Pulmonary vein occlusion and veno-occlusive disease in a bilateral lung transplant patient: A case report

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A B S T R A C T

A pulmonary vein occlusion and biopsy proven pulmonary veno-occlusive disease (PVOD) and hemangiomatosis is found in a bilateral lung transplant patient. A 61-year-old male presents with dyspnea and chest pain with minimal exertion at routine follow up on post-transplant day of 50. Chest CT demonstrates new occlusion of bilateral superior pulmonary veins and diffuse pulmonary edema. Pulmonary vein occlusion is confirmed by *trans*-esophageal echocardiogram, and PVOD and hemangiomatosis is corroborated with lung biopsy. Normal pulmonary capillary wedge pressure (PCWP) and reduced DL_{CO} are also consistent with PVOD. Vigilant evaluation of large pulmonary venous thrombus is as important as of arterial thrombus in a postsurgical transplant status. A dedicated protocol of pulmonary venous phase scan would be beneficial to identify subtle pulmonary venous abnormalities. Although PVOD/PCH is normally considered in patients with nonspecific PAH symptoms, lacking of direct manifestation of PAH should not dismiss the diagnosis of PVOD/PCH, particularly in lung transplant individuals with large pulmonary vein occlusion, progressive respiratory symptoms, DLCO abnormalities, and pulmonary congestion since it may represent a wide spectrum of occlusive vascular disease.

1. Introduction

Since the first successful surgery involving lung in the early eighties of last century [1], lung transplantation has gained widespread acceptance as a treatment option for end stage pulmonary disease [2–5]. According to the 2017 report of the International Society for Heart and Lung Transplantation (ISHLT) [6], among 53,396 adult patients who underwent primary lung transplant between January 1990 and June 2015 had a median survival of 6.0 years. Bilateral lung transplant recipients had better survival than unilateral recipients beginning in the first year after transplant and this difference increased during the next 14 years of follow-up [6].

Tremendous knowledge has been gained regarding the post-transplant complications and survival after lung transplants has steadily improved during the past four decades [4,6,7]. A common approach of understanding post lung transplant complications depends on the postoperative time frame in which they typically occur. For example, complications along a continuum ranging from the immediate (<24 hours) to late (>4 months) postoperative period [5,8–10], including: (first 24 hours) donor-recipient size mismatch, hyperacute rejection; (24h–1 week) reperfusion injury (primary graft dysfunction), acute pleural complications; (8 days–2 months) acute rejection,

bronchial anastomosis complications, infections; (2–4 months) bronchial stenosis and bronchomalacia, pulmonary embolism and infarct; (over 4 months) chronic rejection, cryptogenic organizing pneumonia, posttransplantation lymphoproliferative disorder, bronchogenic carcinoma, primary lung disease recurrence, and lung/skin cancer etc.

In the current report, we would like to present a sophisticated and intriguing case of pulmonary vein occlusion associated with pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH), a rare complication in a post-lung transplant patient.

1.1. Clinical course

A 61-year-old male underwent bilateral lung transplant for end stage idiopathic pulmonary fibrosis. The transplanted lungs were from the same deceased donor with identical blood type and negative human leukocyte antigen (HLA) cross match. His course was complicated by post-op haemorrhage, coagulopathy, tracheitis, and retrosternal abscess and osteomyelitis. He presents with dyspnea and chest pain with minimal exertion in the clinic for his routine 50-day post-transplant follow up. His current oral medication includes mycophenolate mofetil, tacrolimus, prednisone, voriconazole for Aspergillus fumigatus, and oxycodone prn. In addition, trimethoprim-sulfamethoxazole,

