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Case report

Upfront triple combination therapy-induced pulmonary edema in a case of pulmonary arterial hypertension associated with Sjogren's syndrome

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ABSTRACT

Clinical efficacy of combination therapy using vasodilators for pulmonary arterial hypertension (PAH) is well established. However, information on its safety are limited. We experienced a case of primary Sjogren's syndrome associated with PAH where the patient developed pulmonary edema immediately after the introduction of upfront triple combination therapy. Although the combination therapy successfully stabilized her pre-shock state, multiple ground glass opacities (GGO) emerged. We aborted the dose escalation of epoprostenol and initiated continuous furosemide infusion and noninvasive positive pressure ventilation (NPPV), but this did not prevent an exacerbation of pulmonary edema. Chest computed tomography showing diffuse alveolar infiltrates without inter-lobular septal thickening suggests the pulmonary edema was unlikely due to cardiogenic pulmonary edema and pulmonary venous occlusive disease. Acute respiratory distress syndrome was also denied from no remarkable inflammatory sign and negative results of drug-induced lymphocyte stimulation tests (DLST). We diagnosed the etiological mechanism as pulmonary vasodilator-induced trans-capillary fluid leakage. Following steroid pulse therapy dramatically improved GGO. We realized that overmuch dose escalation of epoprostenol on the top of dual upfront combination poses the risk of pulmonary edema. Steroid pulse therapy might be effective in cases of vasodilator-induced pulmonary edema in Sjogren's syndrome associated with PAH.

1. Introduction

Combination therapy with pulmonary vasodilators for patients with pulmonary arterial hypertension (PAH) has been proven to be effective in improving the prognosis by recent clinical trials. Upfront dual combination is more effective than mono-therapy [1,2]. Furthermore, sequential triple combination is superior to dual combination [3], which led to the new clinical trial on upfront triple combination (TRITON study: NCT02558231). However, the safety profile of upfront triple combination and the approach to possible complications remain unclear [4].

Here we report a case of pulmonary edema emerging in the treatment of a connective tissue disease (CTD) associated with PAH with upfront triple combination therapy. Although we were unable to control the pulmonary edema by continuous intravenous diuretic infusion under noninvasive positive pressure ventilation (NPPV), steroid pulse therapy successfully ameliorated the pulmonary edema.

2. Case description

A 67-year-old woman complained of exertional dyspnea for four months and was admitted to our hospital with deteriorating resting dyspnea in recent weeks. She had no past history of previous respiratory or cardiac disease. Her blood pressure was 118/90 mmHg and heart rate was 120/minute. Clinical evaluation revealed mild jugular venous distention, bilateral leg edema, and a pan-systolic murmur at the 4th left sternal border. The plasma brain natriuretic peptide level was high (930 pg/mL). Electrocardiography revealed right axis

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Abbreviation

PAH	pulmonary arterial hypertension
GGO	ground glass opacities
DLST	drug-induced lymphocyte stimulation tests
PVOD	pulmonary veno-occlusive disease

deviation with SIQIIITIII (Fig. 1A). A chest X-ray showed cardiomegaly with a dilated right pulmonary artery (Fig. 1B). Echocardiography detected 56 mmHg of a tricuspid regurgitation pressure gradient, hypertrophy (RV free wall thickness: 7.3 mm) and low systolic function of right ventricle (TAPSE: 12 mm), and a compressed left ventricle forming a D-shape (Fig. 1C). Chest contrast-enhanced computed tomography (CT) revealed no lung diseases, pulmonary embolism, pleural effusion, or lymphadenopathy (Fig. 3B). Right heart catheterization (RHC) documented an increase in mean pulmonary arterial pressure (mPAP: 45 mmHg) with a normal pulmonary capillary wedge pressure (PCWP: 7 mmHg), and elevated pulmonary vascular resistance (PVR: 2156 dyne·sec/cm^5), decreased cardiac index (CI: 0.85L/min/m^2) as measured by Fick method. Antinuclear antibodies were positive at a titer of 1: 320 without positive findings of any specific antibodies including both Ro (SS-A) and La (SS-B) antibodies. On the basis of the complaint of a dry mouth, the patient underwent salivary gland scintigraphy showing reduced uptake in the left parotid gland (Fig. 1D). Shilmer's test and lip biopsy (Fig. 1E) were positive. Serum complement protein C3, C4, and total hemolytic complement (CH50) were within the normal range (103 mg/dl, 21.4 mg/dl, 48U/ml). Immunoglobulin G (IgG), A (IgA), and M (IgM) were also normal (930 mg/dl, 123 mg/dl, 85 mg/dl). Based on all the above findings, we diagnosed the patient with primary Sjogren's syndrome associated with pulmonary arterial hypertension.

