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Rapid acute onset of bronchiolitis obliterans syndrome in a lung transplant recipient after respiratory syncytial virus infection

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Abstract: Bronchiolitis obliterans syndrome (BOS) can have either an acute or chronic onset with an abrupt or insidious course. The diagnosis is typically achieved by physiological criteria with development of a sustained decline in expiratory flow rates for at least 3 weeks. We review the rapid development of acute BOS and bronchiectasis after respiratory syncytial virus infection in a lung transplant recipient, who had been doing well with normal pulmonary function for 3 years after lung transplantation.

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Key words: bronchiectasis; bronchiolitis obliterans syndrome; inhaled ribivirin; lung transplantation; respiratory syncytial virus

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The diagnosis of bronchiolitis obliterans syndrome (BOS) is currently achieved using spirometric criteria, with a sustained decline in expiratory flow rates for at least 3 weeks and the exclusion of other alternative causes, including acute allograft rejection, anastomotic complications, infection, and recurrent/progressive native lung disease (1). The diagnosis of BOS actually does not require histological confirmation, but is considered a surrogate physiological marker of the presence of obliterative bronchiolitis (OB). The etiology of BOS is not completely understood, but there are several associated risk factors, including alloimmune-dependent risks such as acute allograft rejection, lymphocytic bronchitis/bronchiolitis, organizing pneumonia, and human leukocyte antigen (HLA) mismatches, and nonalloimmune-dependent risks, such as primary graft dysfunction, gastroesophageal reflux, and numerous infectious agents (bacterial, fungal, and viral) (2).

The timing of the development of BOS is highly variable, with either an insidious course with gradual decline over months to years, or an abrupt course with severe decline over a few weeks (1–4). Moreover, acute and chronic onset of BOS can also occur (3). Patients with acute onset of BOS typically have an irreversible steep decline in pulmonary function, and are more likely to have had multiple episodes of acute allograft rejection in the first 6 months after surgery, with the main cause of death being OB (3). Patients with chronic onset of BOS have a more indolent course, with acute allograft rejection not being a marker, inflammation from infection being more important, and OB playing a smaller role in the cause of death (3).

We review a case involving a patient with cystic fibrosis (CF) who had a completely uneventful course for 3 years after bilateral sequential lung transplantation, until an acute respiratory syncytial virus (RSV) infection triggered the sudden onset of acute allograft rejection that subsequently led to the rapid development of acute onset of BOS and bronchiectasis.

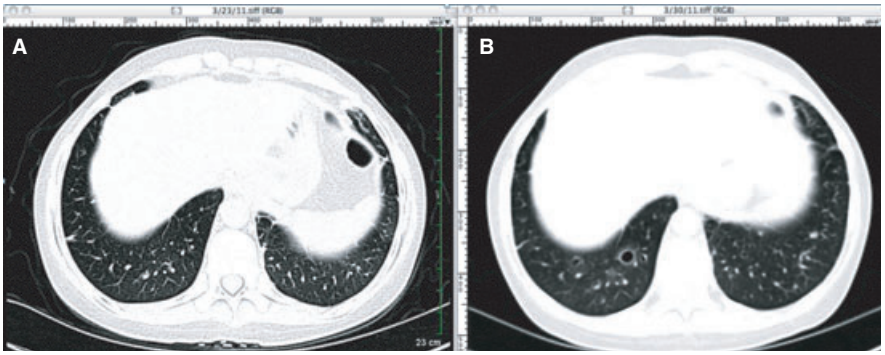

Fig. 1. Computed tomography scan of chest with cuts through the right lower lobe demonstrating (A) clear lung fields in the allograft on high-resolution scan and (B) new development of bronchiectasis on routine scan 1 week later.

Case report

A 23-year-old woman with CF (homozygote for ΔF508), who underwent bilateral sequential lung transplantation 3 years earlier, developed new cough and rhinorrhea for 5 days. The cough worsened abruptly with development of both fatigue and dyspnea at rest and with exertion. She had no previous episodes of acute rejection and no known viral respiratory tract illnesses since her transplant. Spirometry demonstrated forced vital capacity (FVC) of 3.45 L (97% predicted) and forced expiratory volume in 1 sec (FEV_1) of 2.42 L (78% predicted). A recent high-resolution computed tomography (CT) of the chest demonstrated chronic changes with clear lung fields (Fig. 1A). Her only other surgical history was a Nissen fundoplication for symptomatic gastroesophageal reflux that was performed before discharge after lung transplantation with complete resolution of symptoms. There was no history of HLA mismatch at the time of the transplant. Her current immunosuppression therapy was tacrolimus 3 mg twice daily, mycophenolate 500 mg twice daily, and prednisone 5 mg daily with other medications including trimethoprim/sulfamethoxazole prophylaxis and pancreatic enzyme supplementation. Her tacrolimus level was acceptable in the 7 ng/mL range.

She was unable to perform spirometry with her current acute presentation. Nasal swab sample identified RSV by real-time polymerase chain reaction. Bronchoscopy was performed and revealed well healed anastomoses. Transbronchial biopsies showed giant cells (Fig. 2) consistent with RSV, as well as signs of acute allograft rejection that was classified as A3B2, so she was treated with both inhaled ribavirin and high-dose daily intravenous methylprednisolone at 1 g daily for 3 days. Tissue and bronchoalveolar lavage fluid cultures found no other infectious agents. Upper gastrointestinal study along with pH probe with impedance revealed no evidence of gastroesophageal reflux or aspiration. Blood was negative for both cytomegalovirus and Epstein-Barr virus.