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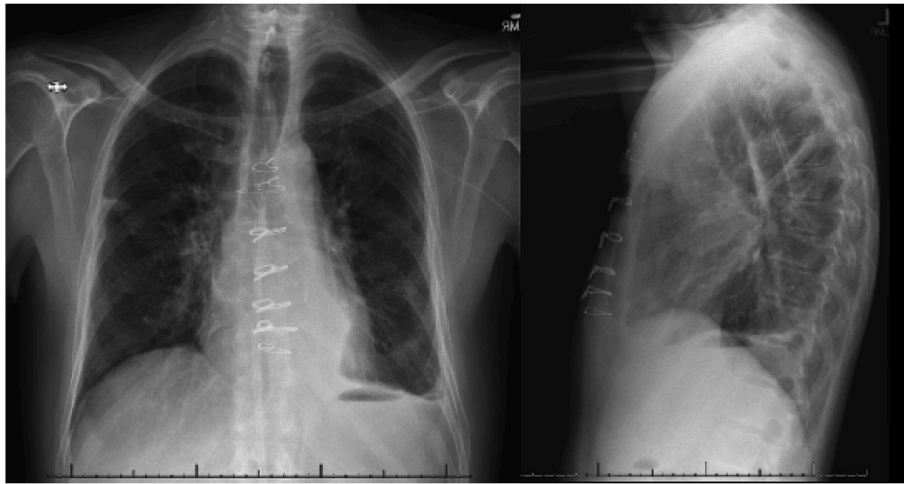
Fig. 1. PA and lateral view of the chest demonstrates post-operative changes of bilateral lung transplant and mild interstitial pulmonary edema. There is small left pleural effusion.
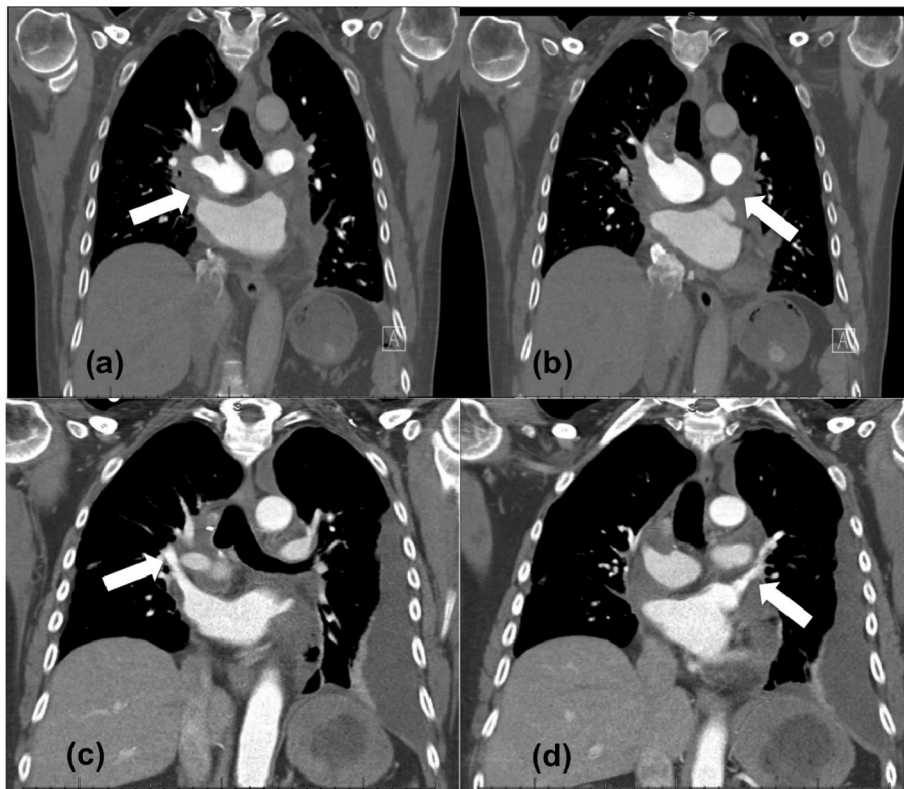
Fig. 2. Representative coronal contrast CT images on the day of 50 status post-transplant ((a) and (b)), demonstrating complete occlusion of the superior pulmonary veins bilaterally. In comparison with similar coronal images on the day of 16 status post-transplant ((c) and (d)), on which showing both superior pulmonary veins are patent.

valganciclovir and nystatin cream for his sternum wound. Physical exam demonstrates decreasing breath sound in the left base, otherwise unremarkable. BP 119/79, HR 83, RR 16, O_2 saturation 93%. The patient's ESR 91 mm/h and CRP 58.5 mg/L are increased while WBC is within normal limits.

