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CASE REPORT

A Case of Microscopic Polyangiitis Following Mycoplasma Infection in a Patient with MPO-ANCA Positive Pulmonary Fibrosis

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ABSTRACT

Background: Microscopic polyangiitis is a vasculitic disease that may result in a pulmonary renal syndrome. Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is strongly associated with infection.

Case Summary: We describe a case of microscopic polyangiitis that developed in a patient with MPO-ANCA positive pulmonary fibrosis following infection with mycoplasma. A renal biopsy was undertaken following the detection of microscopic hematuria during follow-up but no abnormal findings were evident. The MPO-ANCA titer increased following infection with mycoplasma pneumonia and a second renal biopsy demonstrated crescentic glomerulonephritis. The degree of pulmonary fibrosis was unaffected.

Discussion: The present case suggests that the mycoplasma infection triggered the elevation of MPO-ANCA titer and provoked glomerulonephritis in a patient with MPO-ANCA positive IPF. This case indicates the importance of testing for MPO-ANCA at the time of initial diagnosis, performing urinalysis and examining the urine sediment during follow-up and being alert to the potential onset of vasculitis in cases of pulmonary fibrosis.

KEY WORDS

ANCA, microscopic polyangiitis, mycoplasma, pulmonary fibrosis

INTRODUCTION

Myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) is frequently positive in patients with microscopic polyangiitis and allergic granulomatous angiitis (Churg-Strauss syndrome). In addition, the clinical course of MPO-ANCA positive patients is frequently complicated with lung involvement such as interstitial pneumonia or alveolar hemorrhage.[1] We report a case of microscopic polyangiitis (MPA) that developed after mycoplasma infection in a 47-year-old woman with a history of MPO-ANCA positive pulmonary fibrosis. To our knowledge, cases of MPA triggered by mycoplasma pneumonia have not been previously described.

CASE REPORT

A 47-year-old woman with a one-year history of a dry cough was referred to our hospital in September 1995. The chest X-ray showed bilateral reticular shadowing affecting the lower lung fields. She was a non-smoker and had no history of occupational inhalation of stone dust. She was hospitalized for detailed examination but, despite numerous investigations, the etiology of the lung fibrosis was not determined. She was in a stable condition at that time and was therefore followed up without therapy being initiated. However, she later presented with shortness of breath on exertion (Hugh- Johns II°) since October 2004 and was admitted to hospital for further investigations in April 2005.

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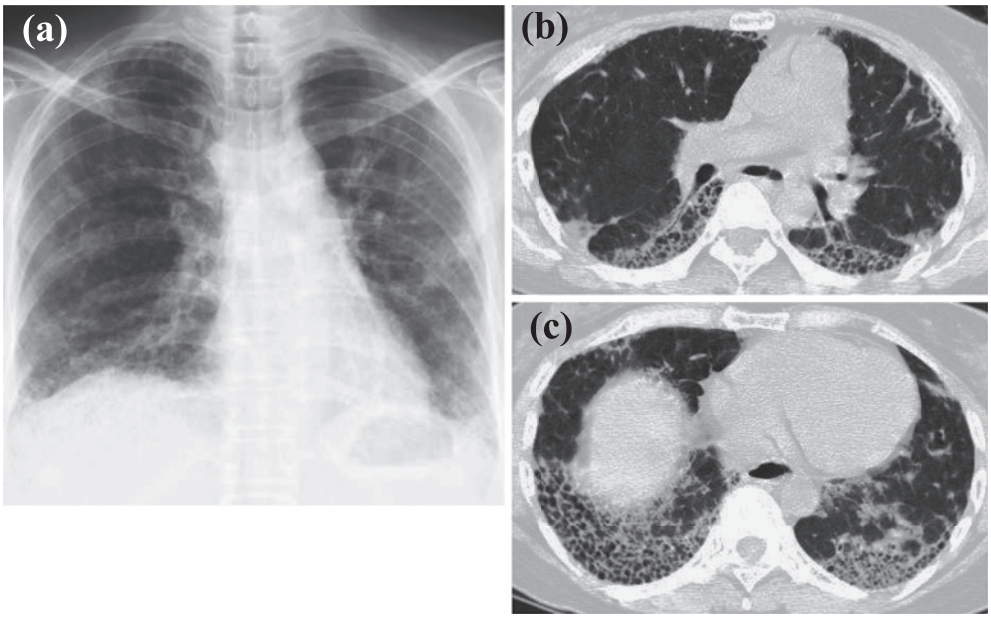

