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CASE REPORT

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# Pulmonary hypertension secondary to interstitial fibrosis with pulmonary venous lesions masquerading pulmonary veno-occlusive disease

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## Abstract

We present a 41-year-old man with idiopathic interstitial pneumonia and pulmonary hypertension (PH) in the setting of a non-autoimmune background whose clinical presentation masqueraded pulmonary veno-occlusive disease (PVOD). Because of no histological evidence of venous occlusion in his previous lung biopsy, phosphodiesterase type-5 inhibitor was given, resulting in sudden onset of pulmonary edema. At autopsy, there were histological features of interstitial fibrosis with occlusion of the lobular septal veins and venules. Clinical presentations of PH due to interstitial fibrosis with pulmonary venous lesions may simulate those of PVOD and careful diagnostic and therapeutic approaches are required.

**KEYWORDS**
interstitial fibrosis, pulmonary edema, pulmonary hypertension, pulmonary veno-occlusive disease, targeted pulmonary arterial hypertension drugs

## INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic state of the pulmonary circulation defined by a mean pulmonary artery pressure (PAP) > 20 mmHg.[1] PH is a common complication of chronic fibrosing idiopathic interstitial pneumonia (IIP) which is characterized by viable amounts of fibrosis and inflammation.[2] The pathophysiologic basis for PH is not completely understood although microvascular rarefaction may play a role. On the other hand, pulmonary veno-occlusive disease (PVOD) is a very rare form of PH which is characterized by fibrotic narrowing and occlusion of the pulmonary venules.[3] Diagnosing PVOD is challenging and a definite diagnosis remains difficult.

We herein present a patient with PH secondary to fibrosing IIP with obstructed pulmonary venous lesions in the setting of a non-autoimmune background whose differential diagnosis from PVOD was clinically difficult.

## CASE REPORT

A 41-year-old man with the previous diagnosis of chronic fibrosing IIP and PH was admitted because of worsening dyspnea on exertion. One year prior to this admission, he underwent thoracoscopic lung biopsy of the left lower lobe which revealed the histological evidence of interstitial fibrosis. There were arterial stenoses probably secondary to PH but no pulmonary venous occlusion (Figure 1A). The diagnosis of chronic fibrosing IIP associated with PH and right heart failure was confirmed. Invasive hemodynamic studies at that time revealed elevated mean PAP (32 mmHg) with normal pulmonary capillary wedge pressure (PCWP)

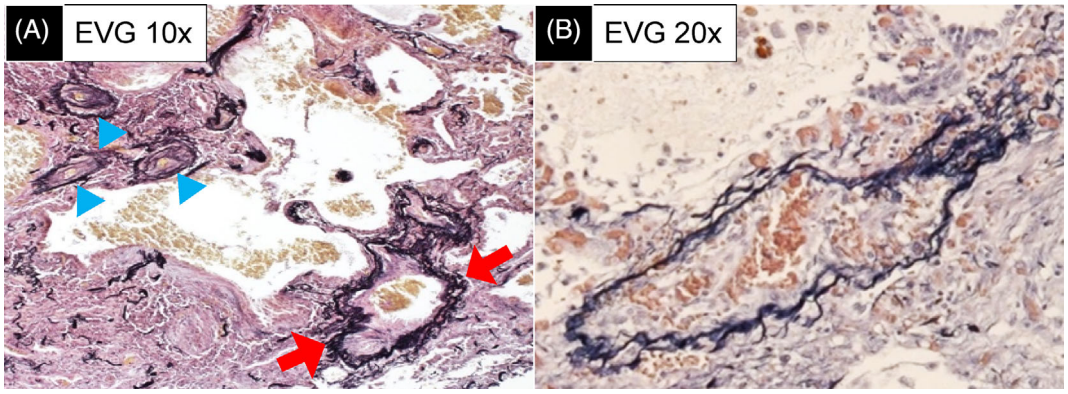


**FIGURE 1** (A) Thoracoscopic lung biopsy revealing histological features of arterial stenoses with muscular hypertrophy/intimal proliferation secondary to pulmonary hypertension (blue arrow heads). Patent pulmonary vein with mild intimal thickening (red arrows) was demonstrated. (B) Histological findings at autopsy showing pulmonary venous occlusion with intimal thickening caused by the increase of elastic fibres. EVG, Elastica van Gieson.