Chest radiograph and subsequent high-resolution computed tomography (HRCT) with contrast are obtained. Chest radiograph (Fig. 1) shows mild interstitial pulmonary edema and small left pleural effusion. Mediastinal window chest CT demonstrates new occlusion of the bilateral superior pulmonary veins in comparison with prior contrast HRCT (Fig. 2). There is no significant mediastinal lymphadenopathy. Lung window images (Fig. 3) show slightly respiratory phase with geographic mosaic attenuation, mild ground glass opacities and interlobular septa thickening. Emergent finding of superior pulmonary vein occlusion was then relayed to the clinicians. Given patient's dyspnea, chest pain, mild hypoxia, as well as all the radiologic abnormalities, differentials at this time including pulmonary edema, parenchymal disease such as infection, rejection, pulmonary veno-occlusive vascular disease, and obstructive small airway disease.

Meanwhile, extensive infectious workup was negative with the exception of sputum growth of Enterococcus faecium which was treated appropriately without improvement of his dyspnea. Overall infection
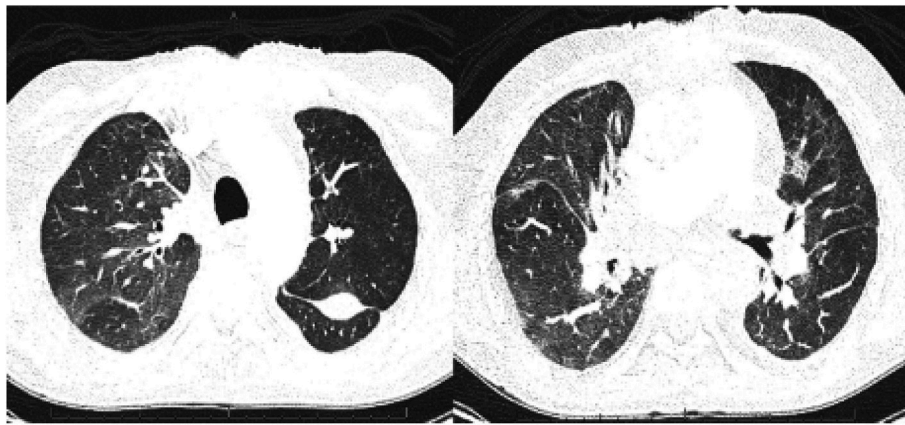
Fig. 3. Representative high-resolution axial CT lung window images though the upper and lower lobes on the 50 days status post-transplant. It demonstrates ground glass opacities and interlobular septa and fissure thickening, suggestive of pulmonary edema.
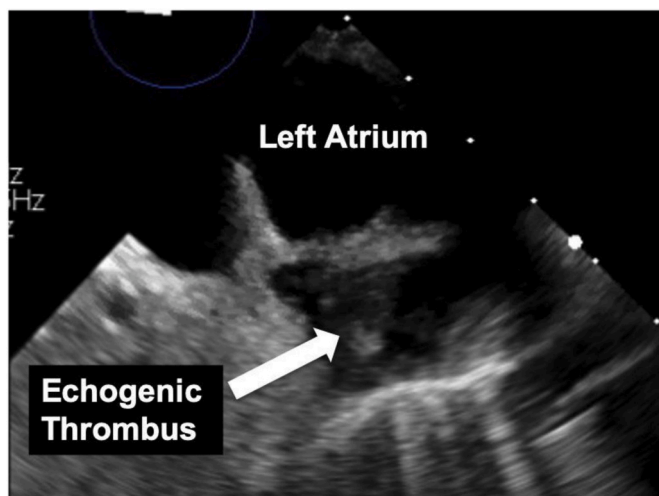

Fig. 4. *Trans*-esophageal echocardiogram demonstrates echogenic thrombus within the superior pulmonary vein.

felt less likely to be the cause of his progressive dyspnea and chest pain.

