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【 CASE REPORT 】

Immunosuppressive Treatment for an anti-U_1 Ribonucleoprotein Antibody-positive Patient with Pulmonary Arterial Hypertension

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Abstract:

A 34-year-old woman with pulmonary arterial hypertension (PAH) was admitted to the hospital. She had been diagnosed with PAH three years earlier and treated with triple vasodilator therapy. She was positive for anti-U_1 ribonucleoprotein antibodies but did not show any other symptoms associated with autoimmune diseases. Corticosteroid and cyclophosphamide therapy was administered, suspecting the involvement of immunological pathophysiology. After 3 weeks, the mean pulmonary artery pressure decreased from 50 to 38 mmHg without any change in the vasodilators. Immunosuppressive therapy was effective in this patient with PAH with an anti-U_1 ribonucleoprotein-antibody-positive response and might be an option for patients with these specific features.

Key words: pulmonary arterial hypertension, anti-U_1 RNP antibody, corticosteroid, cyclophosphamide

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Introduction

Pulmonary arterial hypertension (PAH) is a disease with a poor prognosis characterized by pulmonary artery remodeling and increased pulmonary artery pressure (PAP), typically leading to right ventricular failure and death and/or the need for lung transplantation. It has various causes, and the standard clinical classification of pulmonary hypertension (Nice classification) is used to divide the disease into five groups (1).

Both idiopathic PAH (IPAH) and PAH with connective tissue disease (CTD-PAH) are considered group 1, although they differ in not only pathophysiology but also treatment strategy. In IPAH, combination oral therapy with an endothelin receptor antagonist plus a phosphodiesterase type 5 inhibitor or prostanoid therapy infused with either treprostinil or epoprostenol combined with oral therapy is recommended to improve the outcome (2). For patients with PAH associated with systemic lupus erythematosus or mixed CTD (MCTD), immunosuppressive therapy combined with pulmonary vasodilators is suggested in the guidelines (3). In one case of PAH with immune thrombocytopenia, immunosuppressive therapy improved the functional status with better hemodynamics (4). However, whether or not immunosuppressive therapy improves the prognosis of patients with PAH who have autoimmune features but do not meet the CTD criteria remains unclear.

We herein report a PAH case positive for anti-U_1 ribonucleoprotein (RNP) antibody in which the PAP notably decreased with the off-label use of glucocorticoids and subsequent immunosuppressive therapy.

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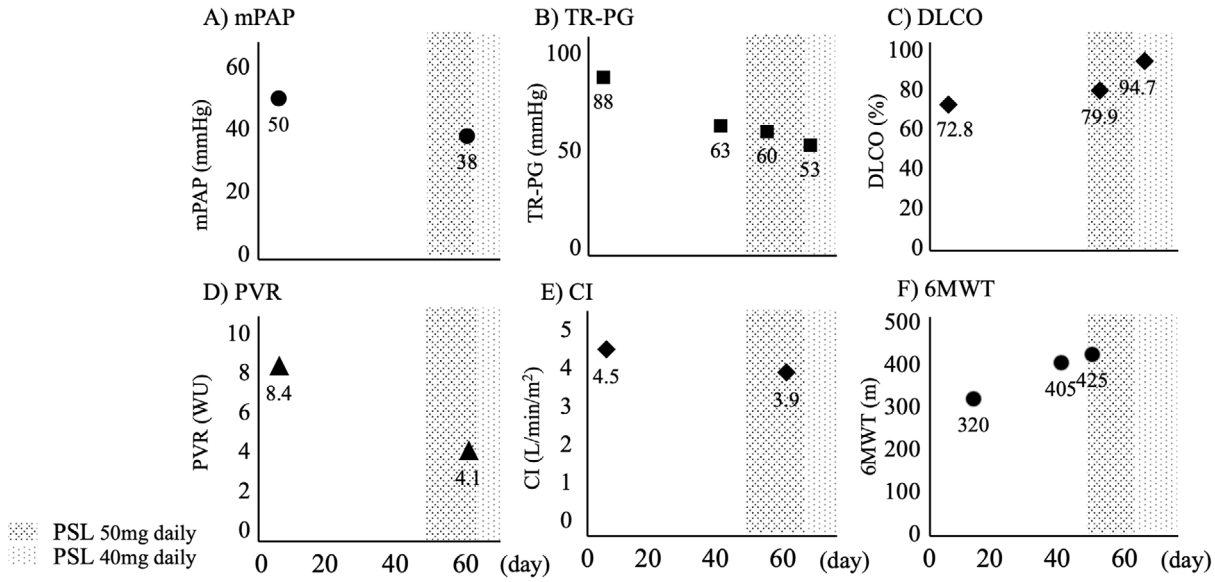

