Severe Pulmonary Hypertension Associated with Primary Sjögren’s Syndrome

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Abstract

Severe pulmonary hypertension is one of the fetal complications in various connective tissue diseases. We report a case of severe pulmonary hypertension associated with primary Sjögren’s syndrome. In a lung biopsy specimen, there were findings of intimal and medial hypertrophy with narrowing vessel lumina and plexiform lesions. Moreover, deposits of immunoglobulin M, immunoglobulin A and complement protein C1q were found in the pulmonary arterial walls. Although pulmonary hypertension was refractory to oral prostacyclin, steroid therapy improved the clinical and hemodynamic conditions. In the present case, the immunological etiology may be related to the mechanisms of pulmonary hypertension associated with Sjögren’s syndrome.

Key words: pulmonary hypertension, Sjögren’s syndrome, steroid therapy, immunofluorescent stain

Introduction

It has been reported that pulmonary hypertension (PH) is associated with various connective tissue diseases (CTD), such as scleroderma (1), mixed connective tissue disease (2), CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome (3), systemic lupus erythematosus (SLE) (4) and rheumatoid arthritis (5). Although there is frequently pulmonary involvement in primary Sjögren’s syndrome (SS), such as interstitial fibrosis, tracheobronchial sicca, lymphoma, amyloidosis, pleurisy (6) or bronchial hyperresponsiveness (7), PH associated with SS has rarely been reported in the English language literature (8–14).

We describe a case of severe PH, resembling primary pulmonary hypertension (PPH), associated with primary SS and the microscopic findings of a lung biopsy. Moreover, recovery from PH with steroid therapy was observed in this case.

For editorial comment, see p 1163.

Case Report

A 42-year-old woman was diagnosed in 1995 with primary SS on the basis of oral sicca symptoms, hypergamma-globulinemia, positive antibodies to Ro (SS-A), and findings of ocular, oral and salivary test. Shlmer’s test (right eye, 7 mm/5 min; left eye, 3 mm/5 min), Rose-Bengal test, and chewing gum test (2 ml/10 min) were all positive, and although no labial salivary gland biopsy was carried out, the sialography demonstrated chronic sialoadenitis. After a three-year follow-up at a local hospital, she was admitted to Asahikawa Medical College Hospital because of progressive dyspnea in 1998. On clinical examination, blood pressure was 90/60 mmHg and pulse rate was 60 bpm and regular. Cardiovascular examination showed slight distension of jugular vein, a systolic murmur of grade II/VI in the left parasternal area and narrow splitting of second heart sound. Raynaud’s phenomenon, photosensitivity, butterfly and discoid eruption, Gottron’s sign, sclerodactyly, hypodynamia, arthritis, and edema were not noted.

On laboratory examination, white blood cell count and platelet count were decreased to 2,950/μl and 11.0×10^4/μl, respectively. Gammaglobulin and immunoglobulin G (IgG) were increased to 3.4 g/dl and 5,290 mg/dl, respectively. Immunoglobulin A (IgA) and immunoglobulin M (IgM)
Figure 1. Transthoracic echocardiograms on admission (A, C, E) and at 5 weeks after treatment with corticosteroids (B, D, F). The left ventricle is deformed by the markedly enlarged right ventricle (A, C, E). The size of the right ventricle is reduced (B), and the deformation of the left ventricle is improved with corticosteroids (D, F). A, B: Apical four-chamber views. C to F: Parasternal short-axis views in diastole (C, D) and systole (E, F).
thoracoscopy was carried out to determine the significance to pulmonary thromboembolism. However, there was no significant decrease by approximately 25%. Also, the pulmonary artery pressure was significantly decreased by approximately 25%. Also, the pulmonary artery pressure was significantly decreased by approximately 25%. Mean systemic arterial pressure, mSAP; mean pulmonary artery pressure, CO; Cardiac output, SaO2; Systemic systemic arterial oxygen saturation.

