Refractory Pulmonary Edema Caused by Late Pulmonary Vein Thrombosis After Lung Transplantation: A Rare Adverse Event

Eve J. Denton, MBBS, MPH, Adam Rischin, MBBS, David McGiffin, MBBS, FRACS, Trevor J. Williams, MBBS, FRACP, Miranda A. Paraskeva, MBBS, FRACP, Glen P. Westall, MBBS, FRACP, and Greg Snell, MBBS, FRACP

Lung Transplant Unit, and Cardiothoracic Surgical Unit, Alfred Hospital, Melbourne, Victoria, Australia

After lung transplantation, pulmonary vein thrombosis is a rare, potentially life-threatening adverse event arising at the pulmonary venous anastomosis that typically occurs early and presents as graft failure and hemodynamic compromise with an associated mortality of up to 40%. The incidence, presentation, outcomes, and treatment of late pulmonary vein thrombosis remain poorly defined. Management options include anticoagulant agents for asymptomatic clots, and thrombolytic agents or surgical thrombectomy for hemodynamically significant clots. We present a rare case highlighting a delayed presentation of pulmonary vein thrombosis occurring longer than 2 weeks after lung transplantation and manifesting clinically as graft failure secondary to refractory pulmonary edema. The patient was treated successfully with surgical thrombectomy and remains well. We recommend a high index of suspicion of pulmonary vein thrombosis when graft failure after lung transplantation occurs and is not responsive to conventional therapy, and consideration of investigation with transesophageal echocardiography or computed tomography with venous phase contrast in such patients even more than 2 weeks after lung transplantation.

(Ann Thorac Surg 2016;102:e197–9)

Pulmonary vein thrombosis is a rare, potentially life-threatening adverse event of lung transplantation, arising at the pulmonary venous cuff, anastomosis and is typically an early adverse event presenting as early graft failure or hemodynamic compromise [1–3]. There has been one case report of this adverse event occurring later, 24 days after lung transplantation, in a patient presenting with a middle cerebral artery stroke [4]. We report a unique late adverse event after bilateral sequential lung transplantation manifesting as refractory pulmonary edema that resolved after surgical thrombectomy.

Accepted for publication Jan 23, 2016.

Address correspondence to Dr Denton, Lung Transplant Unit, Alfred Hospital, 5th Fl, 91 Commercial Rd, Prahran, Melbourne, Victoria, 3181, Australia; email: eve.denton@gmail.com.

A 64-year-old man with advanced idiopathic pulmonary fibrosis was listed for lung transplantation. His lung disease was complicated by mild pulmonary hypertension, with a mean pulmonary artery pressure of 27 mm Hg on a right heart catheterization, type 2 diabetes, minor coronary artery, disease and dilated cardiomyopathy, with a left ventricular ejection fraction of 43%.

The patient underwent transplantation during an admission with respiratory failure secondary to disease progression and underwent bilateral sequential lung transplantation with the use of cardiopulmonary bypass. At induction of anesthesia, acute right ventricular dysfunction with subsequent cardiac arrest occurred, requiring 3 minutes of cardiopulmonary resuscitation. The donor lungs, taken after circulatory death, were well matched in size, and the procedure was otherwise uncomplicated. The pulmonary venous anastomosis was performed by a continuous suture of Prolene, assuring apposition of the endothelial surfaces. Standard triple immunosuppression of methylprednisolone, mycophenolate and tacrolimus was commenced.

The early course was uneventful, with extubation occurring on day 3 and transfer to the ward on day 6. The patient initially progressed well toward discharge. He was treated with prophylactic enoxaparin throughout the admission. At 14 days after transplantation, he experienced rapid atrial fibrillation with hypotension, dyspnea, and hypoxemia (arterial blood gas P_aO_2 71 mm Hg and F_iO_2 0.6, p_aCO_2 34 mm Hg, pH 7.50). A chest roentgenogram demonstrated left lower lobe infiltrates that progressed to extensive bilateral infiltrates (Fig 1). The differential diagnoses included cardiogenic pulmonary edema, noncardiogenic pulmonary edema (secondary to infection or acute rejection and exacerbated by hypoalbuminemia), pneumonia, or acute rejection. The patient's condition was deemed too unstable to allow performance of bronchoscopy and biopsy, and thus empiric treatment with diuretics, antibiotics, high-flow oxygen, and continuous positive airway pressure was initiated. Despite this treatment, there was no improvement over 6 days, with progressive bilateral chest radiographic opacities.