Figure 1. **A-F) The hemodynamic parameters after admission. The x-axis indicates days from admission, with day 0 set as the admission day. The y-axis indicates A) the mean pulmonary artery pressure (mPAP), B) the tricuspid valve regurgitation pressure gradient (TR-PG), C) the percentage diffusing capacity for carbon monoxide (DLCO), D) the pulmonary vascular resistance (PVR), E) the cardiac index (CI), and F) the distance covered in the 6MWT. The shaded area overlaid on the line graph indicates prednisolone (PSL) treatment. On day 65, 500 mg of intravenous cyclophosphamide (IVCY) was administered.**

Case Report

A 34-year-old woman had been diagnosed with PAH 3 years earlier based on her dyspnea and high PAP. At the time of the diagnosis, the tricuspid regurgitation pressure gradient (TR-PG) on the echocardiogram was 75.7 mmHg, and the mean PAP (mPAP) on right heart catheterization was 62 mmHg. Anti-U_1 RNP antibody was positive with a titer of 39.2 U/mL, while anti-SS-A and SS-B antibodies were negative. CTD was suspected because of positive anti-U_1 RNP antibody at another expert center but eventually was not diagnosed as CTD-PAH, and she had been treated with vasodilators as per the diagnosis of PAH (3). She was admitted for registration for lung transplantation. At the time of admission, she was receiving oral therapy (macitentan and riociguat) and intravenous prostacyclin (epoprostenol) at a dose of 47 ng/kg/min. She also took spironolactone, furosemide, and azosemide; however, her hemodynamic control remained poor, with elevated mPAP and TR-PG values. While she had a history of hypertension, gestational diabetes, and polycystic ovary syndrome, she had no history of alcohol consumption or smoking and no family history of autoimmune diseases.

On admission (day 0, Fig. 1), her temperature was 36.3°C; blood pressure, 98/53 mmHg; heart rate, 70 beats/min; respiratory rate, 18 breaths/min; and oxygen saturation, 94% while receiving supplemental oxygen through a nasal cannula at a flow rate of 2 L/min. She weighed 61.1 kg, and her body-mass index was 28.8 kg/m^2. A physical examination revealed a malar rash but no evidence of a discoid rash, Raynaud's phenomenon, oral or nasopharyngeal ulcers, photosensitivity, lower leg edema, skin hardening, swollen fingers, arthritis, myalgia, or neurological abnormalities.

Heart auscultation revealed an increased intensity of secondary heart sounds, but lung auscultation was unremarkable. An electrocardiogram showed right-axis deviation, suggesting a right heart load (Fig. 2). Chest radiography indicated protrusion of the bilateral pulmonary artery and did not show signs of pleural fluid or cardiac dilatation (Fig. 3). Contrast-enhanced computed tomography (CT) showed dilatation of the right heart and bilateral pulmonary arteries, with no thrombus in the pulmonary arteries. Centrilobular ground-glass opacities were also observed in both lungs, which may reflect plexogenic pulmonary arteriopathy related to PAH (Fig. 4). Ventilation-perfusion lung scintigraphy showed no signs of chronic thromboembolic pulmonary hypertension.

Pulmonary function tests revealed a restrictive pattern (forced expiratory volume, 88.5%; forced vital capacity, 71.7%; and diffusing capacity of the lungs for carbon monoxide, 72.8%). An echocardiogram showed a normal left ventricular function but right atrial dilation and mild-to-moderate regurgitation of the tricuspid valve (Fig. 5). The tricuspid regurgitation pressure gradient was 88 mmHg, suggesting PAH. The tricuspid annular plane systolic excursion and right ventricular fractional area change were 17 mm and 30%, respectively. A small amount of pericardial effusion was found. Right heart catheterization revealed an mPAP of 50 mmHg and a pulmonary artery wedge pressure of 12

