Severe Pulmonary Hypertension in Primary Sjögren’s Syndrome

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A 65 year-old female with a history of xerostomia and xerophthalmia was presented with dyspnea on exertion (New York Heart Association class III). Echocardiography and cardiac catheterization demonstrated severe pulmonary hypertension (PH). Laboratory examinations showed positive anti-nuclear and anti-Ro/SS-A antibodies. Schirmer’s test was positive and salivary gland scintigraphy revealed severely decreased tracer uptakes in both parotid and submandibular glands. By excluding other possible causes of PH during further examinations, she was diagnosed with severe PH associated with primary Sjögren’s syndrome. Her dyspnea symptom was much improved with endothelin receptor antagonist and azathioprine. (Korean Circ J 2013;43:504-507)

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Anti-human immunodeficiency virus antibodies, hepatitis B virus antigen and antibodies, and anti-hepatitis C antibodies were all negative. Erythrocyte sedimentation rate was increased (42 mm/hour, normal 0–20 mm/hour). Hemoglobin, white blood cell and platelet counts, and urine test were within normal limits. N-terminal pro B-type natriuretic peptide level was 1469.1 pg/mL (normal 0–125 pg/mL). Creatinine kinase-MB and troponin-I were also within normal limits. Arterial blood gas analysis in room air showed pH 7.44, pO2 78 mm Hg, and pCO2 34 mm Hg.

Pulmonary function test revealed normal ventilatory pattern with normal CO diffusion capacity. Chest X-ray demonstrated grossly normal lung fields with a mildly enlarged right ventricle. Electrocardiogram showed tall, peak P waves in lead II, III, and aVF, suggesting right atrial enlargement. Transthoracic echocardiography showed a mildly enlarged and thick right ventricle, hypokinetic right ventricular free wall, grade II tricuspid regurgitation, and peak tricuspid regurgitation jet velocity of 4.64 m/s with an estimated right ventricular systolic pressure (RVSP) of 91.1 mm Hg (Fig. 1A and B). Trans-thoracic and transesophageal echocardiography excluded any other congenital, valvular, and myocardial diseases. Right heart catheterization also revealed severe PH. Pulmonary artery pressure was 74/27 mm Hg (mean 46 mm Hg) with a pulmonary capillary wedge pres-
sure of 7 mm Hg (Fig. 2). Cardiac index was calculated as 2.27 L/min/m² and pulmonary vascular resistance was 11 Wood units. Elevated pulmonary artery pressure was not significantly decreased with adenosine infusion. Chest computed tomography and lung perfusion scan did not show abnormal findings compatible with pulmonary embolism. Schirmer’s test was positive. Salivary gland scintigraphy disclosed severely decreased tracer uptakes in both parotid and submandibular glands.

Considering her clinical, laboratory, cardiologic, imaging findings and the Revised International Classification Criteria for Sjögren’s Syndrome by the American-European Consensus Group,⁴¹ she was clearly diagnosed with severe PH associated with primary Sjögren’s syndrome. She was treated with 62.5 mg endothelin receptor antagonist (Bosentan)⁴⁶ twice a day for the initial month and 125 mg twice a day for the following months, 200 mg hydroxychloroquine twice a day, 50 mg azathiprine twice a day, and topical corticosteroid and sodium hyaluronidate eye drops. A follow-up transthoracic echocardiography after 6 months of treatment showed somewhat improved right ventricle contractility and decreased estimated RVSP (65.5 mm Hg) compared to the initial exam (Fig. 1C and D). Equally, her dyspnea symptom was much improved and uneventful, she is being followed up at an outpatient clinic.