Given the macroscopic pulmonary venous occlusion, pulmonary arterial hypertension (PAH) was suspected. The right heart catheterization is subsequently performed and showing normal pulmonary arterial pressure 18 mmHg and unremarkable pulmonary vascular resistance 152 dyn s cm^{-5}. Pulmonary capillary wedge pressure (PCWP) measures 8 mmHg on right and 6 mmHg on the left, respectively, which is also within normal limits. These results are somewhat unexpected in the circumstances of large pulmonary vein occlusion, but assumptions were made that it might be in a very early and acute venous occlusion phase while the abnormal PCWP/PAH has not been developed yet. *Trans*-esophageal echocardiogram is performed, intraluminal echogenic thrombus is demonstrated in the expected location of the superior pulmonary veins (Fig. 4) bilaterally. This is consistent with contrast HRCT chest study. There is no thrombus visualized in the cavity of the left atrium or the left atrial appendage. The pulmonary spirometry is notable for an FEV1 of 1.79 L (47%), slightly decreased from his best post-lung transplant FEV1 of 1.88 L. Six-minute walk test was unsuccessful due to fatigue and shortness of breath. Overall pulmonary function test (PFT) picture is suggestive of restrictive physiology with reduced DL$_{CO}$ (34%). In the setting of recent bilateral lung transplant with new pulmonary vein occlusion and geographic mosaic attenuation, acute allograft rejection or pulmonary venoocclusive vascular disease remains in the differentials.

In order to confirm or rule out the rejection and/or pulmonary veno-occlusive disease (PVOD), the patient then underwent video-assisted thoracoscopic (VATS) surgical wedge biopsy of the right upper lobe the same day as the *trans*-esophageal echocardiogram. The pathological microscopic images of H&E stain and CD31 immunohistochemistry (Fig. 5) demonstrates thickening of the small blood vessels/venules in the pleura and subpleural space, as well as alveolar septa small capillary proliferation, compatible with PVOD/PCH. No evidence of acute cellular vascular or airway rejection, acute bronchopneumonia or granulomatous inflammation identified.

Since there is no definite optimal treatment of PVOD/PCH in this newly lung transplant patient, the decision from the multidisciplinary team meeting was made to proceed with a pulmonary venous thrombectomy and stent the occluded superior pulmonary vein [11] via interventional access to the left atrium via *trans*-septal puncture from right heart (Fig. 6). The patient demonstrated improvement in symptoms after the intervention. Defibrotide, an antithrombotic agent used for hepatic veno-occlusive disease, was considered and approved but was not administered to our patient given the need for anticoagulation in the setting of pulmonary venous stent.

2. Discussion

Pulmonary venous stenosis is a rare complication of lung transplant [6] and the incidence of isolated pulmonary venous thrombosis is reported to be 15% [12,13]. Although its incidence is much lower than pulmonary artery embolism but potentially could result in a devastating consequence. The evaluation of the pulmonary venous patency is often overlooked but should be exclusively included in the radiographic search pattern, especially in a postsurgical transplant status. Timing of contrast bolus sometimes makes the evaluation suboptimal since most of the time the studies are ordered and performed for pulmonary arterial embolus assessment. The literature report on post-lung-transplant PVOD and (PCH) [14,15] is even fewer. To our best knowledge, the current case is the first case reported with both pulmonary vein occlusion (macroscopically) and PVOD/PCH (microscopically) in a bilateral lung transplant patient.