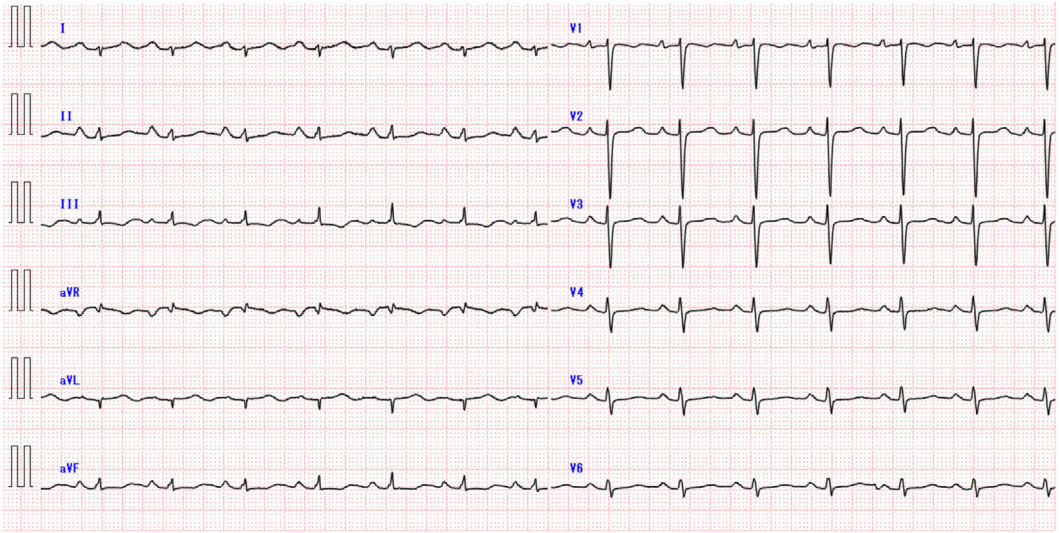

Figure 2. **Electrocardiogram findings showed right-axis deviation, suggesting right heart load.**

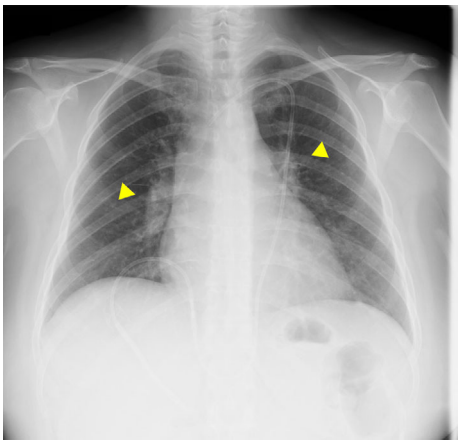

Figure 3. **Chest radiography findings indicating protruding bilateral pulmonary artery (yellow arrowheads) with no signs of cardiac dilatation or pleural fluid.**

mmHg. The cardiac output and cardiac index were 4.4 L/min and 2.9 L/min/m^2, respectively. Acute vasodilator response testing was not performed.

The serum levels of brain natriuretic peptide (BNP, 18.4 pg/mL) and Krebs von den Lungen 6 (KL-6, 112 U/L) were normal. Anti-nuclear, anti-double-stranded DNA, anti-aminoacyl-+RNA synthetase (ARS), anti-SS-A, anti-SS-B, anti-phospholipid, and myeloperoxidase- and proteinase 3-antineutrophil cytoplasmic antibodies were all negative. She did not show false positivity for syphilis. However, anti-single-stranded DNA (46.4 U/mL) and anti-U_1 RNP antibodies (23.0 U/mL, measured 6 months before admission with a normality value of 0-9.9 U/mL) were positive. The white blood cell count was 10,330/μL (neutrophils 78.7%, lymphocytes 16.0%, monocytes 3.0%, eosinophils 1.7%, basophils 0.5%), and the platelet count was 141×10^3/μL, whereas the serum C-reactive protein and serum creatinine levels were 0.08 and 0.61 mg/dL, respectively. Serum complement levels and urinalysis findings were normal. Diagnostic tests for Sjögren's syndrome (SS), such as a minor salivary gland biopsy, were not performed in the absence of ocular and oral dryness during the course. Based on the hypoxic state measured during a six-minute walk test, we determined her status as functional class (FC) III, as defined by the World Health Organization (WHO) classification.

