Airway Dehiscence After Lung Transplantation in a Patient With Cystic Fibrosis

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The presence of resistant pathogens in the lower airways of patients with cystic fibrosis (CF) is not an absolute contraindication for lung transplantation. We describe a case in which a patient with CF died as a result of an anastomotic dehiscence, ischemia, and infection with linezolid-resistant methicillin-resistant *Staphylococcus aureus*. We review infection issues during the post-lung-transplant period and related anastomotic dehiscence in CF. *Key words: anastamosis; anastomotic failure; anastomotic ischemia; dehiscence; cystic fibrosis; CF; lung transplantation; linezolid; resistant; methicillin-resistant Staphylococcus aureus; MRSA; airway-pressure-release ventilation.* [Respir Care 2010;55(12):1746–1750. © 2010 Daedalus Enterprises]

Introduction

For the first 15 years of lung transplantation, a common cause of early death was airway dehiscence.[1] Because the systemic arterial blood supply is not restored during transplantation, anastomotic complications have primarily been attributed to ischemia of the donor bronchus.[2] Several other factors can compromise airway healing, including inadequate organ preservation,[2] invasive infection,[3] intensive immunosuppressive therapy,[4] and rejection.[5] Furthermore, severe reperfusion injury and early rejection are independent predictors of bronchial complications.[6] Recently, Weder and colleagues used a simple standardized surgical technique and demonstrated avoidance of bronchial complications after lung transplantation in 235 patients over a 15-year period.[7] Their technique included shortening the donor bronchus to the plane of the lobar carina, including the medial wall of the intermediate bronchus; peribronchial tissue was left untouched, and the anastomosis was carried out with a continuous absorbable running polydioxanone suture (PDS 4/0) at the membranous part, and interrupted sutures at the cartilaginous part.[7] In those patients, 441 bronchial anastomoses were performed with no important dehiscence observed. There was discrete narrowing of the anastomotic lumen, without need for intervention, in 4.9% of patients at 1 month, and in 2.4% at 6 months.[7] Weder et al used aggressive antibiotic and antifungal therapy, and they concluded that antimicrobial therapy probably played an important supportive role.[7] Despite advancements in both lung transplantation and related therapy, sporadic anastomotic complications still occur. We present a case of anastomotic failure associated with ischemia and a linezolid-resistant strain of methicillin-resistant *Staphylococcus aureus* (MRSA) in a young adult patient with cystic fibrosis (CF) after lung transplantation.

Case Report

A 21-year-old white male with advanced CF lung disease underwent bilateral sequential lung transplantation, without complications. His sputum cultures isolated multiple-drug-resistant *Pseudomonas aeruginosa* and linezolid-resistant MRSA prior to lung transplant. We were comfortable with our plan of treatment for the *P. aeruginosa* isolate post-transplant, but we had little experience with linezolid-resistant MRSA, so antimicrobial treatment

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was dictated by microbiological evaluation of the isolate before transplant. The minimum inhibitory concentration for the MRSA strain was > 256 μg/mL, as measured with an automated microbiological testing system (Phoenix, BD Diagnostic Systems, Sparks, Maryland). The only antimicrobials with activity against this MRSA strain were vancomycin (minimum inhibitory concentration 1 μg/mL), tigecycline (minimum inhibitory concentration 0.5 μg/mL), and daptomycin (minimum inhibitory concentration (≤ 1 μg/mL).

His antimicrobial treatment in the post-transplant period was: intravenous meropenem (6 g via continuous infusion every 24 h); intravenous tigecycline (100 mg initially, then 50 mg twice daily); intravenous vancomycin (750 mg every 12 h); and aerosolized tobramycin (300 mg twice daily via nebulization) for treatment of pathogens cultured in his sputum prior to the lung transplant. To minimize the risk of nephrotoxicity, we commonly use aerosolized tobramycin in this patient population, with good success. Blood cultures obtained 12 hours after the lung transplant were negative. The target trough level for the vancomycin at that time was 10–15 mg/L. Our center does not use induction therapy prior to transplantation, so the patient received intravenous methlyprednisolone (250 mg prior to the surgery, 250 mg intravenous intraoperatively, then 125 mg daily), intravenous tacrolimus (1 mg/d via drip), and intravenous mycophenolate (1,000 mg twice daily). He was extubated to room air on the second postoperative day, with normal vitals signs and good oxygenation on 2 L/min supplemental oxygen via nasal cannula. Methlyprednisolone was changed to prednisone (30 mg enterally once daily) on the third postoperative day, and intravenous tacrolimus and mycophenolate was changed to enteral dosing. Chest radiographs in the immediate postoperative period demonstrated clear lung fields, with small pleural effusions bilaterally.