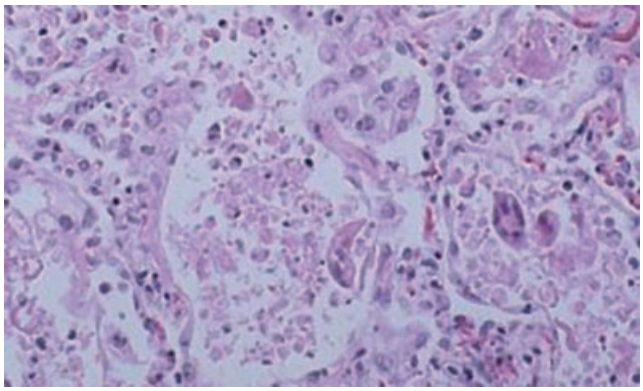

Fig. 2. Giant cells with a round, pink intracytoplasmic inclusion on allograft tissue sample obtained by transbronchial biopsy. (Hematoxylin and eosin stain.)

Spirometry was performed 6 days after presentation and revealed severe airway obstruction with FVC 1.90 L (54% predicted) and FEV_1 0.67 L (22% predicted). One week after her initial presentation, a routine CT scan of the chest was performed because of vague chest pain and it showed ground glass opacities and the new development of bronchiectasis (Fig. 1B). Repeat transbronchial biopsies 2 weeks after the initial presentation demonstrated complete resolution of acute rejection with A0B0 histological findings. However, her pulmonary function did not improve, so she eventually met diagnostic criteria for BOS and has since been listed for re-transplantation.

Discussion

Our understanding of the pathogenesis of RSV in BOS after lung transplantation remains limited and with

conflicting evidence. In 2005, community-acquired respiratory viruses were reported to be associated with the development of acute rejection and BOS in a small cohort of patients (5). A total of 50 of 100 (50%) patients developed a respiratory viral illness with 33 (33%) having a specific viral etiology identified, including rhinovirus (n = 9), coronavirus (n = 8), RSV (n = 6), influenza A (n = 5), parainfluenza (n = 4), and human metapneumovirus (n = 1). A specific viral etiology was identified in 7 of 8 patients with subsequent acute rejection, including rhinovirus (n = 4), coronavirus OC43 (n = 1), RSV (n = 1), and influenza A virus (n = 1) (5). Moreover, 9 patients experienced a 20% or greater decline in FEV_1 by 3 months, with 4 being positive for a respiratory virus (rhinovirus [n = 1], coronavirus [n = 2], and influenza A [n = 1]) (5). However, in another study, investigators reported that respiratory viral infection was not associated with subsequent graft dysfunction in a smaller cohort of 50 patients followed during a single winter season (6). A total of 32 (64%) patients had 49 symptomatic respiratory viral episodes, with documented infections including RSV (n = 8), influenza (n = 10), and parainfluenza (n = 1) (6).

More recently, Hopkins and colleagues (7) reported that, in a cohort of 89 patients with respiratory viral infections, a significant percentage of patients with metapneumovirus (63%) and RSV (72%) developed graft dysfunction, with average declines in FEV_1 of $30 \pm 12.4\%$ and $25.9 \pm 11.2\%$, respectively. Subsequently, BOS onset or progression occurred in no patients with human metapneumovirus compared with a total of 5 of 13 (38%) patients with RSV at 6 months (7). Of these 5 patients with BOS, each of them reportedly had graft dysfunction at the time of the diagnosis of RSV infection (7). Of these, 3 of 5 patients with RSV initially recovered to baseline respiratory function after therapy but subsequently developed BOS, with a mean time to diagnosis of 11 weeks (7).

In this case, we were impressed with the timing of the acute onset of BOS in relation to the RSV infection, especially based on her completely uneventful course for the past 3 years after the transplant. We think that the aggressiveness of BOS was further supported by the rapid changes on CT imaging (Fig. 1 A and B). A myriad of abnormalities can be seen on CT imaging of the chest in BOS, including bronchiectasis, hyperlucency (air-trapping), mosaic pattern of attenuation, thickening of septal lines, or tree-in-bud (8). CT imaging is often used as a complement to pulmonary function testing and bronchoscopy, to help differentiate causes of dyspnea and declines in pulmonary function in lung transplant recipients.

As reported by Jackson et al. (3), BOS is more than a single process, with acute BOS being defined as a sharp, steep, and irreversible decline in FEV_1, triggered by an acute event, associated with episodes of acute allograft rejection in the first 6 months with a poor prognosis, while a more chronic form of the disorder has a smooth linear decline in pulmonary function and is less likely to be associated with acute events with a better prognosis. This case further illustrates that different phenotypes of BOS do exist, and the fact that acute or chronic phenotypes can occur at any time after lung transplantation. The aggressiveness of this disorder was even more impressive in the patient presented herein, as compared with the cases reported in the prospective study by Hopkins et al. (7). Additional research is needed to identify the pathogenesis of RSV infection in relation to the development of BOS in lung transplant recipients, to help identify therapeutic targets to optimize outcomes in lung transplantation.

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