were within the normal range. Antinuclear antibody was positive at a titer of 1:640 (speckled type) and antibody to Ro (SS-A) was positive at a titer of 1:256. Antibodies to La (SS-B), double-stranded DNA, single-stranded DNA, Sm, ribonucleoprotein (RNP), topoisomerase-I (Scl-70), histidyl-tRNA synthetase (Jo-1) and centromere were negative. Antibody to cardiolipin and lupus anticoagulant were negative. Serum complements protein C3, C4, and total hemolytic complement (CH50) were within the normal range. Chest X-ray on admission demonstrated clear lung fields with enlarged pulmonary arteries. Chest computed tomography revealed no interstitial shadow in lung fields and no lymphadenopathy in mediastinum. Electrocardiogram showed right axis deviation and right ventricle hypertrophy. Pulmonary function test was normal and arterial blood gas analysis on room air disclosed pH of 7.42, PaCO2 of 34.9 Torr and PaO2 of 92.5 Torr. Echocardiography and Doppler echocardiography showed enlargement of the right ventricle, paradoxic interventricular septal movement, and severe tricuspid regurgitation (Fig. 1A, C, E). Pulmonary perfusion scintigraphy showed no segmental defect. Pulmonary arteriography demonstrated absence of necrotizing vasculitis and thromboembolism. Right heart catheterization revealed severe precapillary PH (Table 1). Under continued intravenous infusion of alprostadil (prostaglandin E1) to 30 ng/kg/min to test vasoreactivity, the pulmonary artery pressure was significantly decreased by approximately 25%. Also, the pulmonary resistance was reduced by approximately 20%.

At that time, the cause of PH in this patient was suspected of being pulmonary vasoconstriction. Treatments with oral prostacyclin (prostaglandin I2 analogue) and warfarin were selected to reduce the pulmonary artery pressure and prevent to pulmonary thromboembolism. However, there was no significant reduction of the estimated pressure of the right ventricle seen on Doppler echocardiography after administration of oral prostacyclin. Lung biopsy with video-associated thoracoscopy was carried out to determine the significance and pathogenesis of the association with PH and SS. During the perioperative period, hemodynamics were carefully observed and there was no exacerbation of PH. Upon microscopic examinations, intimal and medial hypertrophy with narrowing vessel lumina and plexiform lesions in the pulmonary arterioles were observed (Fig. 2A). The PH was given a pathological classification of Heath-Edwards IV (15). Neither vasculitis nor microthrombosis of the blood vessels was demonstrated. Interstitial pulmonary fibrosis related to CTD was not recognized. Upon immunofluorescent examinations, depositions of complement protein (C1q) and immunoglobulins (IgA and IgM) were observed in the pulmonary arteriolar walls (Fig. 2B, C, D). There was no deposition of IgG, complement protein C3 or C4.

After one month of treatment with prednisolone (50 mg/day), there was improvement of dyspnea and reduction in the size of the right ventricle was observed in the echocardiogram (Fig. 1B, D, F). Gammaglobulin and IgG levels fell to 1.7 g/dl and 1,860 mg/dl, respectively. The patient was discharged in June 1998, and the PH was treated with prednisolone (40 mg/day), prostacyclin and warfarin for one month. After further treatment with prednisolone (30 mg/day) for two months, she had no complaints of dyspnea and right heart catheterization showed a marked improvement in pulmonary artery pressure (Table 1).

### Discussion

It is well known that the prognosis for patients with CTD complicated severe PH is miserable and no curative treatment is available (16, 17). The difficulties of therapy in PH secondary to CTD may be related to its complex mechanisms. It has been reported that the condition may result from multiple etiological factors, such as pulmonary vasospasms induced by hypoxia and reduced pulmonary vasculature associated with disorders in the airway and interstitial lung diseases (18); thromboembolism related to abnormal coagulation (19); necrotizing vasculitis (20); hypervascconstriction in the pulmonary artery (18); endothelial injury associated with deposition of immune complexes (10, 21); hyperviscosity syndrome (22); and imbalances in the production and metabolism of several vasoactive substances produced in the pulmonary arteriolar endothelium (23, 24). After severe PH occurs, regardless of the type of primary pathological factor, interaction among vasoconstriction, remodeling and in situ thrombosis of the pulmonary artery may modify the prognosis (25).