Although the patient did not meet any of the criteria for CTD, her positivity for anti-U_1 RNP and anti-single-stranded DNA antibodies suggested an autoimmune pathophysiology. Because she did not respond well to vasodilator therapy, we administered immunosuppressive therapy consisting of glucocorticoids (50 mg prednisolone equivalent daily, i.e., 1 mg/kg/day during the first month, with a subsequent gradual reduction to a maintenance dose of 5 mg/day) before lung transplantation. The doses were based on reports on the treatment of CTD-PAH (5, 6), in agreement with the cardiologist and lung transplantation surgeon. At one week after treatment initiation, her shortness of breath partially improved, and the pressure gradient of tricuspid regurgitation on echocardiography decreased to 53 mmHg. Right heart dilatation and left ventricular flattening also improved (Fig. 6). Three weeks later, the mPAP measured during right heart catheterization had decreased as well (Fig. 1). Her oxygen requirements did not change significantly. The centrilobular ground-glass opacities on CT were unchanged after treatment. Because of the markedly positive hemodynamic response to glucocorticoids (decrease in mPAP by 24%, from 50 to 38 mmHg), intravenous cyclophosphamide (500 mg i.v., once per month) was also used as combination therapy starting on day 27 of treatment.

The patient was discharged six weeks after admission. No other vasodilators were administered during the hospitalization period.

Discussion

An anti-U_1 RNP antibody-positive patient with PAH clas-

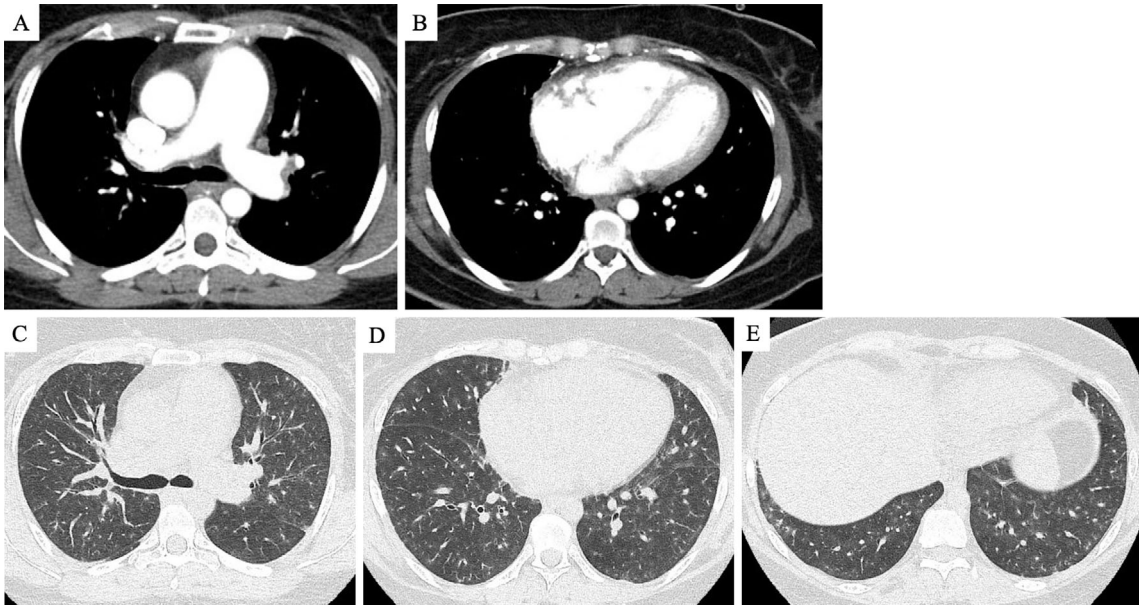

Figure 4. **Computed tomography findings of the chest. A-B) Contrast-enhanced computed tomography findings showing dilatation of the bilateral pulmonary arteries and right heart. No thrombus was visible in the pulmonary arteries. C-E) Centrilobular ground-glass opacities are visible in both lungs. Pleural effusion was not detected.**

