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Pulmonary arterial hypertension in antisynthetase syndrome without myositis

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The idiopathic inflammatory myopathies are a heterogeneous group of rare chronic autoimmune diseases that include polymyositis (PM) and dermatomyositis (DM). Antisynthetase syndrome (ASS) is recognized as a subset of the idiopathic inflammatory myopathies and the syndrome is characterized by myositis associated with interstitial lung disease (ILD) and autoantibodies against aminoacyl-tRNA synthetases (ARS) with anti-Jo-1 being the most commonly found antibody (1,2). ILD is occurred in 70-89% of patients and it is the most common manifestation of ASS (3,4). In a subgroup of patients, without myositis the ILD may dominate the clinical manifestation and it is termed as amyopathic ASS (2).

Pulmonary arterial hypertension (PAH) may be associated with connective tissue diseases, such as scleroderma, systemic lupus erythematosus. However, PAH associated with ASS and unrelated with ILD is extremely rare and only a few cases has been reported previously (5,6).

CASE REPORT

A 69-year-old woman was admitted with dyspnea, cough and swelling in the legs. She was nonsmoker and there was no history of occupational or environmental exposure. The patient was not taking any regular medication. On physical examination inspiratory crackles at the lung bases and pretibial edema were detected. Physical examination was otherwise normal. Laboratory test revealed a normal biochemistry and hemogram. However, the C-reactive protein (CRP) level was 19.9 mg/L (0-3) and erythrocyte sedimentation rate (ESR) was 20 mm/hour (0-25). Arterial blood gases measurement revealed PaO_2 value as 51 mmHg. On chest radiograph bilateral opacities at lower zones (Figure 1) and on chest computed tomography (CT) (Fi-

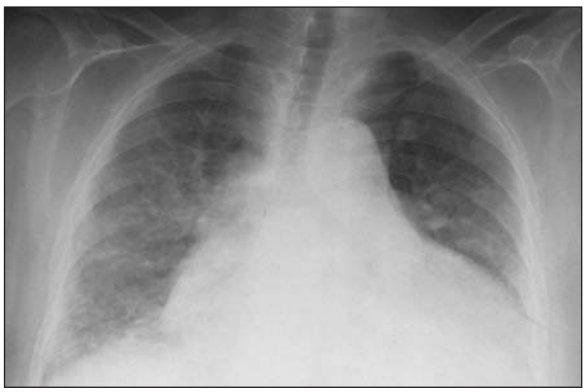

Figure 1. Chest radiograph revealed bilateral opacities at lower zones.