A computed tomographic (CT) pulmonary angiogram was negative for pulmonary embolism, and high-resolution images revealed asymmetric bilateral ground-glass opacities. An empirical 3-day steroid pulse with intravenous methylprednisolone was administered to cover for acute rejection. Owing to a lack of response, he underwent elective endotracheal intubation to facilitate transbronchial biopsy, whose specimens subsequently showed the nonspecific finding of organizing pneumonia and interstitial pneumonitis without infection or rejection (ISHLT AO BX). Immediately after the biopsy, a transesophageal echocardiogram (TEE) identified a large thrombus in the right upper pulmonary vein and another smaller thrombus in the left lower pulmonary vein (Fig 2). A CT scan of the chest with venous phase contrast confirmed these findings (Fig 1). Although thrombolytic therapy was considered, because of the likely age of the

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.01.090

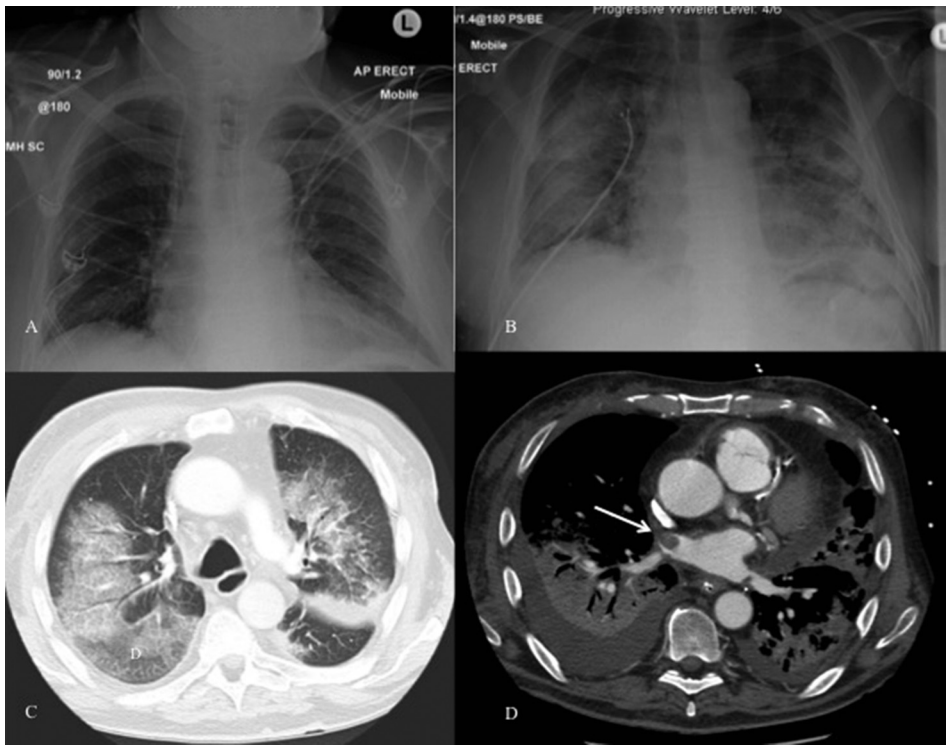

Fig 1. (A) Roentgenogram of the chest, which is relatively clear on day 6 after bilateral lung transplantation. (B) Roentgenogram of the chest on day 27, showing worsening of bilateral infiltrates despite extensive treatment. (C) Computerized tomographic (CT) image revealing bilateral ground-glass opacities. (D) CT venogram showing right superior pulmonary vein thrombus.

thrombus and the risk of systemic embolization, an urgent surgical approach was deemed most appropriate.

The previous right anterolateral thoracotomy was reopened. With the use of cardiopulmonary bypass and cold cardioplegic myocardial protection, the left atrium was entered through Sondergaard's groove rather than the pulmonary venous anastomosis to avoid potential fragmentation of the thrombus. A 2-cm semiorganized