Due to the severity of the patient's hemodynamics and resting dyspnea with a WHO functional class IV, upfront combination therapy using intravenous epoprostenol, macitentan, (10 mg/day), and sildenafil (60 mg/day) was initiated from day 0 together with dobutamine (Fig. 2A). The epoprostenol was initiated at a dose of 1 μg/kg/min, and was increased by 1–2 μg/kg/min every day up to 7 μg/kg/min. Her cardiac index markedly improved from 0.85 to 2.8 L/min/m^2 on day 4. However, multiple slight ground glass opacities (GGO) and bilateral pleural effusion (PE) emerged as well (Fig. 3B). To improve the congestion, we introduced continuous intravenous furosemide and a NPPV with 6 cmH_2O positive end-expiratory pressure (PEEP) (Fig. 2B) and stopped the dose escalation of epoprostenol. Regardless, the patient experienced intensive dehydration (2.2–5.7 L of urine volume/day), weight loss (64–54 kg), and a reduced PE during days 5–10, and low oxygen saturation (SpO_2 93%) (Fig. 2C) and GGO exacerbated (Fig. 3B) during days 10–14. We excluded left sided heart failure by a low PCWP (7 mmHg) and no feature of left ventricular diastolic dysfunction (E-Dct: 226msec from trans-mitral inflow, S/D 2.05 from pulmonary venous flow), infectious pneumonia by the negative sputum culture result, and interstitial pneumonitis by a normal level of KL-6 (231 U/ml). Drug-induced lymphocyte stimulation tests (DLST) for epoprostenol and the other medications used (heparin, atorvastatin, lansoprazole) were all negative.

We doubted that the pathophysiology of the pulmonary edema was due to transcapillary fluid leakage promoted by upfront triple combination of pulmonary vasodilators. We then tried intravenous steroid pulse therapy (Methlprednisolone 1000 mg/day for 3 days) from day 14. After steroid administration, pulmonary edema dramatically improved (Figs. 2C and 3B) and finally returned to baseline (Fig. 3B) on day 32. We continued the upfront combination therapy, terminated NPPV on day 24, and discontinued daytime-oxygen therapy on day 32. Follow-up RHC at day 31 showed a significant improvement of hemodynamics (mPAP: 20 mmHg, PCWP: 2 mmHg, PVR: 236 dyne·sec/cm^5, CI: 3.94 L/min/m^2). Upon notification of stable hemodynamics, we replaced intravenous epoprostenol with oral beraprost (360 μg/day) on days 33–43 without any deterioration of hemodynamics or symptoms (WHO functional class II). She was discharged on day 57 and was followed for over one year without any worsening of symptoms.