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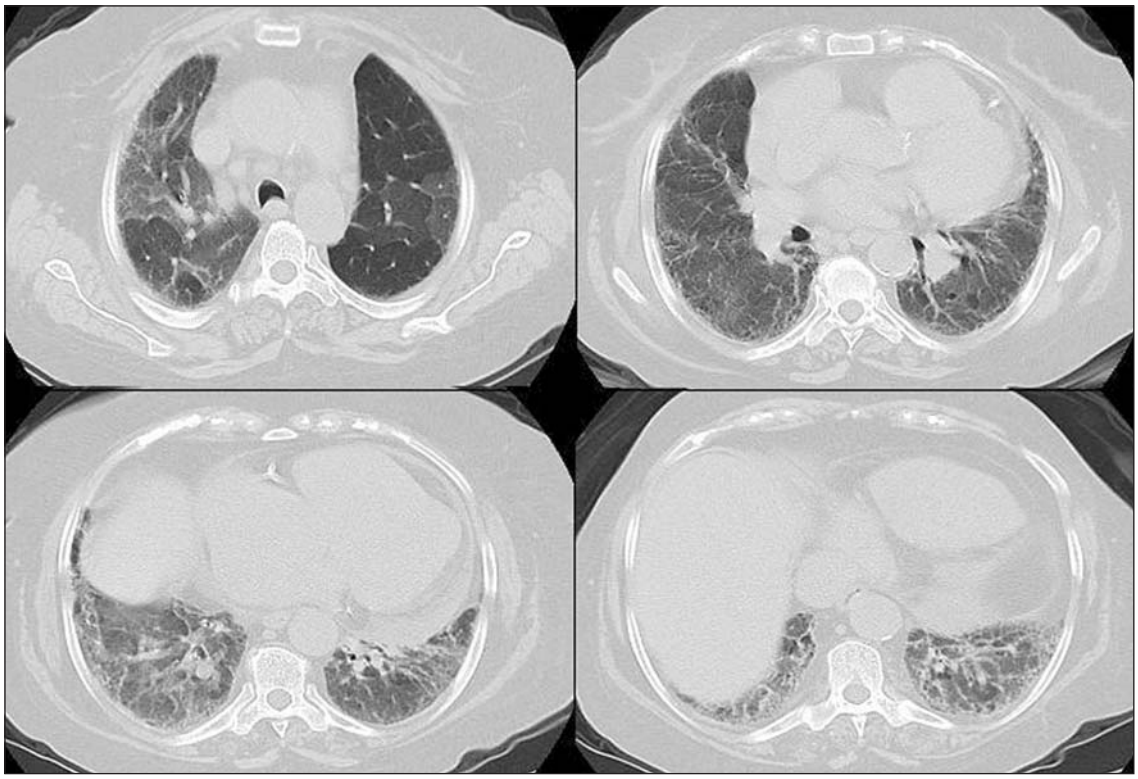

Figure 2. On the chest computed tomography; the upper and lower lobe section of the lung revealed dilated pulmonary artery, cardiomegaly and bilateral interstitial septal thickening with ground-glass opacities particularly at the basal segments consistent with interstitial lung disease.

gure 2) dilated pulmonary artery, cardiomegaly and bilateral interstitial septal thickening with ground-glass opacities particularly at the basal segments consistent with interstitial lung disease was observed. Serologic investigation revealed anti-nuclear antibody (ANA) (++++) and anti-Jo1 (++) positivity. The other auto-antibodies and creatine kinase (CK) were in normal scale. The patient did not complain of any muscle weakness. A capillaroscopy was performed and there was no evidence of scleroderma. Echocardiogram (ECHO) demonstrated elevation of systolic pulmonary arterial pressure (PAP) to 115 mmHg, right heart enlargement and normal systolic function. The pulmonary capillary wedge pressure was measured as 14 mmHg and mean PAP was 50 mmHg via the right heart catheterization and vasoreactivity test was negative. On ventilation/perfusion scintigraphy there was no evidence of acute or chronic pulmonary thromboembolism. Hence, the patient was diagnosed as ASS with PAH.

The medical therapy that consist of sildenafil (started with 20 mg/kg/day and increased to a maintenance dose of 60 mg/kg/day), methylprednesolone (0.5 mg/kg/day and decreased to 0.125 mg/kg/day in a month) and azathioprine (0.5 mg/kg/d and increased to 1.5 mg/kg/day) was administered to the patient. After two months of treatment, there was a clinical improvement with decrease in her dyspnea complaint and also PAP was decreased to a value of 90 mmHg demonstrated by ECHO. The PaO_2 was measured as 51 mmHg on admission and improved to 59 mmHg two months later, while the NYHA functional class was declined to III from the admission value of IV. The patient is still under our follow up.

DISCUSSION

The ASS is a subgroup of idiopathic inflammatory muscle diseases. The major clinical features of this syndrome are PM/DM, fever, arthritis, mechanic's hand, Raynoud's phenomenon and ILD (2). In the majority of cases, the occurrence of myositis precedes or is concurrent with the development of lung disease. However, even rarely, myosits may be absent or pulmonary symptoms may precede. Patel et al. reported a rare manifestation of ASS in which the pulmonary symptoms predated the onset of DM by two years (7). Although the positivity of antiJo-1 in the setting of ILD without any other crieteria for ASS remains unclear, the hallmark of diagnosis is the presence of an antisynthetase antibodies (8). In presented case, the diagnosis

was made according to the antisynthetase antibody positivity and ILD. Also, the patient is still under our regular follow-up for the possible development of myositis.

