We report a case of a patient with anti-PL-12 antibody accompanied by interstitial pneumonia and severe pulmonary hypertension. At first presentation, hyperkeratotic skin lesions were found, although the diagnosis of CVD was not conclusive. Lung histology showed diffuse fibrosing interstitial pneumonia predominantly in the subpleural regions. During the seven-year follow-up period, severe pulmonary hypertension developed, although the progression of lung fibrosis was relatively limited. Anti-PL12 antibody was detected, and therefore the patient was diagnosed as having antisynthetase syndrome. Lung histology and pulmonary arteriogram suggested that vascular involvement of the disease contributed to the development of severe pulmonary hypertension.

Key words: antisynthetase syndrome, interstitial pneumonia, pulmonary hypertension

Introduction

Collagen vascular disease (CVD) is considered to be a major cause of interstitial pneumonia, and assessment of co-morbid CVD is necessary for the evaluation of patients with interstitial pneumonia (1). The presentation of interstitial pneumonia precedes other organ involvement in some patients with CVD (2), and the diagnosis is challenging in such patients. In such situations, the detection of a specific auto-antibody is sometimes helpful for the diagnosis of CVD.

The antisynthetases are the most widely recognized myositis-specific autoantibodies. They are directed at aminoacyl-tRNA synthetases (ARS), cytoplasmic enzymes that catalyze the binding of amino acids to their cognate tRNAs for incorporation into growing polypeptide chains. Among the antisynthetases, anti-Jo-1 antibody (anti-histidyl-tRNA synthetase antibody) was the first to be discovered (3), followed by anti-PL-7 (4), anti-PL-12 (5), anti-EJ, anti-OJ (6), and anti-KS (7) antibodies. In patients with polymyositis/dermatomyositis (PM/DM) carrying the antisynthetases, an increased frequency of interstitial lung disease (50–100% versus 10%) and arthritis (60–100% versus 30%) compared to patients without the antibody has been reported (8). Other characteristic clinical features include Raynaud’s phenomenon, fever, and hyperkeratotic skin lesions called mechanic’s hand (9, 10). The disease characterized by positive antisynthetase, accompanied by some of these clinical features is called antisynthetase syndrome.

Anti-PL-12 antibody (anti-alanyl-tRNA synthetase antibody) is one of the antisynthetases; an association of anti-PL-12 antibody with a high frequency of interstitial lung disease, myositis, arthritis, skin rash, Raynaud’s phenomenon, and fever has been reported (11–14), although the number of patients described in such reports was limited.

Pulmonary hypertension is a life-threatening complication of patients with interstitial pneumonia. However the incidence of pulmonary hypertension in patients with antisynthetases is unknown.

Here, we report a patient with anti PL-12 antibody complicated by interstitial pneumonia and severe pulmonary hypertension.
Case Report

In August 1994, a 44-year-old Japanese man underwent a pulmonary function test as part of his annual medical check-up, and he was found to have a reduced vital capacity (%VC 73%). However, he did not visit a hospital because of the absence of symptoms. In April 1996, he noticed xerosis of the fingertips, and on August 1996, he was first found to have abnormal opacities on chest X-ray. Two months later, he suffered from cough, and in March 1997, he visited a hospital because of dyspnea on exertion (Fletcher-Hugh-Jones II°) and exacerbation of the cough. At this time, chest computed tomography revealed reticular and ground glass opacities at the level of the bilateral lung bases, and his pulmonary lesion was diagnosed as interstitial pneumonia. He was subsequently admitted to our hospital in May 1997 for further investigations and treatment of interstitial pneumonia.

Physical examination revealed a body temperature of 36.6 °C, blood pressure of 104/62 mmHg, and pulse rate of 94/min with a regular rhythm. Though hyperkeratosis of the fingers was found, it was not specific for any CVD. There was no other skin lesion such as Gottron’s sign or Heliotrope rash. Finger clubbing and Raynaud’s phenomenon were not apparent. In the lung auscultation, fine crackles were audible in the bilateral lower lungs. Heart auscultation, abdominal and neurological examinations were normal. There was no superficial lymph node swelling. The patient had no history of smoking or previous illnesses. The laboratory tests (Table 1) showed elevation of WBC (10,900/µl), CRP (2.2 mg/dl), and erythrocyte sedimentation ratio (38.2 mm/h). Rheumatoid factor was significantly elevated to ×1,280 (normal range: <×40), although antinuclear antibody and autoantibodies for CVD were negative.

