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Anti-Jo-1 Syndrome presenting as cryptogenic organizing pneumonia

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A 50-year-old Chinese lady presented with subacute onset of dyspnoea, bilateral infiltrates on chest X-ray and type I respiratory failure. There were minor symptoms of arthralgia and myalgia. Subsequent investigations confirmed that she had organizing pneumonia, polymyositis and serum anti-Jo-1 antibody. Treatment with corticosteroids resulted in prompt improvement of the respiratory condition and myositis.

Introduction

The anti-Jo-1 antibody (anti threonyl-tRNA synthetase) is found in about 25% of patients with adult polymyositis (1). It is associated with interstitial lung disease, usually fibrosing alveolitis (2,3). The association of polymyositis and organizing pneumonia (bronchiolitis obliterans organizing pneumonia, BOOP), have been well reported (4), but the association of polymyositis, anti-Jo-1 antibody and organizing pneumonia has rarely been described. We report a patient who presented with subacute respiratory failure due to organizing pneumonia, in whom investigations confirmed inflammatory myositis and the presence of serum anti-Jo-1 antibody.

Case Report

A 50-year-old Chinese female, a non-smoker with unremarkable past medical history, presented with progressive dyspnoea over 4 days. About 3 weeks prior to presentation, she noted mild polyarthralgia of both hands, elbows and shoulders. She then developed fever and unproductive cough for 2 weeks, and chest X-ray showed a small right pleural effusion with bilateral basal infiltrates. She was given erythromycin for 1 week with no improvement.

On examination at admission, the patient was tachypnoeic at rest. There was central cyanosis, no pallor, lymphadenopathy, clubbing, muscle weakness or skin rash. The fingers were slightly swollen but there was no definite evidence of synovitis. Temperature was elevated at 38°C. On auscultation of the chest, there were bilateral mid and late inspiratory crepitations at both lung bases. Other systems were normal.

Chest radiograph on admission showed bilateral lower lobe infiltrates, worse on the right side, and they had progressed slightly compared with 2 weeks previous. Blood gases showed type I respiratory failure with PaO_2 of 7·6 kPa, $PaCO_2$ of 4·2 kPa, pH 7·4 in room air. The blood counts were normal except for a slightly elevated white cell count of $12{\cdot}4 \times 10^9\,l^{-1}$, with 81% neutrophils. The erythrocyte sedimentation rate was 55 mm in the first hour. Renal and liver function tests were normal. After septic work-up, the patient was treated empirically with doxycycline, sulbactam/ampicillin and ceftazidime.

She deteriorated with worsening hypoxaemia. Symptoms of myalgia of the upper arms developed, and the serum creatine kinase (CK) performed on the third day of hospitalization was elevated at $889\,IU\,l^{-1}$ with normal MB fraction. This rose to $2190\,IU\,l^{-1}$ over the next few days. The septic work-up, anti-nuclear factor, rheumatoid factor, anti Sm, Ro, La, anti-ribonuclear protein, and anti-neutrophil cytoplasmic antibody were all negative. In view of the elevated CK, the diagnosis of polymyositis with interstitial lung disease was considered, and serum was sent to be tested for anti-Jo-1 antibody.

Fiberoptic bronchoscopy showed no endobronchial lesion. Bronchoalveolar lavage was negative for micro-organisms. Transbronchial lung biopsy showed non-specific features of a mixed polymorphonuclear and lymphocytic inflammatory cell

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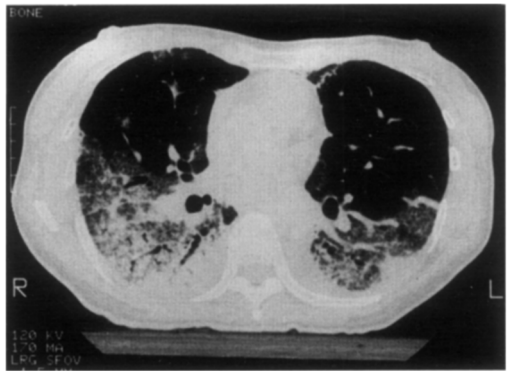

Plate 1 HRCT of the lower lungs shows subpleurally-located consolidation with air-bronchogram effect, and diffuse lower lobe 'ground-glass' opacification which are well demarcated from the relatively normal lung located anteriorly.

infiltration of the interstitium with an abundance of foamy macrophages. A muscle biopsy of the left deltoid was performed but preliminary findings were non-contributory.

High resolution computed tomography (HRCT) of the thorax showed bilateral air-space consolidation with air-bronchograms, located predominantly subpleurally over both lower lobes. There was also increased 'ground-glass' opacification more diffusely distributed in the lower lobes. The margin between normal lung and the abnormal parenchymal zones were well demarcated (Plate 1).