The immunsuppression was changed to oral medicines once he was extubated and tolerating oral intake. He was transferred from the intensive care unit (ICU) to the ward on the fifth postoperative day. His remaining hospital course was complicated by persistent transudative serosanguineous fluid leakage from bilateral single chest tubes. Two weeks after transplantation, surveillance bronchoscopy revealed telescoped anastomoses bilaterally, which were intact (Fig. 1). Transbronchial biopsies found no evidence of acute rejection (A0B0). Bronchoalveolar lavage fluid isolated multiple-drug-resistant *P. aeruginosa* and linezolid-resistant MRSA that had the same antimicrobial susceptibility pattern of isolates cultured from sputum in the recipient prior to the transplant. At the time of the bronchoalveolar lavage, quantitative cultures were not available for the isolated culture. His antibiotic regimen at this point was intravenous meropenem, tigecycline, and vancomycin; and aerosolized tobramycin. He received

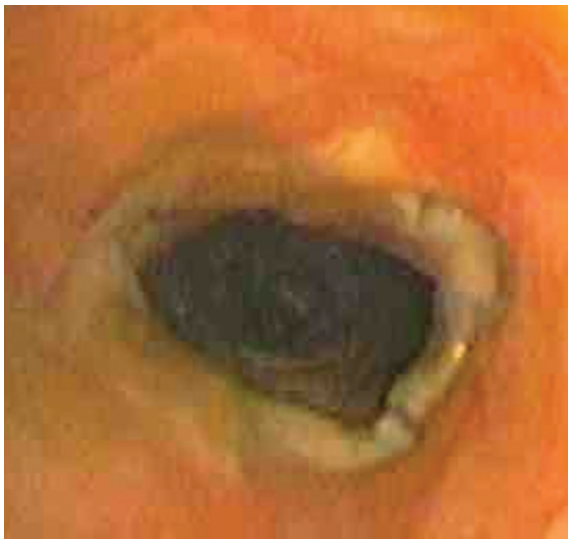

Fig. 1. Bronchoscopic view of intact left anastomosis.

antibiotics during this entire period because of concern that the refractory fluid leakage from the chest tubes could represent infection, and the chest tubes were infection risks.

Four days after the bronchoscopy, despite our efforts to prevent infection with continuing antimicrobials after transplant, he suddenly deteriorated because of pneumonia and resulting septic shock, with acute reduction in systolic blood pressure to 80 mm Hg. At that time, he received aggressive fluid resuscitation and required vasopressin and norepinephrine infusions for hemodynamic stabilization. Immunosuppressant therapy with tacrolimus and mycophenolate was stopped after the development of sepsis, but he continued to receive intravenous corticosteroids throughout the ICU course. At that same time, he required intubation and increased F_{IO_2} for hypoxemic respiratory failure. Blood cultures drawn on admission to the ICU eventually isolated linezolid-resistant MRSA that had the same susceptibility pattern as previous MRSA isolates from respiratory cultures. Adjustments to the antibiotic therapy included continuation of meropenem (6 g intravenous continuous infusion), increase of vancomycin (to 900 mg intravenous every 12 h), daptomycin (500 mg intravenous every 24 h), and tobramycin (560 mg intravenous every 24 h), to broaden coverage. The target vancomycin trough was increased to 15–20 mg/L. Daptomycin was added specifically to treat the MRSA bacteremia. Vancomycin had to be continued for treatment of MRSA in the respiratory cultures because of the inactivation of daptomycin by surfactant.

Upon transfer to the ICU, chest radiograph demonstrated bilateral consolidation in both lower lobes and eventual development of small cavitary lesions identified on chest computed tomogram 1 week after his deterioration. Echocardiogram on arrival to the ICU revealed a hyperdynamic

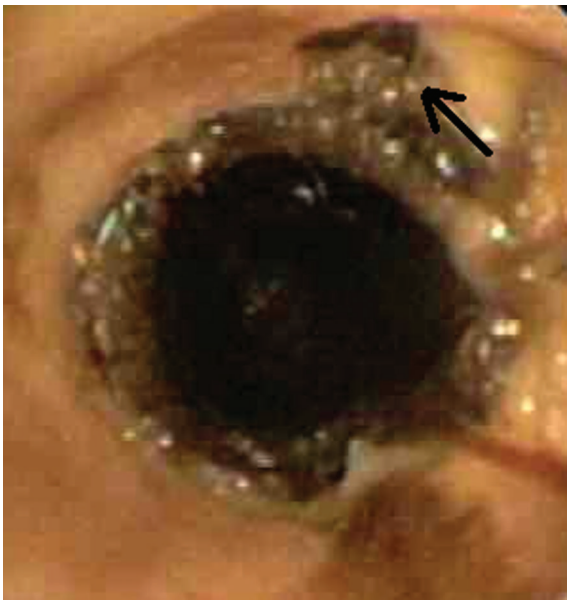

Fig. 2. Bronchoscopic view of left anastomosis shows dehiscence (arrow).