Arterial blood gas measurement revealed mild hypoxia (PaO₂ 78.6 mmHg). A pulmonary function test showed mild reduction of vital capacity (%VC 70.5%). Bronchoalveolar lavage fluid showed an increased total cell recovery (2.68×10⁵/ml), without an increase of lymphocyte ratio (lymphocytes 10.7%), and a slight increase in the neutrophil ratio (neutrophils 9.3%). The pathologic findings obtained from transbronchial lung biopsy were not diagnostic. The electrocardiogram revealed no abnormality. The findings on chest X-ray at admission (Fig. 1A) showed a reduced volume of the bilateral lower lungs with mild reticular shadows. Chest computed tomography showed ground glass opacities and reticular shadows at the bilateral lung bases, while other areas of the lung fields were almost clear (Fig. 2A). In September 1997, a videoscope-assisted lung biopsy was performed, and three specimens were sampled from the left S1+2, the left B8, and the left B9 regions. Lung tissues from the 3 biopsy sites showed fibrotic changes with loss of normal alveolar structure, predominantly in the subpleural and periacinar regions. The fibrotic lesions showed gradual changes from fibrosis with loss of normal alveolar structures, to thickened...
Figure 1. Chest X-ray (A, April 1997 (on admission); B, May 2004). A: On admission, reduced volume of bilateral lungs, and elevation of diaphragm was observed. B: During the follow-up period of seven years, linear and reticular shadows developed in the bilateral lower lungs, however, the lesions were minimal in the upper and middle lung fields.

Figure 2. Chest computed tomography (A, Right lower lobe, April 1997; B, Right lower lobe, May 2004). During the follow-up period, ground glass opacity accompanied by traction-bronchiecasis developed along the broncho-vascular bundles, and subpleural bullae were also found.
and then to normal alveolar walls. Aeration of alveolar regions was about 25% of normal, while the ratio of normal to total alveolar walls in the lung specimen was about 3%. Fibroblastic foci and lymphoid follicles were not marked. These findings are summarized as nonspecific interstitial pneumonia (NSIP), mixed cellular and fibrosing pattern (Fig. 3A). Muscular pulmonary arteries showed mild luminal stenosis (Fig. 3B). The patient was followed in our hospital without treatment until March 1998, by which time vital capacity was decreased to 43.6% and supplemental oxygen treatment was necessary, due to the development of hypoxemia (Table 2). At this time, pirfenidone was prescribed for the treatment of pulmonary fibrosis, but discontinued due to the side effect of fever. Low-dose prednisolone (10 mg/day) in combination with azathioprine was then started. During this period, pulmonary arterial pressure measured using a Swan-Ganz catheter was normal. In December 1998, acute exacerbation of the interstitial pneumonia occurred, and mechanical ventilation was needed to rescue the patient. After three months of steroid treatment including pulse therapy, the patient recovered. In August 2000, right ventricular overload was detected by echocardiogram, and therefore treatment with calcium channel blocker and diuretics was started. On the occasion of a second acute exacerbation in January 2001, severe pulmonary hypertension with right ventricular heart failure was noted. However, after treatment with dopamine and diuretics, the patient recovered again, and the extent of subsequent pulmonary hypertension assessed by echocardiogram was mild. Prostacyclin (beraprost sodium) was also administered, but discontinued due to the side effect of flushing. During the clinical course, pulmonary fibrosis with traction bronchiectasis and the formation of subpleural bullae progressed (Fig. 2B), and the patient suffered twice from right lung pneumothorax; in each case this was successfully treated by application of an autologous blood patch. However, the involved area was limited to both lower lung fields (Fig. 1B), and the progression of lung fibrosis was relatively mild. In November 2003, the dyspnea got worse, and the estimated systolic pulmonary arterial pressure (PAP) measured by cardiac echogram was increased to 83 mmHg. Swan-Ganz catheterization was performed again, which showed that mean PAP was 56 mmHg. At the same time, the response of PAP to the administration of sildenafil was examined, and the mean PAP decreased to 36 mmHg; thus treatment with sildenafil was started soon afterward. In November 2003, antisynthetase antibody was measured by the immunoprecipitation method as described previously (15), and the patient was found to be positive for anti PL-12 antibody. Three months after the administration of sildenafil, the mean PAP had decreased to 40 mmHg, and hypoxemia had improved. Pulmonary arteriography was performed in February 2004, which showed no apparent thrombosis; however, narrowing of the pulmonary arteries of both lower lobes was observed (Fig. 4). Despite the relatively mild development of lung fibrosis, since the progression of pulmonary hypertension is critical, the patient is now undergoing registration as a candidate for lung transplantation.
We encountered a patient with anti-PL-12 antibody accompanied by interstitial pneumonia and severe pulmonary hypertension. At first presentation, skin lesions and marked elevation of rheumatoid arthritis hemagglutinin (RAHA) were found.