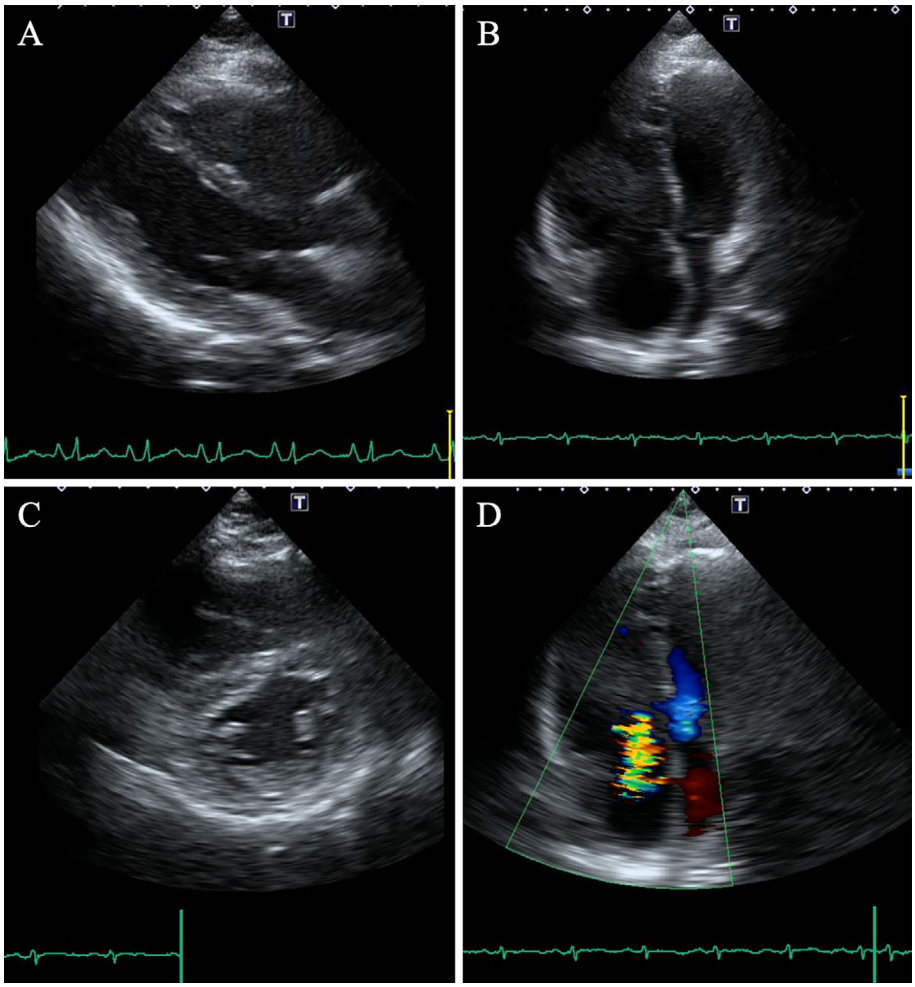

Figure 5. **Transthoracic echocardiogram findings. A) Parasternal long-axis view. B-C) The four-chamber and parasternal long axis views show right heart dilatation and septal flattening. D) Doppler imaging demonstrated mild to moderate regurgitation of the tricuspid valve.**