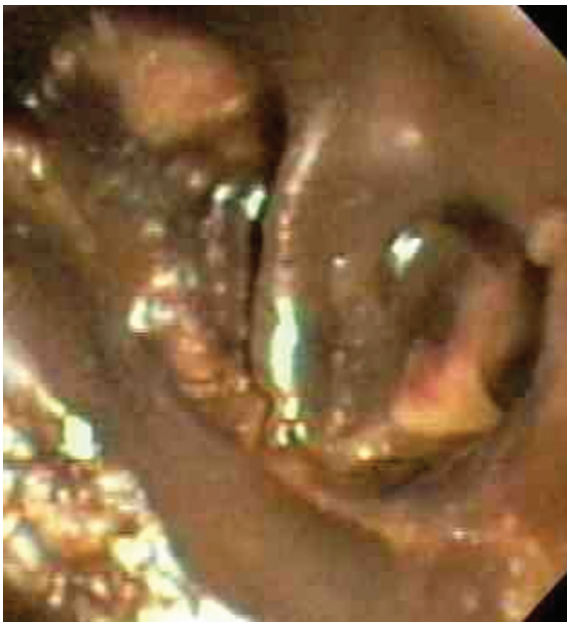

Fig. 3. Bronchoscopic view of thick tenacious black plaque encompassing the airway mucosa of the left lower lobe.

heart, which improved with fluid resuscitation. Three days after readmission to the ICU, he abruptly developed severe hypotension, oxygen desaturation to 85%, and an increase in air leak from 1-chamber to 4-chamber continuous leak via drainage unit (Pleur-evac, Teleflex, Research Triangle Park, North Carolina) suction. At the time of this event he was being ventilated with a pressure-regulated volume-control mode, target tidal volume 6 mL/kg ideal body weight, F_{IO_2} 0.6, PEEP 10 cm H_2O, inspiratory time 1.2 s, and peak airway pressure limit 40 cm H_2O. This acute decline was associated with an acute development of increased airway pressure and triggering of the maximum-pressure alarm, with a new-onset discordance between the measured inspiratory and expiratory tidal volume ($>$ 50% difference). Both PEEP and F_{IO_2} were then titrated stepwise, per the Acute Respiratory Distress Syndrome Network algorithm, to maintain oxygen saturation $>$ 90%.[8] At that time PEEP was 10 cm H_2O and F_{IO_2} was 0.60.

Bronchoscopy was performed at the bedside, through the endotracheal tube, while he was on the ventilator, and revealed pale bronchial mucosa that suggested a component of ischemia and dehiscence of both anastomoses (Fig. 2). There was a thick tenacious black plaque that involved both allografts, starting at the level of the anastomoses and extending down to the first divisional subsegments bilaterally (Fig. 3). Endobronchial biopsies of the plaque revealed fibrinopurulent debris, with no viable respiratory epithelium on histopathological analysis, and linezolid-resistant MRSA, with the same antimicrobial susceptibility pattern as the previous isolates. In an effort to target drug delivery to the lower airways and the anastomoses, we added vancomycin (250 mg via nebulization twice daily). We reconstituted the standard intravenous vancomycin HCl product (APP Pharmaceuticals, Schaumburg, Illinois) in 5 mL of sterile saline, and administered 250 mg twice, in-line with the ventilator circuit.

Confronting anastomotic dehiscence and ongoing severe respiratory failure, we instituted airway pressure-release ventilation, and he was allowed to breathe spontaneously. This ventilation change resulted in an interval improvement in gas exchange and an apparent reduction in the air leak, from a continuous 4-chamber leak to a continuous 1-chamber leak. An emergency chest computed tomogram showed pneumomediastinum with bilateral pneumothoraces and fluid collection in the chest, but there was no clear evidence of mediastinitis. He was taken to the operating room for placement of airway stents (Aero, AlveolUs, Charlotte, North Carolina). There was near complete failure of the anastomosis in the right allograft and partial failure in the left allograft. We placed a 16×40-mm stent in the right airway and an 18×40-mm stent in the left airway. There was no substantial change in the air leak after stent placement. We administered further antibiotics: tigecycline (100 mg intravenous dose, then 50 mg intravenous every 24 h) and Polymyxin B (50,000 units intravenous every 12 h). His clinical status continued to decline due to multiple-organ-dysfunction syndrome, with nonoliguric acute renal failure and hepatic failure with worsening hyperbilirubinemia, and without substantial im-

provement in his respiratory failure or air leak. He also developed altered mental status from hepatic encephalopathy, which only modestly improved with lactulose therapy. His family ultimately elected to withdraw care.