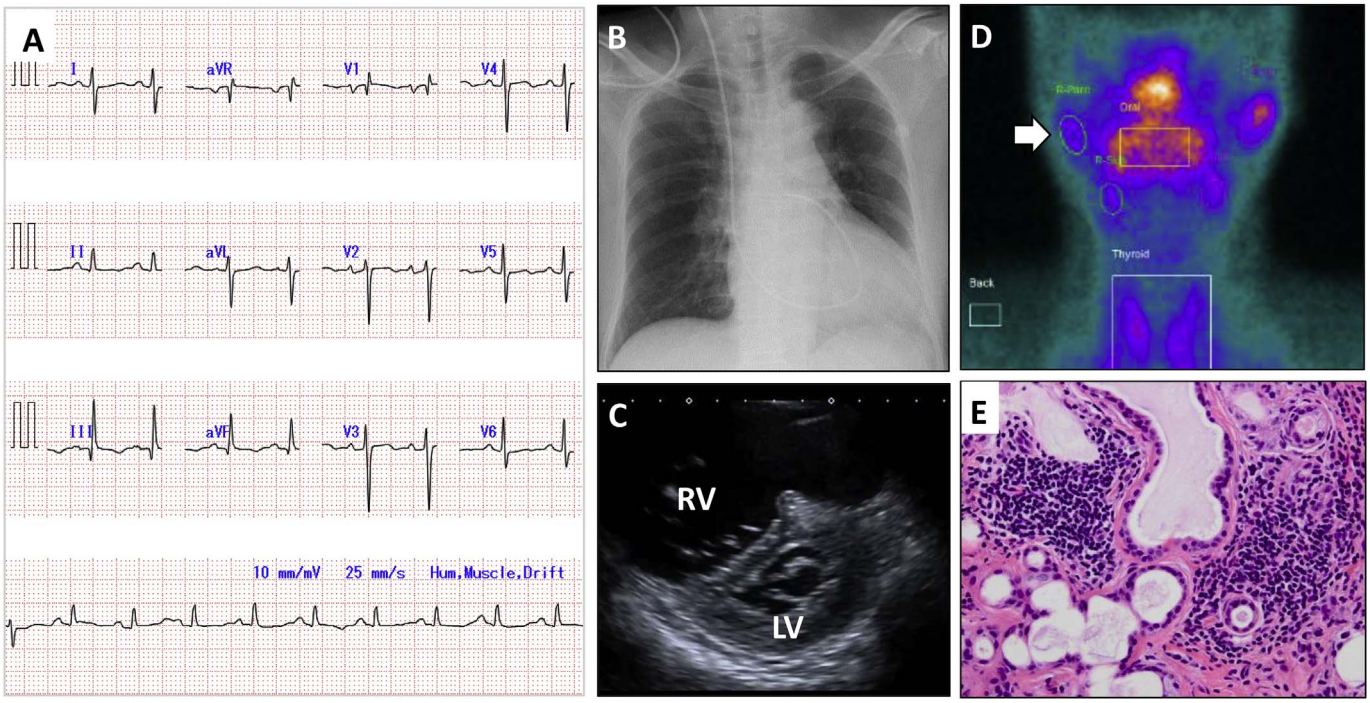

Fig. 1. A: Electrocardiography shows a normal sinus rhythm with right axis deviation and SIQIIITIII. B: A chest X-ray documents cardiac dilation and dilated right pulmonary artery. C: The echocardiographic findings reveal compression of the left ventricular. D: Reduced trace uptake in left parotid gland (⇨). E: Lymphocyte infiltration around acinus were detected in subcutaneous tissue of lip.