Discussion

Sjögren’s syndrome is a chronic inflammatory autoimmune disease characterized by lymphocytic infiltration at the exocrine glands and at other extraglandular sites resulting in the dryness of the mouth and eyes. The disease predominantly affects women in the fourth and fifth decades of life, with a female to male ratio of 9 : 1. It can be either primary or secondary to another CTD, most commonly rheumatoid arthritis. Clinical manifestations of the disease vary from exocrinopathy, such as salivary or ocular involvement (keratoconjunctivitis sicca), less commonly respiratory tree or gastrointestinal tract involvement to systemic extraglandular manifestations, such as arthritis, Raynaud’s phenomenon, lung, kidney involvement, vasculitis, or lymphoma.⁵⁰ Among them, pulmonary manifestations in primary Sjögren’s syndrome include a variety of diffuse interstitial lung disease, airway disease, lymphoma, pseudolymphoma, amyloidosis, pleural involvement, vasculitis, and PH.⁵¹ PH is associated with several CTDs, most commonly with scleroderma,⁴⁵ its limited cutaneous variant, the Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasis (CREST) syndrome,⁴⁶ mixed connective tissue disease (MCTD),⁴⁵ and systemic lupus erythematosus (SLE).⁴⁷ However, the prevalence of PH in primary Sjögren’s syndrome is rare throughout the world and there has been no case report in Korea until now.

The pathogenesis of PH in primary Sjögren’s syndrome is uncertain; however, it is thought result from vasculitis with prolonged vasospasm followed by structural vessel remodeling, eventually leading to the irreversible thrombotic obstruction of pulmonary arteries.¹³ Launay et al.¹³ revealed that compared with primary Sjögren’s syndrome patients without pulmonary artery hypertension (PAH), primary Sjögren’s syndrome patients with PAH experienced Raynaud phenomenon, cutaneous vasculitis, and interstitial lung disease more frequently. They were more likely to have anti-nuclear, anti-Ro/SSA, and anti-RNP autoantibodies, as well as positive rheumatoid factors and hypergammaglobulinemia. These data imply that systemic vasculopathy, B-cell activation, and autoimmunity are involved in the pathogenesis of PAH associated with primary Sjögren’s syndrome, supporting that immunosuppressants play a vital role in the treatment of PAH in primary Sjögren’s syndrome.¹³

In the treatment of PAH associated with primary Sjögren’s syndrome, there has been no best treatment strategy due to the small number of accumulated cases. However, taking into consideration the facts that PAH is the main mechanism of CTD-PH, and that histopathological similarities and shared pathogenic mechanisms exist between idiopathic PAH and PAH associated with connective tissue disease (CTD-PAH), treatment for idiopathic PAH may be applicable to CTD-PAH.¹³¹⁴ Oxygen should be supplemented if hypoxemia exists, and diuretic therapy may be used to reduce the right ventricular preload. Long-term anticoagulant associated with improved survival in idiopathic PAH can be applied, although its efficacy has not been documented in patients with PAH due to other causes, including CTDs.¹⁶ Effective pulmonary vasodilators should be administered to reduce the afterload on the right heart. Calcium-channel blockers should be used for responders to short-acting vasodilator challenge test during right cardiac catheterization. However, it is well-documented that this therapy is effective in less than 10% of patients with idiopathic PAH. Furthermore, in patients with CTD-PAH, the percentage of non-responders to calcium-channel blockers is higher than that in patients with idiopathic PAH.¹⁶ Several drugs targeting the mechanism of PAH have been developed. Prostacyclin analogues, such as Epoprostenol, Treprostinil, Iloprost, which are potent vasodilators, can be used. Endothelin receptor antagonists, such as Bosentan and Ambrisentan, can also be applied by the fact that endothelin, which has powerful vasoconstrictive effects is increased in PAH. Bosentan was approved in the EU and the USA for the treatment of idiopathic PAH and CTD-PAH in patients who have NYHA class III dyspnea. The third is nitric oxide pathway targeted therapy. Phosphodiesterase-5 inhibitors, such as Sildenafil and Vardenafil, block the degradation of cyclic guanosine monophosphate, which is the second messenger in nitric oxide-induced pulmonary vasodilation.¹⁰¹⁴ In addition to these standard PAH therapies, cor-
ticosteroids and/or other immunosuppressants would also be used in CTD-PAH, considering that immune or inflammatory mechanisms play an important role in the genesis or progression of PAH, particularly in CTD-PAH.\(^{19}\) Pulse steroid therapy in PAH associated with MCTD has been suggested to be effective, resulting in the improvement of hemodynamic parameters and dyspnea functional class.\(^{16}\) Furthermore, it was proved that intermittent pulse therapy with cyclophosphamide was effective in mild to moderate PAH associated with SLE.\(^{11}\)

