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ACUTE CONSTRICTIVE PERICARDITIS FOLLOWING LUNG TRANSPLANTATION FOR LYMPHANGIOLEIOMYOMATOSIS: A CASE REPORT

Martha E. Billings, MD¹, Michael Mulligan, MD², and Ganesh Raghu, MD, FACC, FCCP¹ The UW lung transplant team

¹ Department of Medicine, University of Washington, Seattle, WA

² Department of Surgery, University of Washington, Seattle, WA

Abstract

Lymphangioleiomyomatosis (LAM) is a rare cystic progressive lung disease with many extra-pulmonary manifestations which may complicate allograft function after transplantation. We present a LAM patient, one-year status-post bilateral lung transplant, with new dyspnea and declining spirometry without rejection, infection or recurrence. Investigation revealed acute constrictive pericarditis which has not previously been reported in LAM lung transplant patients. This represents a novel complication likely due to progression of extra-pulmonary LAM that should be considered in LAM transplant patients with dyspnea.

Keywords

Lymphangioleiomyomatosis; Lung Transplantation; Constrictive Pericarditis; Immunosuppression

Introduction

Lymphangioleiomyomatosis (LAM) is a rare, cystic lung disease affecting women of child bearing age without an established effective treatment. Pulmonary complications include pneumothoraces, hemoptysis, chylothorax and progressive respiratory failure. Extra-pulmonary manifestations of LAM range from angiomyolipomas within the kidneys and brain to retroperitoneal lymphadenopathy. Rarer complications of chylous pericardial effusions have been found incidentally¹. For patients with advanced LAM, lung transplantation is the only viable option, improving lung function and quality of life² with survival rates comparable to other lung transplant recipients^{3, 4, 5}. After bilateral lung transplant, persistent and/or progressive extra-pulmonary LAM may complicate allograft function and lead to recurrence⁶. A decline in respiratory function in a transplant patient raises concerns of rejection, infection, anastomosis problems as well as recurrence of LAM. The etiology of the decline is crucial as the therapeutic interventions are divergent. We report a novel complication in a LAM

Address Correspondence to: Martha E. Billings, MD, University of Washington, Box 359762, 325 Ninth Avenue, Seattle, WA 98104, Phone: (206) 744-9524, Fax: (206) 744-9982, Email: mebillin@u.washington.edu.

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lung transplant patient of constrictive pericarditis. A 32-year-old woman with lymphangioleiomyomatosis, status-post bilateral lung transplantation one year prior, presented with declining spirometry, worsening dyspnea and new onset orthopnea. She was diagnosed with acute constrictive pericarditis and her symptoms responded to pericardiectomy.

Case Report

After experiencing progressive dyspnea for 5 years, the patient was diagnosed with lymphangioleiomyomatosis (LAM) via characteristic diffuse cystic lesions throughout her lungs on computed tomography (CT) and retroperitoneal lymphadenopathy. She had severe airflow obstruction, recurrent pneumothorax and was oxygen dependent at the time of transplant, a year after diagnosis. She underwent bilateral lung transplantation (cytomegalovirus (CMV) recipient negative, donor positive). She did not require cardiopulmonary bypass and had no immediate post-operative complications. She received 100 days of intravenous ganciclovir per institution protocol following transplant.

She developed CMV viremia six months after transplant resistant to intravenous ganciclovir. Treatment with foscarnet led to renal insufficiency, lower extremity edema and peripheral neuropathy. She developed CMV retinitis after the foscarnet was withheld. She also had a persistent leucopenia. Her mycophenolate mofetil was temporarily discontinued. Her chronic immunosuppression included tacrolimus and prednisone at 10mg daily.

The patient had a progressive decline in her spirometry starting four months after transplant. She was evaluated with bronchoalveolar lavage (BAL); all cultures were negative. Bronchoscopy showed no stenosis at the anastomotic sites. Chest CT showed bilateral small pleural effusions without parenchymal infiltrates. Her spirometry continued to deteriorate (figure 1) and she underwent repeat BAL and transbronchial biopsies which showed no evidence of infection, rejection or recurrent lymphangioleiomyomatosis. She received pulse intravenous steroids empirically. Her FEV1 continued to decline to 20% below her best post-transplant values by nine months. She proceeded to open lung biopsy 10 months after transplant which showed no evidence of cellular rejection or bronchiolitis obliterans syndrome (BOS). There was also no evidence of CMV disease or recurrent LAM. Azithromycin three times weekly was added empirically for possible BOS.

One year after transplant, she complained of new onset orthopnea and paroxysmal nocturnal dyspnea. Her cardiac exam was notable for elevated neck veins which increased with inspiration. Chest X-ray showed moderate bilateral effusions. Thoracentesis demonstrated chylous fluid which was culture negative. Echocardiogram showed a thickened pericardium and signs of constrictive physiology with a septal shift to the left with inspiration and reciprocal respiratory variations noted in the mitral and tricuspid inflow patterns. Of note, an echocardiogram 6 months prior had not revealed pericardial fluid or thickening. An echocardiogram 2 weeks prior showed a suggestion of pericardial thickening but no hemodynamic effects. Chest CT (figure 2) demonstrated new thickening of the pericardium. Simultaneous right and left heart catheterization confirmed constrictive physiology, with equalization of right and left ventricular diastolic pressures and evidence for ventricular interdependence during inspiration and expiration (figure 3). The patient then proceeded to pericardiectomy. Her central venous pressure dropped after pericardial stripping from 25mmHg to 8mmHg. Milky fluid was aspirated from the pericardium. Pathology demonstrated pericardial fibrosis without signs of viral inclusions, infection, active inflammation or LAM cells.