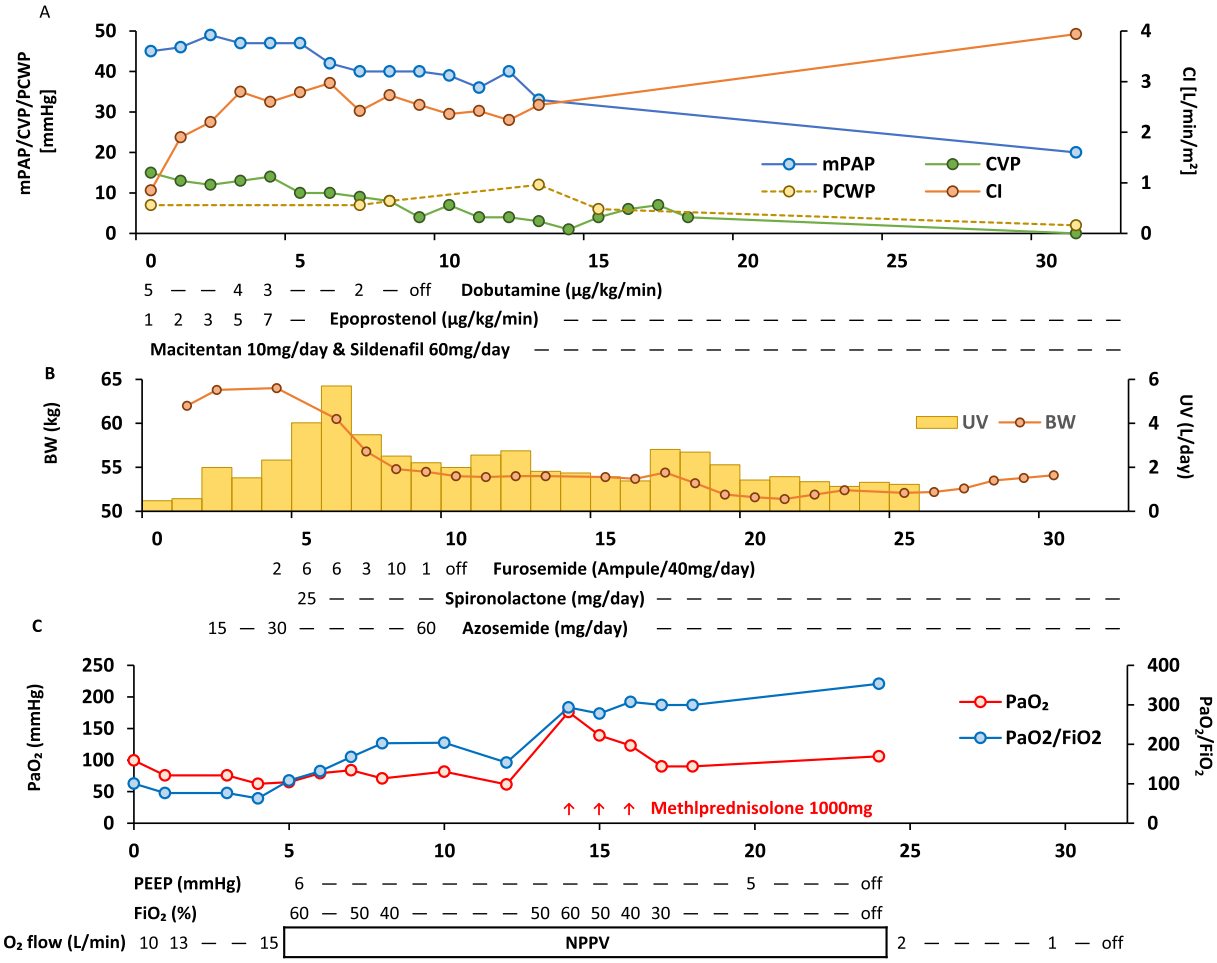

Fig. 2. A: Hemodynamic improvement after upfront combination therapy in the first 3 days. B: Fluid retention was also treated by diuretics from day 4–8. C: Low oxygen saturation sustained until day 14 under noninvasive positive pressure ventilation (NPPV: day 5-). Pulmonary edema was dramatically improved steroid pulse therapy (day 14–16). CI: Cardiac index, BW: Body weight, UV: Urine volume.

3. Discussion

3.1. Pulmonary edema induced by upfront combination therapy

In this case report, we described an instructive case that emphasized the complications of upfront triple combination therapy in treating PAH associated with Sjogren's syndrome. Although pulmonary edema as a side effect of oral combination therapy has not been reported in previous clinical trials [1–4], similar findings have been reported in cases where epoprostenol infusion was used in idiopathic PAH [5–7], scleroderma [8–10], pulmonary capillary hemangiomatosis [11], and pulmonary veno-occlusive disease (PVOD) [12,13]. Amelioration by steroid pulse therapy was also reported in some of those cases [6,7]. But, the mechanism of drug-induced pulmonary edema was not well described. This case let highlights a rare complication of upfront combination with pulmonary vasodilators and the optimal management for it.

