CASE REPORT

Characteristics of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis and Anticentriole Autoantibodies

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Summary

Anticentriole autoantibodies-positive systemic sclerosis (SSc) has been reported to develop pulmonary arterial hypertension (PAH) at a high rate. In this report, we describe two patients with anticentriole antibodies-positive SSc-PAH who were treated with pulmonary vasodilators. Both cases were elderly women with poor physical conditions and clinical findings of SSc. Case 1 was resistant to combination therapy with pulmonary vasodilators; in Case 2, hemodynamic improvement was obtained by upfront combination therapy at an early stage. Because anticentriole antibodies-positive SSc-PAH rapidly deteriorates, careful hemodynamic observation and timely aggressive use of pulmonary vasodilators should be considered.

Key words: Elderly

Anticentriole antibodies were first reported by Brenner, et al, in 1980.1,2 Previous studies have demonstrated that anticentriole antibodies are specifically identified in patients with systemic sclerosis (SSc).3,4 Hamaguchi, et al, proposed that patients with anticentriole antibodies-positive SSc may have a higher probability of emerging pulmonary arterial hypertension (PAH).5 However, little is known about the clinical picture of PAH in patients with anticentriole antibodies-positive SSc. Here, we describe two patients with anticentriole antibodies-positive SSc-PAH who were treated with pulmonary vasodilators.

Case Reports

Case 1: A 65-year-old woman admitted to our hospital for worsening exertional dyspnea and general fatigue. She had a 15-year history of Raynaud’s phenomenon and was diagnosed with Raynaud’s disease at first. However, finger ulcers and sclerodactyly of her hand appeared 5 years ago and were exacerbated by cold stimulation. She was referred to our dermatologist and diagnosed with limited cutaneous systemic sclerosis. She also experienced shortness of breath for 7 years when going up hills and her exertional dyspnea has intensified over the past 6 months. She was suspected of having pulmonary hypertension (PH) by echocardiography and was introduced to our department 9 months after the first visit to a dermatologist. On admission, physical examination revealed a height of 152.3 cm, weight of 60.5 kg, regular heart rate of 97 beats per minute, arterial blood pressure of 140/80 mmHg, resting oxygen saturation of 95% with room air, and her World Health Organization function class (WHO-Fc) was class II. There were no significant physical abnormalities in her chest and abdominal signs and no general congestion signs such as cervical vein dilatation or peripheral edema. Although her plasma brain natriuretic peptide (BNP) level rose slightly to 20.5 pg/mL, no abnormalities were found in other laboratory blood count testing and biochemical profiles. The results of serological analysis showed high antibody titers to centriole (1:320) in the indirect immunofluorescence (IF) antinuclear antibody (ANA) test using HEP-2 cells as a substrate without any elevation of other autoantibodies. Electrocardiography showed almost normal findings except left ventricular high voltage in the V1, V5 and V6 leads. Chest X-rays showed a normal cardiothoracic ratio (= 45%) and no significant abnormality in lung fields. Right heart catheterization (RHC) showed mean pulmonary artery pressure (mPAP) elevation of 24 mmHg and pulmonary vascular resistance (PVR) of 3.8 Wood Units (WU) above the normal range but they did not meet the diagnostic criteria for PH. In addition, mean right atrial pressure (mRAP) was 3 mmHg, pulmonary arterial wedged pressure (PAWP) was 7 mmHg, and cardiac index was 2.8 L/minute/m², suggesting her pulmonary hemodynamics were less severe. The results of the respi-
ratory function test indicated mild reduction of %vital capacity (%VC = 79.1%) but an extremely low level of %diffusing capacity of the lung for carbon monoxide (%DLCO = 37.6%). Slight interstitial reticular shadows in both lungs were seen on computed tomography (CT), however, the activity of the interstitial pneumonia was low (Figure 1A). As the dermatologist had started beraprost sodium (120 mg/day) for improvement of peripheral circulation 9 months previously, we continued it and observed her clinical situation in our outpatient department. Six months later, her exertional dyspnea worsened to WHO-Fc III and SpO2 at rest decreased to 91%, and furthermore, her estimated systolic PAP by echocardiography increased from the previous 51 mmHg to 90 mmHg. We added the endothelin receptor blocker bosentan (62.5 mg b.i.d) and introduced home oxygen therapy (HOT). A second RHC, performed 9 months after the first RHC, revealed marked hemodynamic exacerbation (mPAP 44 mmHg, PVR 7.4WU, mRAP 6 mmHg). After that we administered sildenafil (25 mg t.i.d. for the first 6 months during the doctor-led clinical trial following 20 mg t.i.d. for insurance treatment), increased bosentan (125 mg b.i.d.) and added imatinib mesylate as a doctor-led clinical trial (started 100 mg s.i.d. and increased to 200 mg s.i.d. after 12 months). This sequential combination therapy partially and temporally relieved her clinical symptoms and hemodynamic parameters but could not suppress the worsening symptoms (Figures 2A, 3A). Her right heart failure was deteriorating day by day and she died of a traumatic epidural hematoma 36 months after the first visit to our department (27 months after diagnosis of PAH).