Discussion

The concern for rejection in lung transplant recipients with unexplained progressive dyspnea, and spirometry decline is appropriate and is quite high. In our patient, since this occurred in the setting of decreased immunosuppressive regimen one year after lung transplant and there were no other obvious explanations for the respiratory decline, the decrease in FEV1 raised concern for bronchiolitis obliterans syndrome. Furthermore, with the discontinuation of her mycophenolate mofetil, she was at high risk for acute cellular rejection. However, both transbronchial and open lung biopsy showed no evidence of acute or chronic rejection. CMV pneumonitis was a possibility but CMV was never isolated from her bronchoalveolar lavage nor histologically detected in tissue. She continued to deteriorate and developed new orthopnea despite augmentation of her CMV therapy and immunosuppression. Based on her exam as well as the thorough evaluation of her transplanted lungs, the etiology of her dyspnea appeared to be cardiac. Echocardiograph, chest CT and simultaneous right and left heart catheterization were all supportive of constrictive pericarditis as the cause of her new onset orthopnea. As spirometry typically reveals normal or restrictive physiology in constrictive pericarditis in patient with normal lungs⁷, the reason for the decrease in FEV1 and airflow obstruction in our LAM transplant patient is unclear. It is possible that the impaired cardiac filling and increased pulmonary pressures producing bronchial cuffing may have in part contributed to the reduced FEV1. The diagnosis of rejection and bronchiolitis obliterans syndrome was definitively ruled out and the diagnosis of constrictive pericarditis was confirmed by pericardiectomy with hemodynamic, spirometric and symptomatic improvement.

Constrictive pericarditis has not been previously described in the literature among lung transplant recipients. Constrictive pericarditis complicates an estimated 0.1% of cardiac surgeries⁸ and can develop any time the pericardium is disturbed due to surgery or trauma⁹. It is a rare, but known complication of orthotopic heart transplantation (OHT), described in six of 133 patients followed after OHT¹⁰. There are case reports of constrictive pericarditis developing following bacterial¹¹ and fungal pericarditis¹² and intrathoracic infection¹³ after OHT. It has also been reported after OHT in patients with serosal injury, hematomas or pericardial effusions¹³. Constrictive pericarditis typically occurs 3 months to 2 years out from heart transplantation¹⁰. The causes of constrictive pericarditis identified in OHT seem unlikely culprits in our patient given the limited pericardial sac disruption in lung transplantation.

Pericardial effusions have been found rarely in lymphangioleiomyomatosis patients but not subsequent constrictive pericarditis. In a series of 35 woman with LAM, 2 (6%) were found to have pericardial effusions. These were asymptomatic effusions, presumed to be chylous, discovered incidentally on chest CT¹. The mechanism of pericardial chylous effusion is likely secondary to LAM involvement of the pericardium with lymphatic obstruction as in chylothorax. Chylothorax after lung transplantation for LAM is well described but not common¹⁴, occurring in 6–9% of patients^{4,6}. Pericardial effusions are described in LAM patients after lung transplantation, but no reports of confirmed chylous effusions. Early post-operative pericarditis was observed in one out of 14 LAM lung transplant patients in a case series⁵. In another series of 13 LAM lung transplant patients, one patient was found to have a non-chylous pericardial effusions 2.5 years post-transplant and another developed uremic pericarditis 14 months out¹⁵. Constrictive pericarditis is not reported amongst these patients.

The cause for the pericardial fibrosis in our patient is unclear; we speculate that it may be due to chronic irritation induced by accumulated chyle due to primary LAM itself rather than a result of a superimposed inflammatory process. Our patient had no evidence of an occult infectious pericarditis such as mycobacterial or fungal infections underlying her fibrotic response; all cultures were negative and pathology showed no granulomas. The constrictive pericarditis did not manifest until one year after transplantation and after reduction in

immunosuppression due to CMV infection. A CMV mediated etiology for her constrictive pericarditis was considered but the pericardial pathology also showed no evidence of CMV. Another etiologic possibility was uremic pericarditis, but typically this is associated with effusion and not fibrosis. The constrictive pericarditis in this patient likely evolved from a chylous effusion into fibrosis as immunosuppressants were tapered. Thus, this represents an unusual and novel complication in a LAM patient after lung transplantation.

Conclusion

This case illustrates that acute constrictive chylous pericarditis secondary to underlying LAM must be considered in the midst of differential diagnosis of infection and rejection in the lung transplant recipient with LAM who manifest unexplained dyspnea. Extra-pulmonary complications of LAM may continue to progress despite 'successful' lung transplantation for LAM. Awareness of this possibility should prompt aggressive and appropriate diagnostic and therapeutic interventions.

Abbreviations

LAM	Lymphangioleiomyomatosis
CMV	Cytomegalovirus
BOS	Bronchiolitis Obliterans Syndrome
FEV1	Forced Expiratory Volume in one-second
CT	Computed Tomography
OHT	Orthotopic heart transplantation
BAL	Bronchoalveolar lavage

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Spirometry after transplantation

Figure 1.

Graphic representation of spirometry data in months after transplant. At three months since her transplant, she received pulse steroids after a negative lavage and transbronchial biopsies. At 6 months after transplant, she received a course of empiric antibiotics after a lavage. She underwent open lung biopsy at 10 months after transplantation. At 12 months she underwent pericardiectomy.

Figure 2. Chest CT one-year after lung transplantation without lung parenchymal abnormalities but with bilateral pleural effusions and new pericardial thickening.

Figure 3. Cardiac catheterization tracing of simultaneous left and right heart pressures. Note classic “square-root sign” characteristic of constrictive pericarditis. The tracing reveals equalization of right and left ventricular diastolic pressures and evidence for ventricular interdependence during inspiration and expiration.