The findings on chest radiography and lung histology were not typical for idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP), suggesting the existence of underlying CVD, although the diagnosis of CVD was not conclusive. During the follow-up period, the patient was suspected to have antisynthetase syndrome, and the antisynthetase was measured in November 2003 for the first time. Anti-PL-12 antibody was detected, thus the patient was diagnosed with antisynthetase syndrome. The clinical features of the patient such as young age, concurrent skin lesions, and long duration of the disease were mostly compatible with those in previous reports of antisynthetase syndrome. Retrospectively, the hyperkeratotic skin lesions found on both hands at the presentation seemed compatible with mechanic’s hand (9, 10). However, Raynaud’s phe-nomenon, arthritis, and clinical signs of myositis were not found in this case. Previous reports demonstrated that some patients with anti-PL-12 antibody show interstitial pneumonia without clinical evidence of myositis (11, 16–18). Friedman et al reported 10 cases with interstitial pneumonia and positive anti-ARS antibodies without clinical evidence of myositis (16). Among them, 6 cases had anti-PL12 antibodies, and myositis was not apparent during the average follow-up period of 3.7 years. Hirakata et al reported that none of 6 Japanese patients with anti-PL-12 antibodies fulfilled the criteria for myositis (17). In the present case also, there were no clinical symptoms of PM/DM, and both serum creatine phosphokinase (CPK) and aldolase were negative during the follow-up period of seven years. The patient is now being closely observed to assess whether clinical signs of myositis will appear or not.

On admission, the chest X-ray findings showed volume loss in the bilateral lower lungs, and marked elevation of the diaphragm similar to “shrinking lung”, which is characteristic of CVD such as PM/DM (19). Chest computed tomography showed ground-glass opacities, while honeycombing was not apparent during the development of lung fibrosis.
These findings were compatible with NSIP as confirmed by the lung histology (1).

In general, a favorable response to corticosteroid or other immunosuppressive therapy can be expected in patients with interstitial pneumonia and anti-ARS antibodies (10, 16, 20). Hirakata et al followed 35 patients with PM/DM, and found that anti-ARS antibodies were negative in all 5 patients who showed acute exacerbation of interstitial pneumonia, leading to death in 4 cases. Conversely, anti-ARS antibodies were positive with a high frequency in patients who showed a chronic disease course (20). In the present case, the patient recovered twice from acute exacerbation and survived for 10 years from the onset of the disease.

Regarding pulmonary hypertension, few cases have been reported in patients with anti-ARS antibodies. Among 10 cases with anti PL-12 antibodies reported by Targoff and Arnett (11), 2 cases died of severe interstitial pneumonia, and 1 showed pulmonary hypertension. In the present case, the initial lung histology showed mild to moderate intimal proliferation in the muscular pulmonary arteries. Furthermore, pulmonary arteriography performed after the exacerbation of pulmonary hypertension showed narrowing of the pulmonary arteries in the areas of lung fibrosis. These findings suggest that not only the hypoxic vasoconstriction due to the lung fibrosis, but also the vascular lesion directly contributed to the development of severe pulmonary hypertension. Pronk and Swaak reported that intimal proliferation, narrowing of the vessel lumen, and intimal fibrosis were found in the lung histology of patients with CVD accompanied by pulmonary hypertension without lung fibrosis (21). Similar pathologic events might have occurred in the vasculature in this case, during the development of pulmonary hypertension.

In the present case, echocardiography was useful for serial non-invasive evaluation of pulmonary hypertension. Oudiz and Ginzton showed a high correlation between catheterization and echocardiography in estimating the pulmonary arterial pressure, when performed simultaneously (22). As shown in Table 2, ANP (atrial natriuretic peptide, normal value: 8.0–32.2 pg/ml) and BNP (brain natriuretic peptide, normal value: <18.5 pg/ml) levels correlated with the severity of pulmonary hypertension. Wiedemann et al have reported that ANP correlated with pulmonary vascular resistance in patients with primary and non-primary pulmonary hypertension (23). Based on this evidence, we recommend serial evaluation of pulmonary hypertension by echocardiography and measurement of ANP/BNP levels in patients at high risk for development of pulmonary hypertension.

In conclusion, the measurement of anti-ARS antibodies is recommended in cases with interstitial pneumonia, especially when underlying CVD is suspected. The possibility that patients with anti-ARS antibodies might develop pulmonary hypertension should be taken into consideration, even when the progression of lung fibrosis is not significant. Echocardiography and the measurement of ANP/BNP levels can be useful as non-invasive methods for serial evaluation of the severity of pulmonary hypertension.

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References


Figure 4. Pulmonary arteriogram (three months after the administration of sildenafil). No apparent thrombosis was found, however, narrowing of the pulmonary arteries was found in the area where lung fibrosis was severe (arrow).