as a consequence of AAV. The multisystem features over a period of months, along with the elevated ESR, anaemia, haematuria and proteinuria, absence of upper airway symptoms and a positive MPO-ANCA, strongly supported the diagnosis of MPA. Recurrent pneumonias on a background of ILD, including a possible fungal pneumonia, were in the differential diagnosis. Scleroderma renal crisis was also a differential on presentation, in view of the hypertension and urinary findings.

TREATMENT

The patient started immediate plasmapheresis in combination with methylprednisolone, the first dose of which had been administered at the referring hospital, followed by oral prednisolone. He underwent a total of seven plasma exchanges and did not require ventilatory support. He received six cycles of intravenous cyclophosphamide every 2 weeks, and two infusions of rituximab in an attempt to reduce his cumulative steroid dose.

Figure 1 High-resolution CT showing ground glass shadowing in the left lower lobe consistent with either infection or haemorrhage.

He was started on prophylaxis for TB which included isoniazid 150 mg once daily and 50 mg pyridoxine weekly and on three times weekly cotrimoxazole for *Pneumocystis jiroveci*. He was covered with piperacillin/tazobactam and fluconazole pending results of cultures sent on bronchoscopy at the referring hospital.

OUTCOME AND FOLLOW-UP

In the following weeks, the patient improved clinically and experienced no further haemoptysis. His creatinine remained within the normal range and no further haematuria and proteinuria were detected. He is currently under regular follow-up in our vasculitis clinic and is well 1 year from initial presentation.

DISCUSSION

This case illustrates a new diagnosis of AAV in a patient with SSc. Interestingly, the diagnosis of AAV was only made following presentation with severe haemoptysis. With a background of ILD the respiratory and constitutional symptoms in the preceding months had been attributed to a complicated community-acquired pneumonia. However, in retrospect it seems likely that these symptoms were manifestations of AAV. The ILD preceded ANCA positivity making it less likely that this was a manifestation of AAV.⁵ A renal biopsy would have been a valuable investigation with regard to differentiating between ANCA-associated glomerulonephritis and scleroderma renal crisis; however, there is a high risk of bleeding in patients with scleroderma and in particular patients on aspirin who are hypertensive. The decision was made that risk outweighed benefit in this case and that, given the likely diagnosis of severe PRS in the context of AAV delay in treatment with plasma exchange and cyclophosphamide would be detrimental to the patient.

In patients with SSc, a second insult to the vasculature in the form of AAV is a rare but recognised complication. A review in 2011 reported only 40 patients in the English literature with SSc presenting with AAV.⁶ Rapidly progressive glomerulonephritis was found to be the most common clinical manifestation (83%), 28% suffered from alveolar haemorrhage, 13% from necrotising vasculitis resulting in limb ischaemia and 10% from a vasculitic skin rash. Alveolar haemorrhage (AH) is a heterogeneous syndrome with multiple causes. Vasculitis is reported as the third most common cause of AH requiring intensive care support (19% of patients), after thrombocytopenia (27%) and sepsis (22%).⁷ AAV is the most common immune-mediated cause of AH (80%), with other vasculitides, including systemic lupus erythematosus and anti-GBM disease accounting for 20%. One-quarter of patients with AAV develop AH, which when mild is associated with a good outcome, but mortality rises to 50% for cases with respiratory failure requiring ventilator support.

Treatment often includes plasmapheresis and immunosuppression and follows similar regimens to those used for other presentations of AAV.⁸ The management of this case was complicated by the underlying diagnosis of SSc. It is known that corticosteroids may worsen the prognosis and symptoms of SSc.⁹ In an attempt to minimise cumulative corticosteroid dose, our patient was treated with a rapidly reducing dose, in addition to rituximab. This was in accordance with our published local protocol.¹⁰ Although rare, the possibility of AAV occurring in patients with SSc should always be considered and treated promptly.

Learning points

- ▶ In patients with autoimmune diseases developing new symptoms, physicians should remain alert to the possibility of an additional autoimmune entity.
- ▶ Although rare, the coexistence of systemic sclerosis (SSc) and antibody-associated vasculitides (AAV) is well reported.
- ▶ Alveolar haemorrhage is the second most common clinical presentation of patients with AAV in with SSc.
- ▶ Lung haemorrhage associated with pulmonary-renal syndrome (PRS) is a medical emergency requiring urgent treatment.
- ▶ Any patient presenting with haemoptysis should be tested for an antineutrophil cytoplasm antibody, since AAV is the commonest cause of immune-mediated PRS.

Contributors LT was responsible mainly for the preparation of the manuscript. CDP and AT were responsible for reviewing patient information and also contributed to preparation of the manuscript.

Competing interests None.

Patient consent Obtained.

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