PVOD and PCH is an uncommon subgroup of primary PAH that preferentially affects post-capillary pulmonary vasculature [16,17]. It accounts for 5–10% of cases initially considered to be idiopathic PAH [18] and it's still debating whether PVOD and PCH are varied expressions of same condition or different entities [16,19,20]. PVOD has been reported across all age groups and occurs equally in men and women [21,22]. Clinical presentations are similar to PAH including fatigue, dyspnea, hemoptysis and right heart failure. Radiographic manifestation of PVOD is unfortunately nonspecific. Enlarged pulmonary trunk and interstitial pulmonary edema are main radiographs findings. HRCT
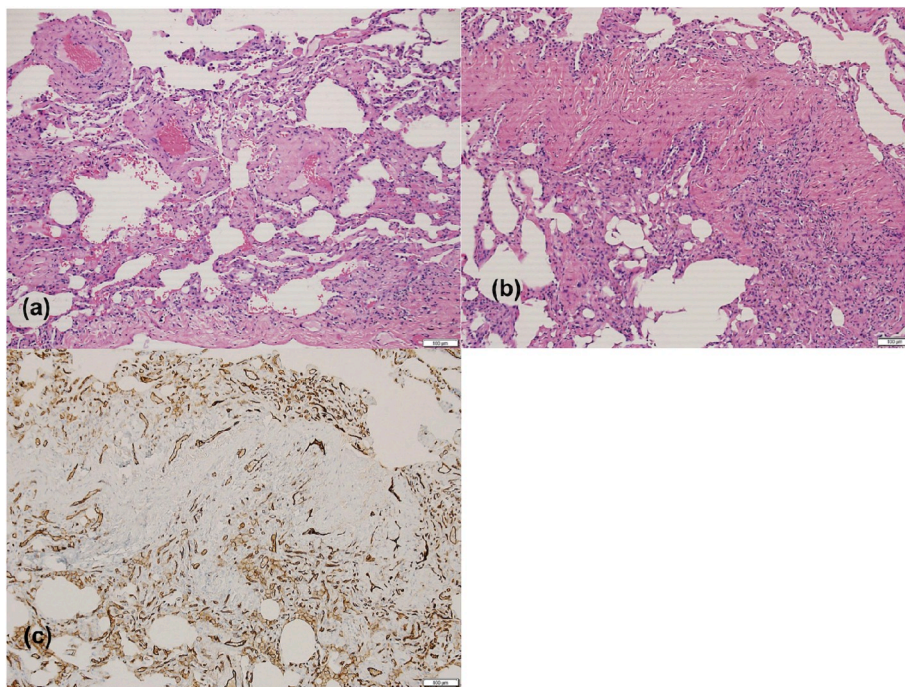
Fig. 5. (a) In veno-occlusive disease, thickening of the small blood vessels and venules in the pleura and subpleural space is a common histologic feature. Proliferation of small capillaries within the alveolar septa is highlighted with CD31 immunostaining, consistent with hemangiomatosis ((b)– H&E stain; (c) – CD31 immunohistochemistry of the same area). Often, hemangiomatosis is more evident adjacent to interlobar septum, as shown here.
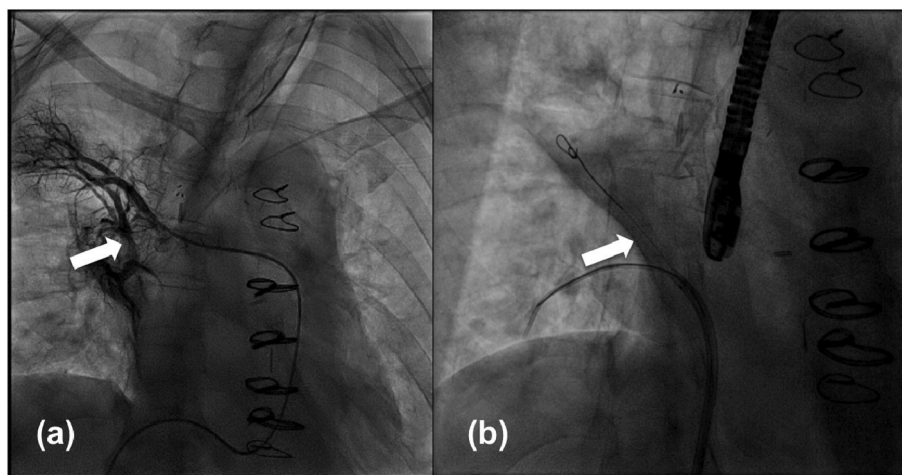
Fig. 6. (a) Delayed phase of right superior pulmonary angiogram demonstrates patent pulmonary artery and significant stenosis/occlusion of the right superior pulmonary vein. (b) Fluoroscopic image status post right superior pulmonary vein stent placement.

