Respiratory Medicine Case Reports 23 (2018) 55–59

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

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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ARTICLE INFO

Keywords:
Steroid therapy
Ground glass opacity
Inter-lobular septal thickening
Epoprostenol
Acute respiratory distress syndrome
Trans-capillary fluid leakage

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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https://doi.org/10.1016/j.rmcr.2017.12.003
Received 6 September 2017; Accepted 6 December 2017

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.

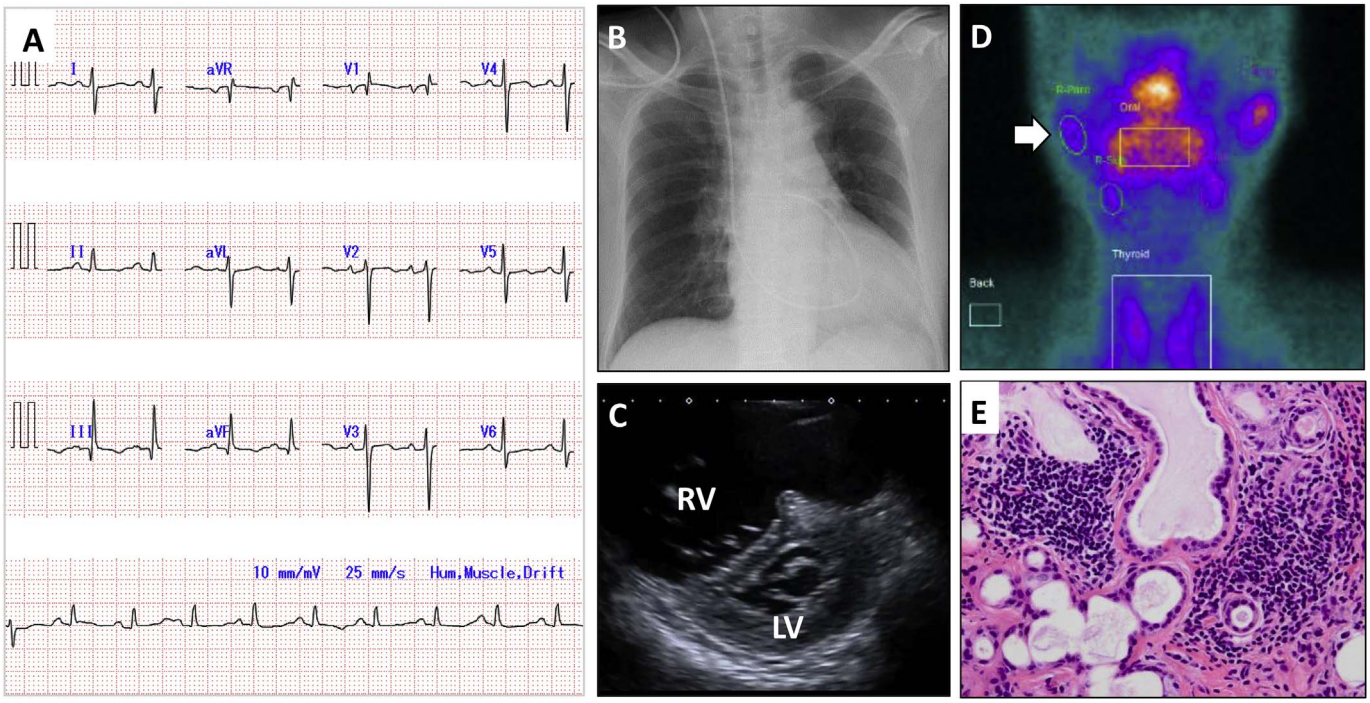

Fig. 1. A: Electrocardiography shows a normal sinus rhythm with right axis deviation and SIQIIITIII. B: A chest X-ray documents cardiac dilation and dilated right pulmonary artery. C: The echocardiographic findings reveal compression of the left ventricular. D: Reduced trace uptake in left parotid gland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