Isolated Pulmonary Hypertension in Overlap Syndrome: Successful treatment by methylprednisolone pulse therapy

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[Summary]

A 43-year-old woman was diagnosed with pulmonary hypertension (PH) associated with systemic sclerosis (SSc). On admission, absence of both thromboembolism and severe interstitial lung disease suggested that vascular damage led to PH. In addition, the patient met the criteria for the classification of SLE. Methylprednisolone pulse therapy was effective not only for the clinical symptoms but also for the laboratory findings. The report of overlap syndrome associated with PH is rare. The prognosis of patients with collagen diseases associated PH has been reported to be extremely poor. Since PH in this case responded favorably to methylprednisolone pulse therapy, this therapy may be effective for PH associated with overlap syndrome.

Key words: adrenomedullin, pulmonary hypertension, systemic sclerosis, systemic lupus erytematosus, overlap syndrome
I. Introduction

Pulmonary hypertension (PH) associated with collagen diseases usually led to a fatal outcome within months or a few years. PH is a common complication of systemic sclerosis; it has been reported to be clinically important in up to 10% of patients in some series, while histopathologic changes consistent with arteriopathy were present at autopsy in up to 80%\(^1\). Pulmonary involvement in systemic sclerosis (SSc) is characterized by varying degrees of interstitial fibrosis and vascular obliteration, and both abnormalities may result in PH\(^1\)–\(^3\). Pulmonary involvement has recently been reported to be the most frequent cause of death in SSc patients. The prognosis in isolated PH, i.e. PH without pulmonary fibrosis, is dismal with a 2-year survival rate of only 40%\(^3\). On the other hand, the report of overlap syndrome associated with PH is extremely rare. We describe a case of PH associated with overlap syndrome in which steroid pulse therapy was effective.

II. Case

A 43-year-old Japanese woman noticed Raynaud’s phenomenon and sclerodactyly of the fingers in June 1996. She was diagnosed with SSc at a local hospital by accepted criteria\(^4\). She experienced shortness of breath on exertion in April 1997, calcium channel blocker (nifedipine) and limaprost altadex were started and was admitted to our hospital for further examination in August 1997.

At the time of admission, the sclerodactyly of the fingers, forearms, legs, feet, and face was presented. She felt dyspnea on walking. New York Heart Association (NYHA) functional classification was III. There was no arthralgia, eruptions, photosensitivity, or neurological deficits. Pulmonic component of the second heart sound was accentuated. Arterial blood gases showed pH 7.41, PaCO\(_2\) 33.1 mm/Hg, and PaO\(_2\) 66.2 mm/Hg on room air. Results of laboratory studies included an erythrocyte sedimentation rate of 117 mm/h, hemoglobin of 11.3 g/dl, and platelet counts of 9.0×10\(^4\)/dl. Urinalysis revealed 3+ protein by the dipstick test and numerous red blood cells in the urine sediment by dipstick test. TP 9.9 g/dl (γ-globulin 62.4%), albumin 2.3 g/dl, ALT 57 U/l, AST 33 U/l, LDH 566 (normal 120–240) U/l, ALP 632 (normal 100–325) U/l, creatine kinase 374 mU/ml (normal 10–110), T-Cho 99 mg/dl were revealed. Serum CRP level was 0.3 mg/dl. Immunological tests revealed an antinuclear antibody titer of 1:40,960 (speckled pattern), anti-RNP antibody of 64, and anti-DNA antibody of 118 (normal <6), ds-DNA antibody of 29.3 (normal <10), anti-SS-A antibody of 64. Anti-cardiolipin antibody (IgG) of 45 index also existed. The prothrombin time (PT) was 10.1 (9.5–12) sec and activated partial PT (APTT) was 42.8 (23.5–42.5). FDP 6.1 (<10) μg/ml, fibrinogen 250 (155–415) mg/dl. Plasmin α 2 plasmin inhibitor complex (PIC) was 1.1 (<1.0) uμg/ng. Anti-Topo I, anti-Sm, anti-SSB, anti-β\(_2\) glycoprotein I antibodies, and lupus anticoagulant were not detected. Coombs tests
Figure 1

a: Before the treatment
Chest radiograph revealed progressively enlarging pulmonary arteries with pleural effusion and cardiomegaly

b: After the treatment
Cardiac effusion disappeared and cardiac size decreased.

Figure 2

a: Before the treatment
Echocardiography revealed cardiac effusion

b: After the treatment
Pleural effusion disappeared and cardiac size decreased.

