Gastroesophageal Reflux as a Reversible Cause of Allograft Dysfunction After Lung Transplantation*

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Gastroesophageal reflux (GER) is increasingly recognized as contributing to a number of pulmonary disorders. The relationship of GER to pulmonary allograft dysfunction after lung transplantation is unknown. In this report, we describe a lung transplant recipient who developed an acute decline in pulmonary function several months after a retransplantation for chronic rejection. A pulmonary workup at that time, including bronchoscopy with biopsy, revealed bronchial inflammation with no allograft rejection or infection. Because of increasing GI symptoms after retransplantation, the patient also underwent additional testing, which revealed severe acid reflux. The treatment of this patient’s acid reflux with Nissen fundoplication surgery resulted in a prompt and sustained improvement in his pulmonary function. We suggest that GER should be considered among the potential causes of allograft dysfunction after lung transplantation.

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Abbreviations: BOS = bronchiolitis obliterans syndrome; CMV = cytomegalovirus; GER = gastroesophageal reflux; OB = obliterative bronchiolitis

A 23-year-old man underwent a bilateral lung retransplantation in March 1997. The patient originally underwent lung transplantation for cystic fibrosis in January 1995. At the time of the first transplant, he received maintenance immunosuppression with cyclosporine, azathioprine, and prednisone. He also received prophylactic ganciclovir and cytomegalovirus (CMV) Ig because of his CMV mismatch status (donor-positive/recipient-negative) and trimethoprim-sulfamethoxazole for Pneumocystis carinii prophylaxis. The patient did well after the initial transplant surgery but experienced several episodes of mild allograft rejection and one episode of moderate acute allograft rejection within the first posttransplant year. Although each episode of acute rejection responded appropriately to bolus corticosteroids, the patient’s pulmonary function began to decline approximately 15 months after transplantation, which is consistent with a diagnosis of bronchiolitis obliterans syndrome (BOS). Bronchoscopy with biopsy at that time revealed moderate bronchial inflammation, but there was no evidence of acute rejection or infection. Despite augmented immunosuppression with tacrolimus and mycophenolate mofetil, the patient experienced a rapidly progressive decline in pulmonary function and, ultimately, underwent bilateral retransplantation for progressive allograft failure. The patient never complained of any symptoms of regurgitation or acid reflux after the first transplantation.

The patient tolerated the repeat transplantation well and was discharged on the seventh postoperative day. His immunosuppressive regimen included tacrolimus, mycophenolate, and prednisone (initially, at a dose of 20 mg/d). He was treated also with ganciclovir and trimethoprim-sulfamethoxazole prophylaxis and received ranitidine for stress ulcer prophylaxis. A histologic examination of the original transplanted lungs revealed obliterative bronchiolitis (OB). The results of bacterial, fungal, and mycobacterial cultures and CMV immunostains performed on

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the explanted lungs were negative. After retransplantation, the patient’s FEV₁ gradually improved over the first few postoperative months (Fig 1).

After this initial improvement in pulmonary function, the patient’s FEV₁ again began to decline approximately 3 months after retransplantation (Fig 1). Pulmonary examination at that time revealed clear lung fields with no wheezes. As an outpatient, the patient underwent bronchoscopy with transbronchial biopsy at 3 months after retransplantation. The transbronchial biopsy at that time revealed bronchiolar inflammation, as shown in Figure 2 (top), but no evidence of pneumonia, infection, or allograft rejection. A chest CT scan also was performed 3 months after repeat transplantation to evaluate the etiology of the patient’s lung disease and revealed mild bronchiectasis, predominantly in the lower lobes. A sinus CT scan also was performed that revealed only mild chronic sinus disease, which would not explain the bronchiectasis observed on the chest CT scan. Additional outpatient bronchoscopy procedures that were performed after the retransplantation also revealed moderate bronchial and bronchiolar inflammation in the absence of any rejection or infection.

About 4 months after the retransplantation, the patient first began to complain of moderately severe heartburn and frequent waterbrash. Additional testing, therefore, was undertaken. First, an upper GI endoscopy procedure was performed, which revealed severe, grade 4 erosive esophagitis. The testing of esophageal biopsy specimens was negative for infection (including stains for viral and fungal pathogens), which is consistent with acid reflux as the etiology of the esophagitis. A gastric-emptying study revealed marked gastroparesis without mechanical obstruction and also revealed reflux of swallowed contrast up to the level of the clavicles. Based on these results, the patient was treated with aggressive medical therapy, which included lansoprazole (30 mg three times daily) and cisapride (20 mg before meals and at night).