Antisynthetase antibodies are directed against cytoplasmic enzymes that catalyze the formation of the aminoacyl-tRNA complex from an amino acid and its cognate tRNA. Previously, eight different anti-ARS antibodies have been described. AntiJo-1 (anti-histidyl-tRNA synthetase), the first discovered antisynthetase is the most commonly identified antisynthetase antibody and also it is related with fibrosing alveolitis (9).

Interstitial lung disease is the major clinical problem in ASS and the incidence of ILD has been previously reported to be as high as 60-80%, which can be a major prognostic factor. The most common radiologic findings on chest radiograph are bilateral and predominantly basiler infiltrates. On thorax CT ground glass, lineer or reticular opacities are usually observed and the most common pattern is nonspecific interstitial pneumonia (NSIP) with or without areas of consolidation. Usual interstitial pneumonia (UIP) pattern can also be seen. On lung biopsy, the most common histopathologic pattern is NSIP, however UIP pattern, diffuse alveolar damage and organising pneumonia may also be detected. In our patients, since we did not perform any procedure for biopsy, the specific histopathologic pattern couldn't be determined.

Although PAH in connective tissue diseases has been reported to be frequently associated with ILD, in a few cases of ASS, PAH which might be unrelated to ILD has also been reported (5,6,10,11). The first case reported by Handa et al. was a patient with anti PL-12 antibody accompanied by ILD and severe PAH (6). Due to lung histology and pulmonary arteriogram, the authors suggested that not only hypoxic vasoconstriction due to lung fibrosis, but also the vascular involvement directly contributed to the development of severe PAH. Another patient reported by Taniguchi et al. was a case of ASS with anti-Jo-1 antibody and PAH (5). In their case, since two years before admission there was no PAH and ILD showed no changes on CT over the past seven years, the authors suggested that, ASS mainly contributed to PAH. Similarly, Cavagna et al. reported two cases of ASS with anti-Jo-1 positivity in whom pulmonary arterial pressures were increased despite stable ILD during a long-term follow-up (11). In our case, because of very high pulmonary arterial pressure which is inappropriate with extension of ILD, we suggested that PAH is mainly secondary to ASS rather than ILD.

In patients with ASS, ILD is the major cause of increased morbidity and mortality. The specific therapy of ILD has not been clearly established, however, corticosteroids are considered the mainstay of treatment, although additional immunosuppressive agents such as azathioprine, mycophenolate and cyclophosphamide is often required (7). For patients in whom ILD worsens despite aggressive conventional therapy, rituximab has been used (12,13).

There is limited data about the treatment of ASS related PAH. In the case, reported by Handa et al., three months after administration of sildenafil, an improvement in both pulmonary arterial pressure and hypoxemia was observed (6). Similarly, sildenafil was effective in patient reported by Cavagna et al. whereas the patient reported by Chatterjee et al. was unresponsive to sildenafil and trepostinil (10,11). Finally, Taniguchi et al. observed a response with bosentan therapy (5). In all patients mentioned above, additional immunosupressive therapy was also given. In contrast, in our case we started sildenafil therapy in addition to corticosteroid and azathioprine and two months after treatment we observed a clinical improvement with a decrease of pulmonary arterial pressure in ECHO.

In conclusion, we report a rare case of ASS accompanied by severe PAH and without myositis. In patients with ILD, even without accompanying myositis, a diagnosis of ASS and also in patients with ASS, PAH should be considered for an early diagnosis and treatment.

CONFLICT of INTEREST

None declared.

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