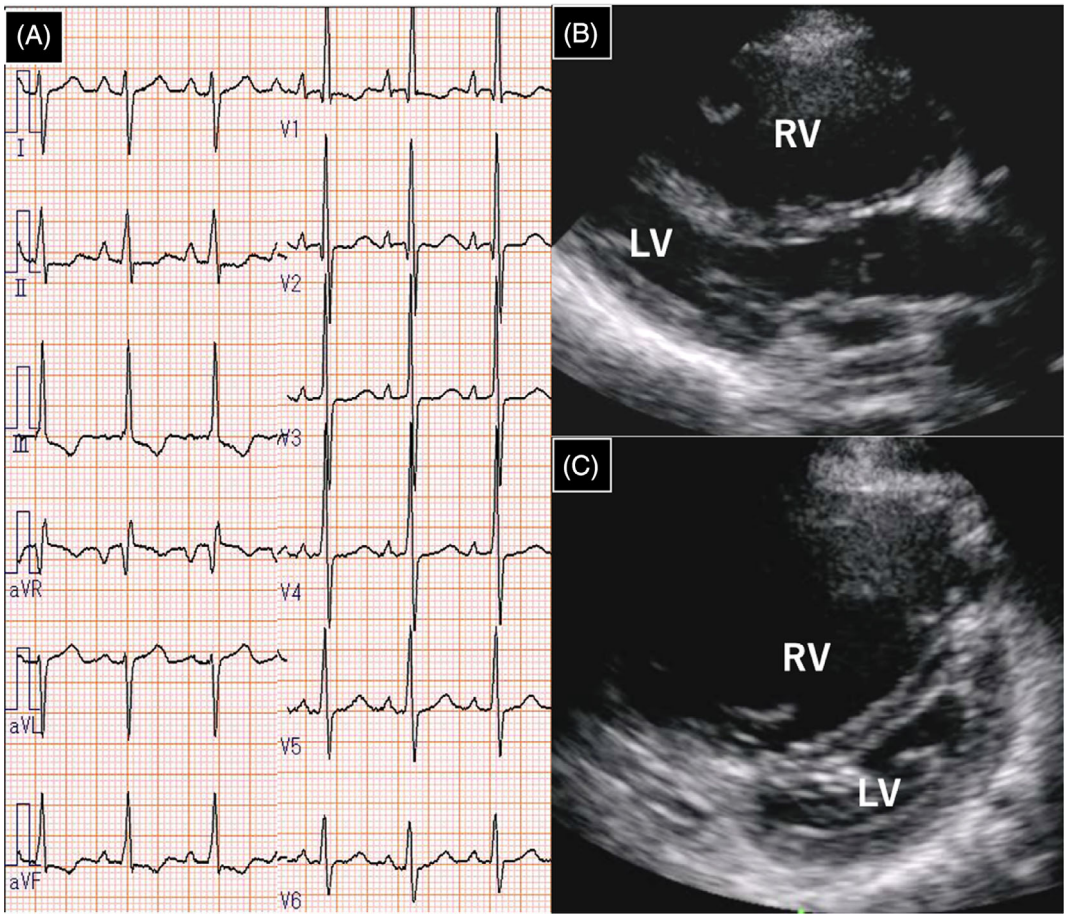


**FIGURE 2** (A) Electrocardiogram showing sinus tachycardia, right axis deviation, prominent P waves, and severe right ventricular hypertrophy. (B, C) Echocardiogram of the long-axis and the short-axis views showing marked right ventricular overload with interventricular septal concavity toward the left ventricle, indicative of severe pulmonary hypertension. LV, left ventricle; RV, right ventricle.