The patient continued to experience frequent heartburn and had no improvement in pulmonary function after 6 weeks of medical management. A repeat upper GI series, however, revealed improved gastric emptying with medical treatment. A radionuclide gastric-emptying study was not repeated. Because of the suspicion that the patient’s persistent decline in pulmonary function after repeat transplantation was related to severe GER and recurrent acid aspiration, he underwent laparoscopic Nissen fundoplication surgery. Prior to the fundoplication surgery, the results of esophageal manometry revealed normal motility and a normal lower esophageal sphincter pressure. Twenty-four-hour pH studies were not performed prior to fundoplication surgery because the multiple studies confirmed the diagnosis of severe acid reflux disease. Because improved gastric emptying was documented after medical therapy, further surgical interventions were not employed to improve gastric emptying.

The patient tolerated fundoplication surgery well and experienced a dramatic and sustained improvement in the FEV₁ after undergoing antireflux surgery (Fig 1). The patient also experienced a significant improvement in the midexpiratory phase of forced expiratory flow after fundoplication (prior to surgery, 24% predicted; 6 months after surgery, 52% predicted). In addition, the patient’s symptoms of heartburn and waterbrash resolved after fundoplication. No other changes were made in the patient’s medical management or immunosuppressive medications at the time of fundoplication. An upper GI series performed after surgery revealed an intact fundoplication with no evidence of GER (as was noted on the prior studies). Because the patient continued to clinically do well with excellent pulmonary function and a stable FEV₁ > 2 years after fundoplication, pH monitoring was not performed to document acid suppression. The results of surveillance bronchoscopy procedures after the fundoplication surgery have been negative with no evidence of acute rejection or OB. In addition, after fundoplication surgery, the bronchial inflammation that had been present in previous biopsy specimens resolved completely (Fig 2, bottom).

**Discussion**

We describe a lung transplant recipient with severe GER after retransplantation for OB. The patient initially experienced an appropriate improvement in pulmonary function after undergoing repeat transplantation but developed a decline in FEV₁ several months later. Based on the current nomenclature, this patient met BOS criteria.
GER and acid aspiration might contribute to posttransplant allograft dysfunction through several mechanisms. Acid reflux has been associated with bronchospasm, heightened bronchial reactivity, and airway edema. In addition, microaspiration has been shown to directly impair pulmonary function. Furthermore, after lung transplantation, cough and mucociliary clearance are significantly impaired. The absence of these normal pulmonary defense mechanisms may lead to an exacerbation of pulmonary dysfunction that is related to acid reflux and microaspiration. Although our patient had no evidence of clinical bronchospasm on examination, the findings of his chest CT scan and transbronchial biopsy suggested a strong component of airway inflammation. We hypothesize that our patient’s severe acid reflux led to acute and chronic bronchial and bronchiolar inflammation, which caused the progressive decline in his pulmonary function. Although recurrent OB might have produced similar radiographic and histologic findings, this explanation is not consistent with the sustained improvement in pulmonary function after fundoplication surgery.

Several factors may explain the occurrence of GER in lung transplant recipients. First, there appears to be a high prevalence of GER before transplantation in patients with certain end-stage lung diseases, such as cystic fibrosis. Second, vagal nerve injury may occur during lung transplantation that will result in delayed gastric emptying and GER. In our case, the risk of vagal nerve injury may have been increased due to prior adhesions related to the first transplant surgery. Third, GI side effects, including gastritis and ulceration, have been reported with commonly used posttransplant immunosuppressive medications, such as cyclosporine or prednisone. Increased acid production related to posttransplant medications, in combination with other factors, might have contributed to the severe esophagitis observed in our patient.

Interestingly, several researchers have suggested a relationship between GER and the development of OB. Reid and colleagues first described an association between gastroparesis and OB in a small series of 11 heart-lung transplant recipients. Reid et al speculated that gastroparesis may lead to recurrent aspiration, airway injury, and impaired pulmonary function. Berkowitz et al also studied gastroparesis after lung transplantation and found that OB developed in four of nine patients with documented gastroparesis. These studies, however, are limited by the small numbers of patients and by a lack of formal controls. Although it interesting to speculate that GER could have contributed to the development of OB after the first transplant, our patient experienced multiple episodes of acute rejection, including a high-grade rejection, which would increase the risk of developing OB. Additional research seems to be needed to clarify the importance of GER in the development of posttransplant OB.