Fig. 1 **a**: Chest X-ray film obtained upon admission in April 2005 showing the volume loss and reticular shadows especially in the lower lung fields. **b**, **c**: Chest CT scan shows volume loss of both lower lobes and reticular shadows with honeycomb changes especially in the two lower lobes.

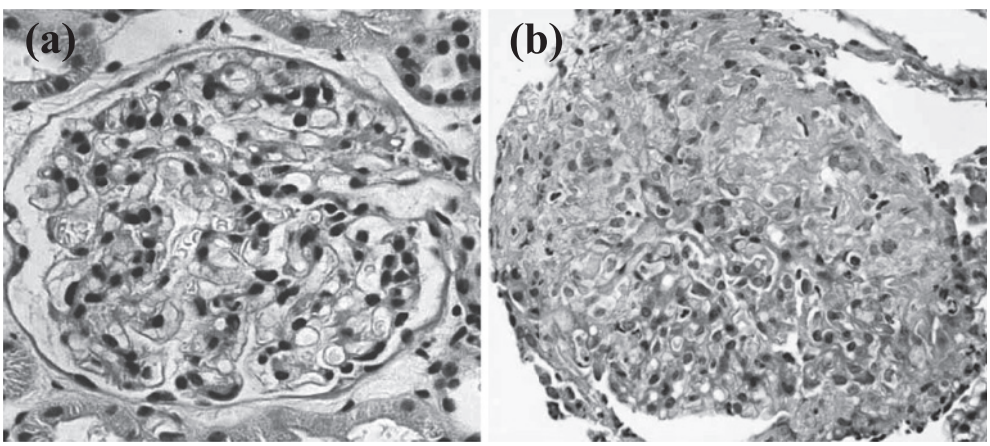

Fig. 2 **a**: Pathological findings of the 1st renal biopsy. There were no special findings. **b**: Pathological findings of the 2nd renal biopsy. Necrotising glomerulonephritis with crescent formation and proliferation of cells and vessels were detected (H&E staining, original magnification ×400).

A physical examination of the chest on admission revealed bilateral inspiratory fine crackles in the middle and lower zones with no peripheral clubbing evident. The oxygen saturation was 96% and she was afebrile. The chest X-ray film obtained on admission showed reticular shadows and loss of volume especially affecting the lower lung fields (Fig. 1a). Chest computed tomography (CT) showed volume loss of the lower lobes and reticular shadows with honeycomb changes especially in the lower lobes (Fig. 1b, 1c). Urinalysis was unremarkable at the time of admission.

The results of respiratory function tests were as follows: vital capacity (VC) 1.74 L (64.2% predicted), forced expiratory volume in one second (FEV_1) 1.48 L (60.4% predicted), residual volume (RV) 1.86 L (78.7% predicted), total lung capacity 2.72 L (63.1% predicted), carbon monoxide diffusing capacity of the lung 12.07 ml/min/mmHg (53.5% predicted).