often demonstrates mosaic attenuation of the lung, ground-glass opacities, and smooth interlobular septal thickening. Micronodular ground glass opacities are more typically seen in PCH [16], which is not demonstrated in this patient. In the current case, there is lack of both radiographic and pathophysiological evidence of PAH. This phenomenon may result from acute large pulmonary vein occlusions associated with PVOD/PCH, which potentially delays the development of the PAH. The nonspecific HRCT manifestations such as geographic mosaic attenuation, ground-glass opacities, and interlobular septal thickening probably are suggestive but not diagnostic of PVOD and PCH, which may represent a wide spectrum of occlusive vascular disease.

Pathological features of PVOD are extensive occlusion of pulmonary veins by fibrous tissue in a patchy distribution. PCWP can be normal due to patchy distribution. PVOD is generally considered idiopathic, but numerous associations have been reported in the literatures, such as

EIF2AK4 mutations [23,24], smoking, connective tissue disease [25], sarcoidosis, HIV infection, bone marrow transplant [26], radiation and chemotherapy. Diagnosis is challenging and lung biopsy is still considered to be the gold standard for PVOD. However, the combination of very low DL_{CO}, resting hypoxemia, severe desaturation on exercise, two or more characteristic radiological signs on chest HRCT and occult alveolar haemorrhage on bronchoalveolar lavage has been proposed to support a diagnosis of PVOD [27].

General prognosis of PVOD is poor. Treatment options are supportive care, targeted PAH therapy, immunosuppressive therapy, and lung transplant. Interestingly, the PVOD was found in a post lung transplant patient in this study. It's unclear what is the predominant etiology of this patient's PVOD, it could be contributed from the donor's genetic predisposition, reperfusion injury, extra-pulmonary factors [15], rejection spectrum secondary to non-HLA antigens [28,29] or chemotherapeutic

medication toxicity. Like any interesting case, this study raises more clinical questions and uncertainties than answers, and our ability to answer these questions can be either enhanced or challenged by the unique presentation in the study.

The caveat from this case are two folds. To begin with, radiographically vigilant evaluation of large pulmonary venous thrombus is as important as of arterial thrombus in a postsurgical transplant status. A dedicated protocol of pulmonary venous phase scan would be beneficial to identify subtle pulmonary venous abnormalities. Second, although PVOD/PCH is normally considered in patients with nonspecific PAH symptoms, lacking of direct manifestation of PAH should not dismiss the diagnosis of PVOD/PCH, particularly in lung transplant individuals with large pulmonary vein occlusion, progressive respiratory symptoms, DLCO abnormalities, and pulmonary congestion since it may represent a wide spectrum of occlusive vascular disease.

Declaration of competing interest

The authors declare no conflict of interest to report.

CRediT authorship contribution statement

Xiao Wang: Conceptualization, Methodology, Software, Validation, Investigation, Project administration, Writing - original draft, Writing - review & editing, Visualization. **Kexin Zheng:** Validation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Emilian Racila:** Visualization, Data curation, Investigation, Writing - original draft. **Tadashi Allen:** Supervision, Conceptualization, Project administration, Writing - review & editing, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101031.

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