(14 mmHg). He was then put on antifibrotic drug, nintedanib. It was thought that he should be referred for lung transplantation in the near future.

On examination at this time, heart rate was regular at 118 beats per minute, blood pressure 98/68 mmHg and respiratory rate 28 breaths per minute. He had engorged jugular vein, accentuated pulmonary component of the second heart sound and fine crackles in both lungs. Pulse oximetry showed an oxygen saturation level of 90% on nasal oxygen of 2.0 L/min. Electrocardiogram revealed sinus

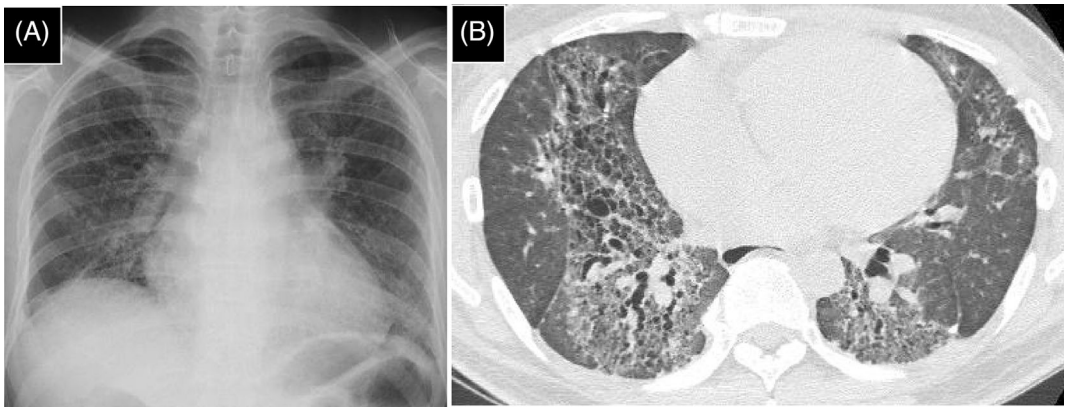


**FIGURE 3** (A) Chest radiograph on admission showing enlarged cardiac silhouette and enhanced interstitial lung shadow. (B) Computed tomography scan of the chest revealing extensive reticular shadows and bronchiectasis in the whole lung field.

tachycardia, right axis deviation, prominent P waves and severe right ventricular hypertrophy (Figure 2A). Chest radiograph revealed enlarged cardiac shadow and enhanced interstitial shadow in bilateral lungs (Figure 3A). Echocardiogram revealed right ventricular overload with interventricular septum pushed toward the left ventricle, indicative of severe PH (estimated mean PAP: 50 mmHg) (Figure 2B, C). CT scan revealed reticular shadow with bronchiectasis in the whole lung field (Figure 3B). A diagnosis of exacerbating heart failure secondary to PH was made. His respiratory state progressively deteriorated with the elevation of mean PAP despite intensive treatment.

Because there were no histological features of venous occlusion in the previous thoracoscopic lung biopsy, the decision was made to give phosphodiesterase type-5 (PDE-5) inhibitor. However, after few hours of initiating the treatment, his respiratory condition further deteriorated with sudden onset of pulmonary edema. Despite intensive treatment with mechanical ventilation, it was not possible to save his life. At autopsy, there were microscopic findings of destruction of alveolar structure, fibrotic change with smooth muscle growth and bronchial epithelial metaplasia suggestive of fibrosing interstitial pneumonia. In addition, there were histological features of occlusion of the lobular septal veins and venules with eccentric intimal thickening (Figure 1B). Obstructed pulmonary venous lesions associated with interstitial fibrosis was thought to be responsible for the sudden onset of severe pulmonary edema most probably initiated by the administration of PDE-5 inhibitor.