Arterial blood gas analysis on room air revealed normal values: PaO_2 90.4 Torr and $PaCO_2$ 43.6 Torr. Peripheral blood tests were as follows: C-reactive pro-

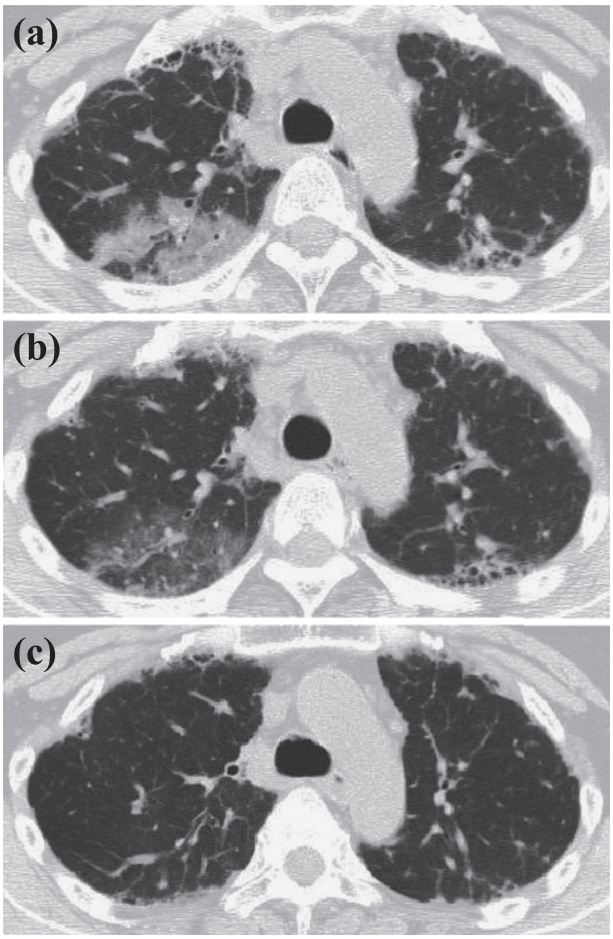

Fig. 3 **a**, **b**, **c**: The course of the chest CT after mycoplasma infection. Lung fibrosis had not changed.

tein 0.2 mg/dl with normal serum electrolytes, renal function and liver function. Notable laboratory values included the following: serum KL-6 601 U/μl (normal: <500 U/μl); SP-D 100 ng/ml (normal: <110 ng/ml); SP-A 35.4 ng/ml (normal <43.8 ng/ml); IgG 2530 mg/dl; positive anti-nuclear antibody (1 in 80, speckled type); MPO-ANCA increased at 158 EU (normal range; <10.0 EU). A bronchoscopy with bronchoalveolar lavage was performed through the right S^8 bronchus and revealed a slight increase in neutrophils: 4.3×10^5 cells/ml (macrophages 74.3%, lymphocytes 5%, neutrophils 5%, eosinophils 1.2%). She was reviewed by our Nephrology colleagues in view of the positive MPO-ANCA. It was felt that there was no indication for a renal biopsy and recommended that urinalysis should be monitored. Microscopic hematuria first appeared a month after discharge from hospital although she had no symptoms. A renal biopsy was performed in July 2005 (Fig. 2a) but there were no specific findings.

She was incidentally hospitalized with a bone fracture in August 2006. Prior to discharge she experienced a high fever and dry cough and the PaO_2 on blood gas dropped to 62.2 Torr. Consolidation in the right S^2 was detected on the chest CT (Fig. 3a) and the mycoplasma IgM was positive. She was subsequently diagnosed with a mycoplasma pneumonia. Treatment consisted of 400 mg gatifoxacine per day. The dry cough and hypoxia promptly recovered and the consolidation in right S^2 on chest CT improved. However, the patient remained febrile (38-39℃) and the CRP level remained high. The urinary β_2 microglobulin increased from 857 μg/l to 8062 μg/l and the MPO-ANCA titer increased from 83 EU to 379 EU. Proteinuria then appeared, although it was very slight. We thought that this might represent the onset of glomerulonephritis.