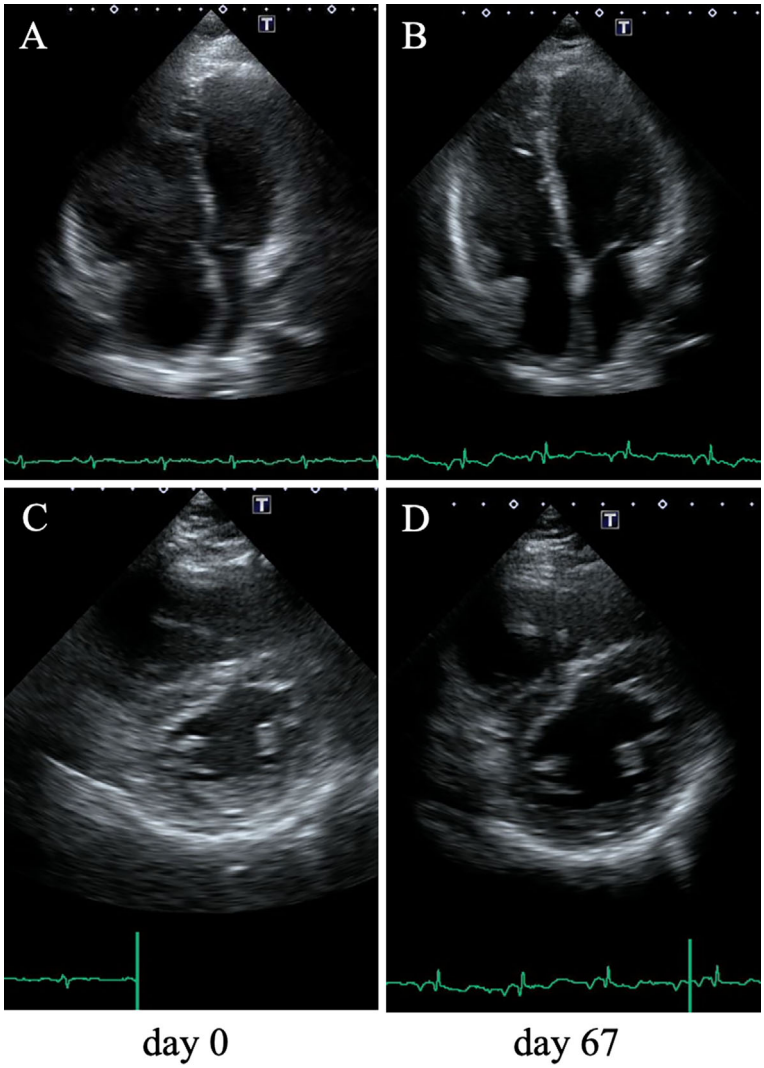

Figure 6. Echocardiogram findings (parasternal long- and short-axis views) on day 0 (A, C) and day 67 (B, D). Dilatation of the right heart and flattening of the left ventricle were improved after immunosuppressive treatment.

sified as FC III (WHO) responded well to the combination therapy of glucocorticoids and cyclophosphamide, with the mPAP measured during right heart catheterization markedly reduced by more than 10 mmHg after immunosuppressive therapy. Despite the positive response to autoantibody tests, she had never received immunosuppressive therapy, as this type of treatment is not recommended for patients without CTD. The rapid clinical course of the disease - only three years passed between the diagnosis of PAH and the registration for transplantation - raised the possibility of an underlying immunological process.

This severe case of PAH with positive anti-U1 RNP antibodies responded favorably to immunosuppressive therapy but did not meet the MCTD criteria. The supplementary statement in the 1996 MCTD criteria (7) stated that "anti-U1 RNP antibody-positive cases with pulmonary hypertension are likely to be classified as mixed connective tissue disease, even if clinical findings are inadequately fulfilled." Notably, in 2004, the criteria were revised to add PAH as a diagnostic category, and this statement was removed (8). This implies that immunosuppressive therapy would be effective if there was potential involvement of immune-mediated pathology, as in the present case; although, there is a lack of high-quality evidence to support this. A recent report suggested that approximately 40% of patients with non-CTD-PAH had some form of autoantibodies, indicating potential differences in the long-term prognosis (9).

Autoantibodies can contribute to the development and progression of PAH, which has been assumed to be through vascular damage due to endothelial cell activation and thrombosis or through occlusion of the vascular lumen due to immune complex deposition (10-12). Although few reports on the efficacy of immunosuppressive therapy in autoantibody-positive patients with PAH exist, glucocorticoid administration led to positive results in PAH complicated by immune thrombocytopenia (4). This successful approach to treatment is remarkably similar to the present case, in which the mPAP decreased from 50 to 38 mmHg in 1 month. The relatively rapid improvement in DLCO, a parameter suggesting the presence of pulmonary vasculopa-

thy (13, 14), was also observed in our case. This may be the result of improved pulmonary hemodynamics as reduced edema of endothelial cells by immunosuppressive therapy, considering that the oxygen demands and CT findings were unchanged after immunosuppressive therapy.

The clinical course suggests an underlying immunological mechanism based on the relatively rapid progression until registration for transplantation, the positive autoantibody test results, and the good response to immunosuppressive therapy. The clinical course of patients with CTD-PAH has been reported to be more rapidly progressive than that of patients with IPAH (15). The clinical course in the present case, in which the pulmonary vasodilator dosage rapidly increased, seemed to closely resemble that of CTD-PAH. The response to immunosuppressive therapy is generally considered to be better at earlier stages than at later stages (5); mPAP in patients with CTD-PAH is expected to decrease by 27.5% on average (from 40±9 mmHg to 29±11 mmHg), comparing values before and after immunosuppressive treatment (16). In the present case, the mPAP decreased by 24% (from 50 to 38 mmHg), showing a good therapeutic response similar to early CTD-PAH.

We acknowledge a remaining concern in this case: the mPAP seemed to be already improving before the start of immunosuppressive treatment. One potential explanation for this phenomenon is that decreased physical activity or dietary changes associated with hospitalization might have contributed to the hemodynamic improvement. Therefore, the benefit of immunosuppressive therapy should be interpreted with caution.

Conclusion

Immunosuppressive therapy can be an effective treatment for anti-U_1 RNP antibody-positive patients with PAH classified as FC III (WHO). Positivity for anti-U_1 RNP antibodies may be an indicator that autoimmune processes underlie the disease. In the future, the potential impact of immunosuppressive therapy on the prognosis should be included in the evaluation as our experience with similar immunotherapeutic cases increases.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The authors state that they have no Conflict of Interest (COI).

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