Case 2: An 82-year-old woman was diagnosed with idiopathic PAH (IPAH) and referred to our hospital. She had experienced worsening exertional dyspnea for a year and her 10-year history of Raynaud’s phenomenon and mild digital ulcers on her fingertips were first pointed out after we thoroughly investigated the cause of PAH. Like case 1, her sclerodactyly was limited to her fingers and mild interstitial pneumonia was seen on CT scan (Figure 1B). Her physical findings on admission were as follows; height 158.5 cm, weight 61.6 kg, regular heart rate 82 beats per minute, blood pressure 100/62 mmHg, oxygen saturation 90% in room air, and WHO-Fc class III. Her BNP level rose 263.9 pg/ml, however, no abnormalities were found in other blood tests. Although the previous hospital reported a negative ANA test by ELISA (enzyme-linked immunosorbent assay), anticentriole antibody was found to be positive with high titer (1:2560) by IF-ANA test at our hospital, which led us to suspect systemic sclerosis. Respiratory function testing indicated mild obstructive pulmonary dysfunction (forced expiratory volume % in one second; FEV1.0% = 67.6%) and relatively low %DLCO of 44%. The RHC showed moderate elevation of mPAP (43 mmHg), PVR (9.3 WU) and relatively low CI (2.3 L/minute/m²). Mean RAP and PAWP were 6 and 7 mmHg, respectively. Instead of the previous IPAH diagnosis, she was finally diagnosed with PAH associated with limited cutaneous SSc. In addition to HOT, we started macitentan (10 mg s.i.d.) and tadalafil (20 mg, b.i.d.) as the initial combination regimen expecting rapid and strong hemodynamic improvement. After 1 month of therapy, her hemodynamic parameters partially improved (mPAP = 40 mmHg, PVR = 5.6 WU and CI = 3.2 L/minute/m²), and furthermore, continuing this therapy for 6 months relieved her symptoms to WHO-Fc II and her mPAP, PVR and CI were additionally improved to 33 mmHg, 4.0 WU, and 3.3 L/minute/m², respectively. She was then continued on the same regimen for 36 months at our outpatient department without hospitalization for worsening heart failure, however, her oxygen saturation at rest and during work
was gradually decreasing. RHC after 33 months of therapy revealed the re-exacerbation of pulmonary hypertension (Figures 2B, 3B).

Discussion
Some specific autoantibodies are positive for systemic sclerosis. Above all, anti-centromere antibody, anti-topoisomerase I antibody, anti-RNA polymerase III are
common in SSc patients and these autoantibodies are known to correlate with specific organ damage. For example, anti-topoisomerase I antibody is highly positive in diffuse cutaneous SSc, which often causes multiorgan damage and poor prognosis, on the other hand, anticentromere antibody is common in limited cutaneous SSc, which rarely causes multiorgan damage except vasculopathy including pulmonary vessels. Anticentriole antibody is not an antinuclear antibody but an anti-cytoplasmic antibody so anticentriole antibodies are hard to detect by ordinary ELISA methods. The indirect immunofluorescence test is important for detecting this type of anticytosolic antibodies. The relationship between anticentriole antibodies and disease features is hardly known. To date, several reports have suggested that patients with anticentriole antibodies-positive SSc have few typical SSc symptoms or