Although there had been no available randomized controlled data with regard to PAH associated with other CTDs, Launay et al.\(^ {11}\) suggested the treatment algorithm of PAH associated with primary Sjögren’s syndrome. They proposed that initial immunosuppressive therapy (cyclophosphamide or azathioprine) should be taken in patients with NYHA class III/IV dyspnea and immunosuppressive therapy; additionally, standard PAH therapy (endothelin receptor antagonists, phosphodiesterase-5 inhibitors or prostanoids) should be given to patients with NYHA class III/IV dyspnea.

The long term prognosis in the majority of patients with CTD-PAH is known to be worse than that in patients with idiopathic PAH. In addition, the survival rates in patients with PAH associated with primary Sjögren’s syndrome were also poor, according to the accumulated data. Therefore, accurate diagnosis and early effective treatment with immunosuppressants and/or standard PAH therapy are very important in patients with PAH associated with primary Sjögren’s syndrome.

References

1. Kokosi M, Riemer EC, Highland KB. Pulmonary involvement in Sjögren syndrome. Clin Chest Med 2010;31:489-500.
2. Ungerer RG, Tashkin DP, Furst D, et al. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. Am J Med 1983;75:65-74.
3. Salerni R, Rodnan GP, Leon DF, Shaver JA. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern Med 1977;86:394-9.
4. Sanchez Q, Humbert M, Sitbon O, Nunes H, Garcia G, Simonneau G. [Pulmonary hypertension associated with connective tissue diseases]. Rev Med Interne 2002;23:41-54.
5. Wiener-Kronish JP, Solinger AM, Warnock ML, Churg A, Ordonez N, Golden JA. Severe pulmonary involvement in mixed connective tissue disease. Am Rev Respir Dis 1981;124:499-503.
6. Kim KH, Jeong MH, Kim W, et al. A case of systemic lupus erythematosus with severe pulmonary hypertension and pericarditis. Korean Circ J 2000;30:605-10.
7. Quismorio FP Jr, Sharma Q, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arthritis Rheum 1984;13:349-59.
8. Nakagawa N, Osanai S, Ide H, et al. Severe pulmonary hypertension associated with primary Sjögren’s syndrome. Intern Med 2003;42:1248-52.
9. Sowa JM. The association of Sjögren’s syndrome and primary pulmonary hypertension. Hum Pathol 1993;24:1035-6.
10. Sato T, Matsubara Q, Tanaka Y, Kasuga T. Association of Sjögren’s syndrome with pulmonary hypertension: report of two cases and review of the literature. Hum Pathol 1993;24:199-205.
11. Launay D, Hachulla E, Hatron PY, Jais X, Simonneau G, Humbert M. Pulmonary arterial hypertension: a rare complication of primary Sjögren syndrome: report of 9 new cases and review of the literature. Medicine (Baltimore) 2007;86:299-315.
12. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren’s syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
13. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med 2004;164:1275-84.
14. Distler O, Pignone A. Pulmonary arterial hypertension and rheumatic diseases—from diagnosis to treatment. Rheumatology (Oxford) 2006;45 Suppl 4:vii2-5.
15. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984;70:580-7.
16. Sanchez O, Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary hypertension secondary to connective tissue diseases. Thorax 1999;54:273-7.
17. Sanchez O, Sitbon O, Jais X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. Chest 2006;130:182-9.
18. Kamata Y, Nara H, Sato H, Masuyama JI, Minota S, Yoshio T. Effect of steroid pulse therapy on mixed connective tissue disease with pulmonary arterial hypertension. Ann Rheum Dis 2005;64:1236-7.
19. Gonzalez-Lopez L, Cardona-Muñoz EG, Celis A, et al. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. Lupus 2004;13:105-12.