Discussion

As the number of CF patients undergoing lung transplant rises and as their long-term survival improves, there is concern regarding resistant bacteria in these patients and whether the presence of certain strains should be considered a major contraindication. The existing research studies in the lung-transplant population on this important issue have not addressed MRSA. In 1997, Aris et al retrospectively studied 66 lung-transplant CF patients over 6 years and found that patients with panresistant *P. aeruginosa* had similar transplant outcomes to patients with sensitive bacteria.[9] More recently, a retrospective study involving 103 patients at 2 centers compared the impact of panresistant bacteria, other than *Burkholderia cepacia*, on the post-lung-transplant survival of CF patients,[10] but MRSA was not addressed in that study. The studies found that Gram-negative pathogens, excluding *B. cepacia*, are not a contraindication to lung transplantation, even if they are panresistant. Bonvillain and colleagues described similar *Staphylococcus* species infection rates after lung transplantation in CF versus non-CF patients,[11] but neither clinical outcomes nor pathogen resistance was discussed regarding the infections identified.

Our understanding of the impact of panresistant bacteria in CF patients after lung transplantation is expanding as more CF patients are receiving lung transplants. However, these studies have not included MRSA in their assessments of the impact of resistant pathogens on lung transplant outcomes in CF patients. The prevalence of MRSA in the lower airways is increasing in CF patients across all age groups, with growing evidence that MRSA impacts clinical outcomes. According to the Cystic Fibrosis Foundation patient registry, there has been a dramatic increase in the prevalence of MRSA: 2.1% of CF patients had MRSA in 1996, whereas 18.9% of CF patients isolated it in 2006.[12] In 2007, Ren and colleagues collected data over a 1-year period from the Epidemiologic Study of Cystic Fibrosis, a large observational study of CF patients in North America, to compare the respiratory tract cultures of CF patients with MRSA to those with methicillin-sensitive *S. aureus* (MSSA).[13] The patients with MRSA had significantly worse air-flow obstruction: the mean FEV_1 in patients 6–17 years old with MRSA was 81% of predicted, compared to 89% of predicted in the MSSA group ($P < .001$).[13] The likelihood of hospitalization and treatment with oral, inhaled, and intravenous antibiotics was significantly higher in patients with MRSA, compared to MSSA.[13] The results were similar in patients ≥ 18 years old.[13] Also using data from the Epidemiologic Study of Cystic Fibrosis, Sawicki and colleagues used multivariable piecewise linear regression and found that patients with MRSA had a lower FEV_1 and received more antibiotic and other therapies than did MRSA-negative patients over a 2-year period.[14] After adjusting for antibiotic therapy and other potential confounders, patients with MRSA had higher rates of FEV_1 decline, both before and after the incident culture, but the rate of FEV_1 decline did not change significantly after MRSA detection,[14] so it is not known whether MRSA causes the steep rate of decline. Dasenbrook and colleagues performed a 10-year cohort study of data from the Cystic Fibrosis Foundation patient registry, with 2 age groups: 8–21 years, and 22–45 years.[15] Despite adjustment for confounders, the rate of FEV_1 decline in the 8–21-year-old patients with persistent MRSA was more rapid, with an average FEV_1 decline of 2.06% of predicted per year, which is 43% more rapid than the 1.44% of predicted per year in those without MRSA.[15] The effect of MRSA on FEV_1 decline in adults was not clinically important.[15]

Regarding lung transplantation, the non-restoration of the systemic blood supply to lung allografts places this area at high risk for complications from ischemia. Evidence suggests that intussuscepting the donor bronchus increases the incidence of airway complications (stenosis and infections).[16-18] Because of improvements in lung preservation, surgical technique, candidate selection, postoperative care, immunosuppression, and antibiotic/antifungal therapy, the prevalence of airway complications has substantially decreased.[7,19] Mughal and colleagues successfully treated life-threatening bronchial dehiscence with self-expanding metallic stents[20] that result in granulation tissue formation, so soft tissue covering the area of dehiscence allows the return of airway structural integrity and thus allows removal of the stent.

The importance of the increasing prevalence of MRSA in the lower respiratory tract in CF patients over the past decade remains unclear, but research in this area is expanding and leading to a better understanding of this important issue. This particular case raises an important question regarding the importance of linezolid-resistant MRSA in the lower airways of CF patients after lung transplantation. The linezolid resistance of this MRSA strain resulted from numerous linezolid courses in the year prior to transplant. Septic shock and the resulting hypotension resulted in low perfusion pressure, which was a contributing factor in the ischemia at the anastomoses. The poor healing at the anastomoses allowed for an opportunistic infection of this linezolid-resistant MRSA strain. Antimicrobial therapy for pulmonary MRSA infections is limited, thus

the acquisition of a linezolid-resistant strain can make treatment very challenging.

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