Figure 3. Changes in respiratory status and SaO₂ in case 1 (A) and case 2 (B). %VC indicates %vital capacity, FEV1.0% forced expiratory volume % in one second, and %DLCO diffusing capacity of the lung for carbon monoxide.
have only Raynaud’s phenomenon. These characteristics may make an SSc diagnosis difficult. On the other hand, one report suggested a high prevalence of PAH in patients with anticentriole antibodies-positive SSc (80%) compared with the prevalence recognized in general SSc (8–12%). Our two cases of anticentriole antibodies-positive SSc patients have some similar features. Firstly, they also had moderate to severe PAH with acute progressive onset requiring combination use of vasodilators from an early stage. Secondly, they had fewer physical findings of SSc other than Raynaud’s phenomenon or significant organ damage in addition to the PAH. Lastly, their %DLCO was a relatively low value, despite the absence of significant lung disorder detected by either CT scan or respiratory function test.

In case 1, rapid hemodynamic worsening was observed 9 months after the first RHC and even sequential quadruple combination therapy did not positively contribute to this patient’s hemodynamics and survival. Meanwhile, case 2 had a diagnosis of PAH 1 year after the appearance of exertional dyspnea; this patient was treated with a potent upfront combination therapy immediately, which resulted in clinical improvement after 6 months. Upfront combination therapy using multiple pulmonary vasodilators at an early stage has been reported to improve the clinical prognosis of PAH and significantly improve hemodynamics, right ventricle structure and function, and functional status in treatment-naïve patients with SSc-PAH. However, in both our cases with anticentriole antibodies-positive SSc-PAH, hypoxemia and PAH worsened over time. These patients should be observed carefully and treated with aggressive use of pulmonary vasodilators including parenteral prostanooids in the same manner as the treatment for IPAH. However, the existence of severe hypoxemia makes us hesitate to use high dosage prostanooids because it could deteriorate any ventilation-perfusion mismatch.

For both cases, no auto-antibodies other than anticentriole antibodies were detected. In case 2, signs of SSc were overlooked and she was misdiagnosed with IPAH at the previous hospital. Caution is required as anticentriole antibodies-positive SSc-PAH, hypoxemia and PAH may be difficult to diagnose even in a patient with scleroderma. N Engl J Med 1982; 307: 253-4. Moroi Y, Murata I, Takeuchi A, et al. Human anticentriole autoantibodies in patients with scleroderma and Raynaud’s phenomenon. Clin Immunol Immunopathol 1983; 29: 381. Tuffanelli DL, McKeon F, Kleinsmith DM, et al. Anticentromere and anticentriole antibodies in the scleroderma spectrum. Arch Dermatol 1983; 119: 560-6. Osborn TG, Ryerse JS, Bauer NE, et al. Anticentriole antibody in a patient with progressive systemic sclerosis. Arthritis Rheum 1986; 29: 142-6. Sato S, Fujimoto M, Ihn H, et al. Antibodies to centromere and centriole in scleroderma spectrum disorders. Dermatology 1994; 189: 23-6. Hamaguchi Y, Matsushita T, Hasegawa M, et al. High incidence of pulmonary arterial hypertension in systemic sclerosis patients with anti-centriole autoantibodies. Mod Rheumatol 2015; 25: 798-801. Hachulla E, Gressin V, Guillemin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005; 52: 3792-800. Sibon O, Jais X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. The European respiratory journal 2014; 43: 1691-7. Hassoun PM, Zamanian RT, Damico R, et al. Ambisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension. American journal of respiratory and critical care medicine 2015; 192: 1102-10. Mukherjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum 2003; 62: 1088-93. Rattner JB, Martin L, Waisman DM, et al. Autoantibodies to the centrosome (centriole) react with determinants present in the glycolytic enzyme enolase. J Immunol 1991; 146: 2341-4.

Conclusion

Our cases indicated that anticentriole antibodies-positive SSc may differ from other types of SSc in that the PH was more severe and more progressive. Therefore, careful hemodynamic observation is needed and timely intensive vasodilatory therapy may be useful for improving hemodynamics, however, tailor-made adjustment of therapy is needed for these patients.

Disclosure

Conflicts of interest: None.

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