3.2. Underlying pathophysiology of pulmonary vasodilator-induced pulmonary edema

For an accurate diagnosis of unexpected pulmonary edema, we excluded the possibility of interstitial and bacterial pneumonia. Cardiac pulmonary edema was also unlikely because of worsening chest CT findings after sufficient diuresis. No kerley B lines in chest X-ray (Fig. 3A) and reduced pleural effusion and cardiomegaly after diuretics and diffuse alveolar infiltration without inter-lobular septal thickening in chest CT (Fig. 3B), all these non-cardiogenic signs denied the possibility of increased capillary hydrostatic pressure from left heart failure [14]. Despite the availability of one case report with Sjogren's syndrome complicating PVOD [15], we also undoubted PVOD because chest CT at admission showed no GGO, thickened inter-lobular septal thickening, or lymphadenopathy. Ogawa et al. established a scoring system to predict PVOD when the score is over 4, sensitivity is 94% and specificity is 91% [16]. The score of our case is 3 (female:0, smoking history:0, ≧9% of oxygen desaturation during 6 minutes walking test:0, %DLco < 34%:0, GGO:1, inter-lobular septal thickening:0, centrilobular nodules:0, upper lobe defects in lung perfusion scintigraphy:0, and pulmonary edema after vasodilator:2). Kudelko et al. suggested that the pathophysiology of epoprostenol-induced interstitial pneumonitis is that of hypersensitive inflammatory response to epoprostenol, which is confirmed by a positive T cell proliferation assay [7]. In this case, however, acute respiratory distress syndrome was also denied from no remarkable inflammatory sign and negative results of DLST for epoprostenol. We speculated that the pathophysiology of pulmonary edema in this case might be due to transcapillary fluid leakage elicited by upfront triple combination therapy. We realized that overmuch dose escalation of epoprostenol on the top of dual upfront combination poses the risk of pulmonary edema.

3.3. Optimal management including steroid therapy

Pulmonary edema in previous reports occurred 15 minutes to 28 days after epoprostenol induction at a dose of 2–20 ng/kg/min. The