In conclusion, we report a lung transplant recipient with allograft dysfunction associated with GER. To our knowledge, this is the first report that demonstrates an improvement in pulmonary function in a lung transplant recipient after undergoing the second transplant procedure. BOS is used describe graft deterioration that is secondary to progressive airway disease and is presumed to represent a manifestation of chronic allograft rejection. Histologic OB is thought to accompany BOS, but, because of the poor sensitivity of transbronchial biopsy, histologic confirmation is not required to make a diagnosis of BOS.

In this case, however, we hypothesize that this patient’s allograft dysfunction was caused by severe acid reflux and not by chronic rejection for the following reasons. First, the results of transbronchial biopsies after repeat transplantation initially revealed bronchial inflammation but no rejection, infection, or OB, which is consistent with this hypothesis. Second, chest CT scans revealed evidence of mild bronchiectasis in the posterior segments of the lower lobes, which is consistent with aspiration. Third, and most important, there were significant improvements in pulmonary function and bronchial inflammation that occurred after fundoplication surgery. No other changes were made in the patient’s medical management at the time of fundoplication to explain these improvements.
after fundoplication surgery. Although some variability in pulmonary function is expected after transplantation, the progressive decline in FEV\textsubscript{1} followed by a sustained improvement after fundoplication is not consistent with the normal variation in posttransplant pulmonary function. Thus, we suggest that GER should be considered as a potentially reversible cause of BOS among lung transplant recipients.

References

Cardiac Rhabdomyoma in an Adult Patient Presenting With Ventricular Arrhythmia*

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Cardiac rhabdomyomas are extremely uncommon in the adult population. It is even more unusual when they are associated with arrhythmic events that are reversible with resection of the tumor. We present such a case and focus our discussion on three unique characteristics this case demonstrates.

Primary cardiac tumors are uncommon, particularly in the adult population. It is even more unusual when they are associated with arrhythmic events that are reversible with resection of the tumor. We present such a case and focus our discussion on three unique characteristics this case demonstrates.

Case Report
The patient is a 35-year-old man with no significant medical history who presented to his local emergency department complaining of palpitations. He had previously been in excellent health and jogged at least two miles at least three times weekly without any symptoms. Two months prior to presentation, he began noting episodes of palpitations. These usually occurred as he was sitting at his desk at work, lasted a few seconds to several minutes, and were not associated with chest pain, shortness of breath, nausea, or presyncope. He initially attributed these to his stressful lifestyle, and did not seek medical attention until the morning of presentation, when he had a prolonged episode that was associated with severe lightheadedness. He had no history of hypertension, diabetes mellitus, or hyperlipidemia. His father required an angioplasty at age 50 for crescendo angina; the patient admitted to smoking 1 pack/d for 20 years.

The patient was taken to the local emergency department by his coworkers, and on arrival again began feeling lightheaded. When seen in triage, his pulse was noted to be rapid and he was placed on a cardiac monitor. He was noted to have frequent premature ventricular contractions and several short runs of nonsustained ventricular tachycardia (Fig 1). He was given an aspirin, IV metoprolol, and started on a lidocaine drip. A chest radiograph demonstrated clear lung fields and no cardiomegaly. Myocardial infarction was ruled out via serial ECGs and creatine kinase measurements. An echocardiogram was subsequently performed to assess his ventricular function. This showed evidence of mild left ventricular dysfunction, but was more notable for the presence of a 2 × 2-cm right ventricular mass attached to the interventricular septum (Fig 2). After transfer to Duke University Medical Center, the patient underwent a metastatic workup, including a CT scan of his chest and abdomen, which was notable only for the right ventricular mass (Fig 3); a MRI scan, which was aborted secondary to his erratic cardiac rhythm; and a total body positron emission tomography scan, which showed no evidence of metastatic disease.

A cardiac catheterization was performed to assess the coronary anatomy and to determine whether a tumor blush was present. The left ventriculogram demonstrated mild diffuse hypokinesis with an estimated ejection fraction of 50%. The coronary arteries showed no evidence of atherosclerotic plaque, but were notable for a tumor blush in the right ventricle originating from the septal perforating vessels of the left anterior descending coronary artery (Fig 4). He was evaluated by the thoracic surgical team and taken

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