were also negative. Other serum data were C$_3$ 14 (normal range 50-110) mg/dl, C$_4$ 4 (normal range 13-45) mg/dl, CH$_50$ 10.8 (normal range 29-48) U/ml, endothelin-1 4.8 (normal <2.3) pg/ml and adrenomedullin 50 (normal <5) fmol/ml; Levels of both endothelin-1 and adrenomedullin were elevated, as we recently reported$^{10}$. X-P of the hand revealed tuft absorption. Chest radiograph revealed progressively enlarging pulmonary arteries with pleural effusion and cardiomegaly (Fig 1 a), but there were no interstitial abnormalities. Electrocardiography showed signs
of right-sided cardiac hypertrophy (Fig 2a). Transthoracic echocardiography revealed PH with right ventricular systolic pressure (RVSP) 59 mmHg with right ventricular enlargement and tricuspid regurgitation. Right heart catheterization showed: right atrial pressure 13 mmHg, right ventricular pressure 77/12 mmHg, pulmonary arterial pressure 78/33, mean 51 mmHg, and left ventricular end-diastolic pressure 14 mmHg. The cardiac index was 2.5 (l/min/m²). Pulmonary infarction and embolism were ruled out by lung perfusion scan. The calculated pulmonary arteriolar resistance was 587 dyne.sec/cm². Administration of isosorbide dinitrate and 100% oxygen led to diminished total peripheral resistance and pulmonary artery pressure (76/34 to 70/28, 77/33 to 68/34, respectively). The patient also satisfied the criteria for the classification of systemic lupus erythematosus (SLE)⁶. Finally she was diagnosed with PH, pleuritis, and pericarditis with overlap syndrome.

She was treated with 1 g pulse of methylprednisolone daily for 3 days, followed by prednisolone (60 mg/day). Pleural effusion disappeared and cardiac silhouette decreased (Fig 1b, 2b). Other laboratory data were improved (Fig 3). The patient reported clinically significant resolution of her dyspnea and was discharged in good condition with 27.5 mg of prednisolone in December 11.

Since echocardiographic data corresponded very well with the measurements obtained by cardiac catheterization, echocardiographic measurements were used for follow-up of pulmonary hypertension. After 18 months, NYHA was II and right ventricle peak systolic pressure was 46 mmHg in good condition with taking 15 mg of prednisolone.

III. Discussion

This patient had demonstrated diffuse type SSc for 1 year, and developed dyspnea due to PH. Since this patient also met the criteria for the classification of SLE, she was finally diagnosed as overlap syndrome associated with PH. After treatment with high-dose intravenous methylprednisolone, her clinical symptoms were improved. Since this patient had no interstitial pneumonia, it was speculated that vascular damage led to PH.

The pathologic findings in PH associated with SSc typically consist of an arteriopathy characterized by concentric fibrointimal proliferation with occlusion of small arteries and arterioles. Thus, findings of PH associated with SSc are very similar
to those noted in the majority of cases of primary PH. The effect of calcium channel blockers\(^7\), angiotensin-converting enzyme inhibitors, serotonin antagonists\(^8\), nitrates, \(\alpha\)-blockers, and peripheral vasodilators such as hydralazine\(^9\) in PH-associated with SSc have failed to show a therapeutic benefit. Continuous intravenous infusion of prostacyclin\(^{1,10,13}\) and long-term continuous intravenous infusion of iloprost, a stable carbacyclin analog of prostacyclin\(^{14}\), has been shown to be an effective treatment for PH associated with SSc. Williamson DJ et al. has recently reported the effectiveness of nitric oxide in patients with limited scleroderma and isolated PH.

The report of PH associated with overlap syndrome is extremely rare. Anderson et al reported the concurrent occurrence of renal crisis and pulmonary hypertension\(^{15}\). Asherson et al. reported 24 patients with PH in their lupus clinic. Only one of 24 patients was diagnosed as PH associated with overlap syndrome\(^{16}\). Recently, several authors have reported that PH with SLE\(^{17}\) or MCTD\(^{18}\) was successfully treated by corticosteroid with or without combination of cyclophosphamide or cyclosporin A. Therefore, we tried treatment with high-dose corticosteroid combined with calcium-channel blocker and angiotensin converting enzyme inhibitor. This therapy was effective and plasma levels of endothelin-1 and adrenomedullin were also decreased after the treatment. Hence, although PH usually has a very poor prognosis in collagen disease patients, high-dose corticosteroid pulse therapy may be effective for PH associated with overlap syndrome.

PH may result from either pulmonary fibrosis or direct vascular damage. The role of recurrent vasospasm remains controversial. The decrease in pulmonary perfusion in response to cold exposure and improvement in PH following treatment with vasodilator support the possibility of a reversible vascular component. In the primary antiphospholipid syndrome, PH resembling primary PH occurs, and thromboembolic and nonthromboembolic pulmonary vascular diseases can also be found. Ihn et al. also reported that about 10% of SSC patients are positive for \(\beta_2\) GPI/antiCLlgG and these patients tend to develop PH\(^{19}\). Thus, in our patient, anti-cardiolipin antibody (IgG) might damage pulmonary endothelial cells, since the anti-cardiolipin antibody (IgG) level was elevated in plasma. However, endothelin-1 may lead to contraction of vascular smooth muscle cells and proliferation of vascular endothelial cells; Stewart et al. have described elevated plasma endothelin-1 levels in patients with both primary and secondary forms of PH\(^{20,21}\). Indeed, since endothelin-1 level was elevated in our patient, endothelin-1 might play a role in the development of PH.

In summary, corticosteroid pulse therapy improved not only clinical symptoms but also clinical data including an elevated level of plasma endothelin-1 and adrenomedullin in PH associated with overlap syndrome. Since the prognosis of PH associated with collagen disease is extremely poor, corticosteroid pulse therapy may be considered if medication is not effective.

References

4) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis
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