The patient was transferred to the Department of Nephrology in October 2006 and a second renal biopsy was performed. The biopsy demonstrated a necrotising glomerulonephritis with crescent formation and cellular proliferation (Fig. 2b). The clinical manifestations of vasculitis other than glomerulonephritis were scarce with no involvement of the skin, nervous system or gastrointestinal tract evident. The first 3-day pulse of methylprednisolone (m-PSL) was commenced on October 11 and the 2nd pulse of m-PSL was administered a week later. Oral prednisolone (PSL) therapy (40 mg/day) was started at the same time. Pulsed cyclophosphamide was added on November 2. The fever and inflammation was promptly relieved. The urinary abnormalities normalized 2 weeks after treatment with a reduced urinary level of β_2 microglobulin. In addition, the titer of MPO-ANCA promptly fell from 379 IU/ml to 77 IU/ml after 1 month of treatment.

The PSL was tapered to 5 mg per day and she visits our hospital regularly for follow-up. There has been no change in the serum levels of KL-6 and SP-D and the chest CT findings remained unchanged indicating no progression in the degree of lung fibrosis (Fig. 3b, 3c).

DISCUSSION

Infection has been suggested as a trigger of ANCA-associated glomerulonephritis since the discovery of ANCA. The first report concerning ANCA-associated necrotising glomerulonephritis was in 1982[2] with Ross River virus (a group A Arbovirus) being suggested as a potential cause of ANCA-associated nephritis. A variety of cases involving ANCA and infection have been reported such as ANCA-associated mPA following a wound infection,[3] mPA triggered by fungal infection[4] and mPA associated with E Coli pyelonephritis.[5] It was also suggested that acute or chronic Chlamydia pneumoniae infection may increase the risk of MPO-ANCA associated glomerulonephritis.[6]

Nada *et al.*[7] described two patients with an initial diagnosis of idiopathic pulmonary fibrosis who were

later correctly diagnosed as having a pulmonary-renal syndrome and microscopic polyarteritis. Review of the two lung biopsy specimens demonstrated a small-vessel vasculitis. These cases illustrate the necessity to consider vasculitis in the differential diagnosis of idiopathic pulmonary fibrosis as it can occur as a feature of microscopic polyarteritis.

This would suggest that repetitive MPO-ANCA induced damage to the alveolar microvascular endothelium may cause pulmonary fibrosis. In addition, TNF-α and IL-6 were detected in the sera in parallel with the MPO-ANCA titers.[8] This suggests that MPO-ANCA antibodies and inflammatory cytokine such as TNF-α and IL-6 induced by the infection may activate neutrophils. MPO can be released from neutrophils and may play an important pathogenic role in glomerular capillary necrosis leading to crescentic glomerulonephritis. The amount of MPO proved to be especially high in the cellular crescent phase of disease and correlated with anti-MPO antibodies.[9]

In the present case, it is unclear exactly when the patient MPO-ANCA became positive. The pulmonary fibrosis preceded the development of microscopic hematuria by more than 10 years. It is also difficult to diagnose when the kidney disease first occurred. The hematuria might be a warning sign and the mycoplasma infection could have activated the ANCA-associated vasculitis. We should have considered a mycoplasma pneumoniae-associated glomerulonephritis in the differential diagnosis. There are some reports of Mycoplasma pneumoniae-associated renal disease such as cresescentic glomerulonephritis[10,11] or IgA nephropathy.[12] The MPO-ANCA was negative in these cases. Determining the level of ANCA might be useful in the differentiation of kidney disease that may follow mycoplasma infection.

This case can be ANCA-associated nephritis with preceding pulmonary fibrosis. Mycoplasma infection could trigger an elevation of MPO-ANCA level and lead to glomerulonephritis. We suggest that it is necessary to examine MPO-ANCA at the time of the initial diagnosis, to monitor urinalysis and the urine sediment during follow-up and to be alert to the possibility of vasculitis in cases of pulmonary fibrosis.

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