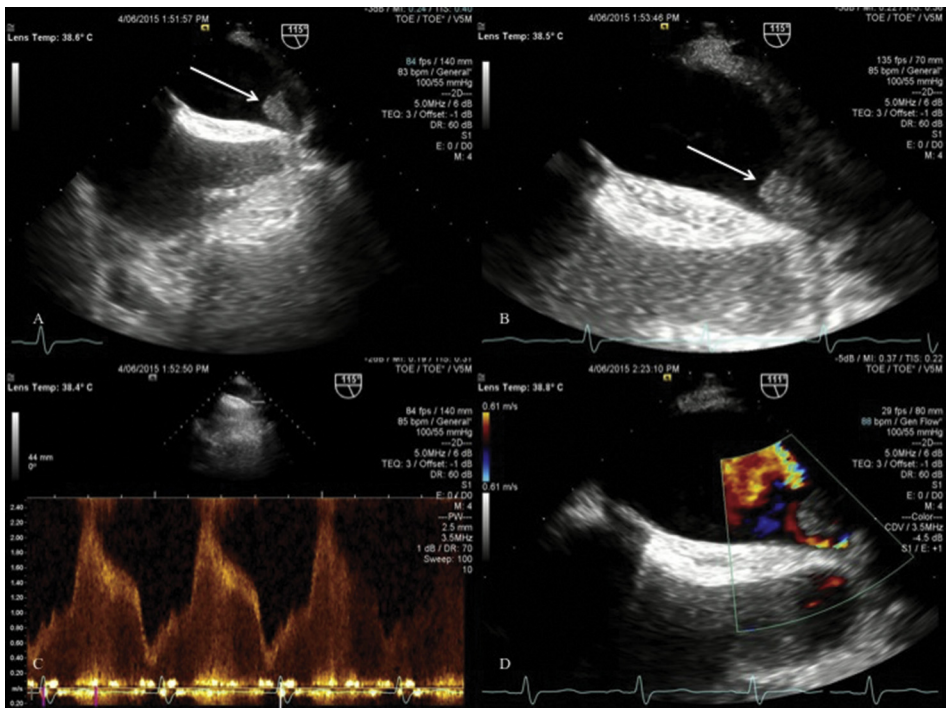

Fig 2. (A, B) Transesophageal echocardiogram showing pulmonary vein thrombus in the left lower pulmonary vein on two-dimensional images. (C) Increased left pulmonary vein Doppler flow velocities of 2.2 meters per second. (D) Flow around the pulmonary vein thrombus on color flow Doppler.

thrombus was removed from the orifice of the right upper lobe pulmonary vein. There was no suggestion of narrowing of the venous anastomosis, and no other thrombus was evident.

The patient's oxygenation, pulmonary infiltrates, and respiratory support improved significantly after operation over a few days. Magnetic resonance imaging of the brain revealed multifocal embolic strokes, although they were subclinical. The patient made a gradual physical recovery and was transferred to rehabilitation before discharge home, where 8 months later he remained well.

Comment

Pulmonary venous thrombus may be underdiagnosed and carries a high mortality. In a prospective, single-center study of lung transplantation patients undergoing TEE 48 hours after transplantation, 15% had thrombus at the pulmonary venous anastomosis [5]. The 90-day mortality in those with pulmonary vein thrombosis was 38%, but this study is of uncertain relevance today, with improved surgical techniques [5]. The incidence, presentation, and outcomes of late pulmonary vein thrombosis remain poorly defined, with no prospective studies and limited anecdotal reports examining this adverse event [4]. The place of various management options, conservative management with anticoagulant agents for small, asymptomatic clots, and thrombolytic agents or surgical thrombectomy for larger, hemodynamically significant clots, [3, 5–8] has not been defined.

This case report highlights a rare late adverse event of pulmonary vein thrombosis in a patient predisposed to inflammation as a result of severe underlying disease, donation from a cardiac death donor, cardiopulmonary bypass, and loss of cardiac output during operation, manifesting as graft failure secondary to refractory pulmonary edema. Diagnosis and treatment with surgical thrombectomy and anticoagulation have resulted in long-term survival with good graft function. Pulmonary vein thrombosis is usually diagnosed early after transplantation with features of pulmonary edema and hemodynamic collapse. The diagnostic delay in this case was due in part to late presentation but also to the multiple potential underlying pathologic conditions. Earlier TTE might have expedited diagnosis and treatment. Furthermore, atrial fibrillation may have precipitated the clot formation and may provide an additional clue to the diagnosis. Consideration should be given to investigation with TTE, CT chest with venous contrast, or both in patients with treatment-refractory graft dysfunction after lung transplantation.

References

1. Cywinski JB, Wallace L, Parker BM. Pulmonary vein thrombosis after sequential double-lung transplantation. J Cardiothorac Vasc Anesth 2005;19:225–7.
2. Nagahiro I, Horton M, Wilson M, Bennetts J, Spratt P, Glanville AR. Pulmonary vein thrombosis treated successfully by thrombectomy after bilateral sequential lung transplantation: report of a case. Surg Today 2003;33:282–4.
3. Nahar T, Savoia MT, Liguori C, DiTullio MR, Schulman LL, Homma S. Spontaneous resolution of pulmonary venous thrombosis after lung transplantation. J Am Soc Echocardiogr 1998;11:209–12.
4. Uhlmann EJ, Dunitz JM, Fiol ME. Pulmonary vein thrombosis after lung transplantation presenting as stroke. J Heart Lung Transplant 2009;28:209–10.
5. Schulman LL, Anandarangam T, Leibowitz DW, et al. Four-year prospective study of pulmonary venous thrombosis after lung transplantation. J Am Soc Echocardiogr 2001;14:806–12.
6. McIlroy DR, Cairo SA, Buckland MR. Pulmonary vein thrombosis, lung transplantation, and intraoperative transesophageal echocardiography. J Cardiothorac Vasc Anesth 2006;20:712–5.
7. Leibowitz DW, Smith CR, Michler RE, et al. Incidence of pulmonary vein complications after lung transplantation: a prospective transesophageal echocardiographic study. J Am Coll Cardiol 1994;24:671–5.
8. Shah AS, Michler RE, Downey RJ, Leibowitz DW, Homma S, Smith CR. Management strategies for pulmonary vein thrombosis following single lung transplantation. J Cardiac Surg 1995;10:169–78.