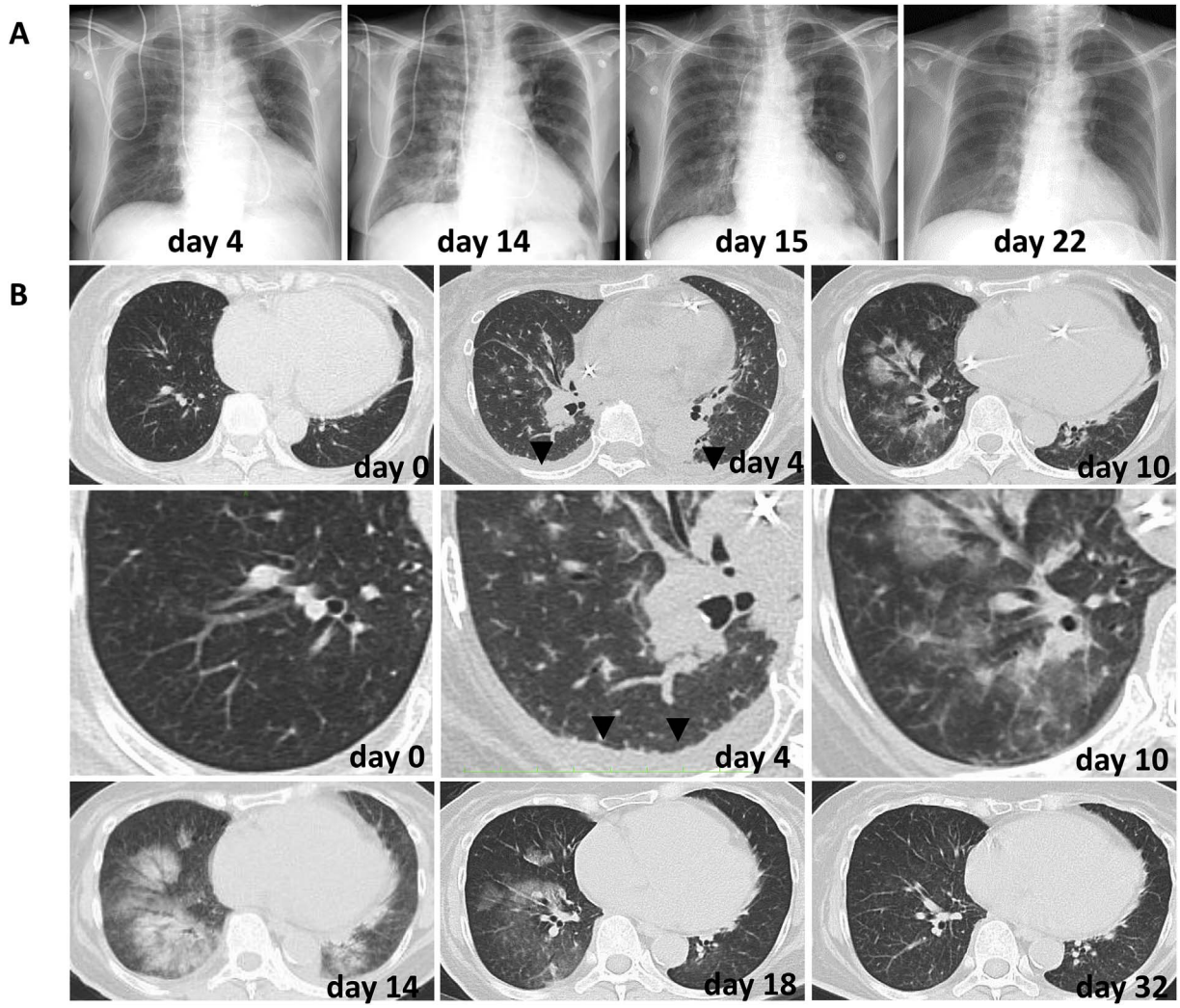

Fig. 3. A: In chest X-ray, pulmonary edema worsening from day 4 to day 14 in spite of reduced cardiomegaly, which improved by steroid at day 15. B: A chest CT-scan at day 0 is within normal limit. Multiple ground glass opacities (GGO) and pleural effusion (PE:▼) emerged from day 4. Regardless PE improvement, GGO without inter-lobular septal thickening became worse from day 10–14. Intravenous prednisolone pulse (1000 mg/day for 3 days) improved GGO at day 18 to normal limit (day 32).

dose escalation speed of epoprostenol was 1–2 ng/kg/min per day, similar to our protocol. Although the frequency of epoprostenol-induced pulmonary edema on the top of oral combination therapy is not known, we should be aware of the possibility of critical side effects so as to appropriately monitor the patient's condition. As we did not perform bronchoalveolar lavage or transbronchial lung biopsy, it was difficult to accurately determine the pathology. However, as seen from a dramatic amelioration by steroid therapy, the strategy to stabilize transcapillary fluid leakage by steroid pulse therapy [17] could be effective as a treatment option for similar cases.

4. Conclusion

We highlighted the rare but critical complication occurring in a patient with PAH associated with connective tissue disease. Exacerbating pulmonary edema against sufficient diuresis emphasized the existence of non-cardiogenic pulmonary edema in this case. The strategy to stabilize trans-capillary fluid leakage by steroid pulse therapy could be effective and considered as a treatment option for similar cases.

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Conflicts of interest (COI)

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