## DISCUSSION

Our case is unique because of the combination of chronic fibrosing IIP and obstructed pulmonary venous lesions with no evidence of autoimmune background. Case reports of such combination are scarce.

Pharmacotherapy with targeted pulmonary arterial hypertension (PAH) drugs, such as prostanoids, endothelin-1 receptor antagonists and PDE-5 inhibitors have significantly improved the quality of life and outlook for patients with PAH. On the other hand and more importantly, it has been recognized that PAH-specific vasodilator therapies carry a high risk of severe drug-induced pulmonary edema in patients with obstructed pulmonary venous lesions.[4] The pathophysiology of pulmonary edema in these patients is thought to be related to proximal arterial vasodilatation with increased pulmonary arteriolar blood flow against the fixed resistance of occluded pulmonary venules and veins. The resultant increase in the transcapillary hydrostatic pressure gradient may progress to severe pulmonary edema. Although we were very cautious to exclude the possibility of obstructed venous lesions by performing thoracoscopic lung biopsy before starting PAH-specific vasodilator therapy with PDE-5 inhibitor in our patient, it was unfortunately not possible to detect histological features of obstructed pulmonary veins. It was previously demonstrated that the significant reduction of the pulmonary vascular bed occurred by the extension of dense fibrosis[5] and that significant differences in vascular changes could be found depending on the background lung regions. It is therefore possible that there was uneven distribution of the lesions. A careful diagnostic approach is thus required to exclude the possible involvement of the pulmonary venous system with repetition of a right heart catheterization which is important to evaluate PCWP.

PVOD may account for approximately 10% of PAH cases.[4] Pathologically, PVOD is characterized by an obliterative fibrotic vasculopathy mainly affecting the smaller branches of the pulmonary venous tree.[3] PVOD was previously linked to occupational exposure to organic solvents such as trichloroethylene. Exposure to different chemotherapeutic agents, particularly alkylating agents, may also etiologically relevant. Bone marrow transplantation and radiotherapy have also been suggested as risk factor for PVOD. In addition, as the molecular pathogenesis of the disorder, biallelic mutations in eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2 AK4) gene was reported as the cause of heritable PVOD.[6] Although diagnosing

PVOD remains difficult, a non-invasive approach is primarily indicated. Important diagnostic information may include high-resolution chest tomography showing centrilobular ground glass nodular opacities, thickening of the interlobular septae, and hilar and mediastinal lymphnode enlargement, bronchoalveolar lavage with occult alveolar haemorrhage and medical history of pulmonary edema with PAH-specific therapy. As for treatment, conventional therapy for PAH with oxygen is basically recommended. Lung transplantation remains the only definitive therapy.

PVOD is characterized by an obliterative fibrotic vasculopathy, mainly affecting the smaller branches of the pulmonary venous tree.[3] Interstitial fibrosis with obstructed pulmonary venous lesions may probably provide similar pathophysiological and clinical condition of PVOD, although the group 3 PH, which is due to lung disease and/or hypoxia is supposed to be categorically distinguished from PAH and PVOD.[1] Although PDE-5 inhibitors do not have a weight of evidence in PH secondary to lung disease, PAH-specific vasodilator-induced pulmonary edema may thus similarly occur in patients with interstitial fibrosis with venous involvement as in those with PVOD. PAH-specific vasodilator therapy should be used with caution in these patients because of the high risk of inducing severe and life-threatening pulmonary edema. Early referral for lung transplantation should be considered at the time of diagnosis for eligible patients.

In conclusion, a patient with combination of IIP with obstructed pulmonary venous lesions in the setting of a non-autoimmune background was presented. Clinical presentations may simulate those of PVOD and careful diagnostic and cautious therapeutic approaches are required in patients with chronic fibrosing IIP.

## AUTHOR CONTRIBUTIONS

All authors contributed to patient care, preparation of the manuscript and have read and approved the text.

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## CONFLICT OF INTEREST STATEMENT

None declared.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

## ETHICS STATEMENT

Appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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