Sato et al reported two cases of SS associated with PH where histopathological information was available (10). They detected the intimal concentric fibrocellular proliferation, medial hypertrophy and plexiform lesion. They also detected depositions of IgG, C1q, C3, C4, and C5 in the pulmonary arterial wall, suggesting an immune complex-mediated injury. In the present case, there were depositions of IgM, A, and C1q in the pulmonary arterial wall, but there was no IgG, C3, or C4. In addition, there have been reports of the presence of antinuclear antibody and rheumatoid factor in the wall of pulmonary vessels in two patients with PH.

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<th>Table 1.</th>
<th>Baseline</th>
<th>PGEi</th>
<th>PSL+PGI2</th>
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<tr>
<td>mSAP (mmHg)</td>
<td>79</td>
<td>61</td>
<td>98</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>43</td>
<td>31</td>
<td>30</td>
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<tr>
<td>CO (liters/min)</td>
<td>5.16</td>
<td>4.69</td>
<td>3.02</td>
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<td>SaO2 (%)</td>
<td>96</td>
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secondary to SLE. Other reports showed that immunoglobulins and complement fraction deposition in the pulmonary arterial wall in various CTD with PH (9, 26–28). These findings suggested that some immunological disturbance promotes the development of pulmonary arteriopathy in the patients with CTD.

Recently, it has been reported that corticosteroids modulate a large number of proinflammatory cytokines and vasoactive substances, such as thromboxane (29) and endothelin-1 (ET-1) (30, 31). Several studies have found high plasma ET-1 concentrations in patients with PH (24, 32); therefore, steroid therapy may contribute to recovery from PH, at least partly through a decrease in ET-1 production in pulmonary vessels and epithelial cells. Also, steroid therapy may reduce pulmonary vascular resistance in hyperviscosity of blood, because it brings about decreases in the excess production of immunoglobulin.

The mechanism of immune deposition in pulmonary vessels has never been revealed in CTD. In the present case, the initial components of the classical pathway of complements were found in the similar parts of the pulmonary vesicles similar to those in previous reports (9, 10, 26). This observation suggests that an antigen in the pulmonary artery may induce activation of the classical complement pathway. On the other hand, it has been reported that immune deposits in the pulmonary vessels resemble those observed in renal glomeruli in patients with SLE. Such immune deposits in the pulmonary vessels have also been observed in patients without PH (27), so it is unlikely that PH is the cause of the immune deposits in the pulmonary vessels. It is possible that immune deposits may be produced through non-immunological mechanisms. However, there is still no evidence that the presence of such deposits in the pulmonary artery is a risk factor in patients with CTD unaffected by PH. The relationship between immune deposition and involvement of pulmonary vessels in the present case is puzzling and there might be an unknown pathogenesis in PH. Although we know that there are many unpublished cases which were not sensitive to immunosuppressive therapy, dramatic improvement has occurred in patients with PH secondary to CTD following steroid therapy similar to the present case (13, 28). There is some opposition to the use of immunosuppressive therapy.
therapy in this context because of the lack of a control study (17). While, immunosuppressive agents have been implicated in adverse effects including severe infections. However, it will be valuable to discuss the possibility of the effectiveness of this therapy in each case now that there are several reports of successful outcome.

In conclusion, endothelial injury due to the deposition of immune complexes may play an important role in PH, and the reversibility of PH with corticosteroids may suggest that an immunological disorder is related to the mechanisms of PH associated with SS.

References