The patient continued to deteriorate in her ventilatory status. She also developed deranged liver function, and hyponatraemia due to inappropriate antidiuretic hormone secretion. On the tenth day after admission, methylprednisolone 80 mg day^{-1} was started on the presumptive diagnosis of rapidly progressing fibrosing alveolitis or organizing pneumonia. Three days later, she underwent a mini-thoracotomy and wedge biopsy, which showed typical changes of organizing pneumonia, with fibroblastic tissue forming myxoid plugs in the bronchioles and alveolar ducts, with minimal interstitial fibrosis. Stains and cultures for micro-organisms were negative.

The muscle biopsy, on further sectioning, showed dense perivascular lymphocytic infiltration around a capillary, with atrophy of the type II fibres and no evidence of vasculitis. The findings were consistent with an inflammatory myopathy. The analysis of serum for anti-Jo-1 antibody showed a positive result.

The patient improved significantly about 5 days after initiation of steroids with gradual resolution of the chest radiographic changes over the following 2 weeks. Azathioprine was added while steroids were tapered. Creatine kinase level normalized at the ninth week. The patient was asymptomatic with regards to her respiratory and muscle status, but developed roughening and cracking of the skin of both hands, typical of 'mechanic's hands', as described in the anti-Jo-1 syndrome, which required frequent application of topical steroid.

Discussion

The association of polymyositis/dermatomyositis and interstitial lung disease has been well documented since its original description in 1956. Most reports refer to the lung involvement as 'pulmonary fibrosis'. In the few studies that addressed the pulmonary pathohistological findings, the interstitial lung disease in polymyositis/dermatomyositis included fibrosing alveolitis, organizing pneumonia, diffuse alveolar damage and cellular interstitial pneumonitis (4). Hence the association of organizing pneumonia and polymyositis is not new. However, the anti-Jo-1 antibody status in most of these cases was not known. Anti-Jo-1 antibody is an auto-antibody (anti ENA) directed at the cellular enzyme histidyl-tRNA synthetase. It is found in 10–50% of patients with myositis but not in other myopathies and rarely in other connective tissue diseases (1–3,5). The finding of anti-Jo-1 antibody is associated with the presence of interstitial lung disease, usually fibrosing alveolitis (UIP), and arthritis (1–3,5). Organizing pneumonia as the form of lung involvement in the anti-Jo-1 myositis has only been rarely reported (6). The presence of anti-Jo-1 antibody and interstitial lung disease may even precede the onset of polymyositis (2,6). It is reasonable to postulate that fibrosing alveolitis and organizing pneumonia are different manifestations of an underlying immunological disease. While its role in the pathogenesis is unclear, it seems unlikely that the anti-Jo-1 antibody is directly responsible for causing disease (5).

In our patient, pulmonary symptoms dominated the clinical picture, with muscle and joint symptoms being minor complaints. Myalgia was not severe and muscle weakness was not clinically apparent, and could have been further masked by incapacitation from respiratory failure. The CK was only moderately elevated. These features are unusual for anti-Jo-1 syndrome in which the myositis is characteristically severe, and led to difficulty in differentiating infective pneumonia with rhabdomyolysis from non-infective interstitial lung disease associated with polymyositis. The lung HRCT findings were

interesting in that areas of dense consolidation with air-bronchograms as well as ground-glass opacification, and clear demarcation of normal and abnormal lung tissue were demonstrated. These features distinguish organizing pneumonia from the better known CT appearance of ground-glass and honeycombing typical of fibrosing alveolitis (7), but they can also simulate infective pneumonia. Although a diagnosis of organizing pneumonia was subsequently established on lung biopsy, histological features cannot usually differentiate 'cryptogenic' organizing pneumonia (COP) and organizing pneumonia associated with different disease conditions. The presenting symptoms and the early course of our patient were quite compatible with that of COP (8,9). Hence, this case highlights the importance of a careful search for associated connective tissue disorder, including polymyositis or dermatomyositis, in patients presenting with 'atypical pneumonia'.

In polymyositis, those presenting with organizing pneumonia have a better prognosis than those presenting with fibrosing alveolitis (4), while polymyositis associated organizing pneumonia probably carries a worse prognosis than cryptogenic organizing pneumonia (4,9), and the presence of serum anti-synthetase antibody is further associated with lesser response to steroids, flair of disease when steroid dose is tapered and lower survival (1,5,9). These distinctions would therefore carry therapeutic implications – while cryptogenic organizing pneumonia could well be treated with corticosteroids alone (8,9), those patients with organizing pneumonia and polymyositis, in particular anti-Jo-1 positive, may require additional immunosuppressive therapy (1,5). The CK levels and anti-Jo-1 antibody should therefore be simple additions to the usual investigations for 'idiopathic' interstitial lung diseases since the muscle symptoms may be overshadowed by respiratory manifestations, and be further complicated if steroids have been given for treatment.

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