Lung Transplantation in a Patient with Pre-transplant Colonization of Extensively Drug-resistant *Acinetobacter baumannii*

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Colonization of the pre-transplant lung by multidrug-resistant bacteria affects short- and long-term outcomes of lung transplantation. However, there are no case reports on the colonization of a pre-transplant lung by drug-resistant *Acinetobacter baumannii*. We report a case of extensively drug resistant (XDR) *A. baumannii* colonization in the tracheobronchial tree that caused severe infectious complications after bilateral lung transplantation. A 23-year-old man diagnosed with bronchiolitis obliterans syndrome (BOS) 4 years earlier with a history of allogeneic bone marrow transplantation for acute lymphoblastic leukemia was admitted to the hospital with dyspnea. Due to progressive hypercapnic respiratory failure, long-term mechanical ventilation was started after a tracheostomy was performed, and the patient underwent a bilateral lung transplantation to treat end-stage BOS. After the transplantation, the colonization of XDR *A. baumannii* caused severe bacterial pneumonia in the early postoperative period. Combined treatment with colistin and meropenem led to recovery from the pneumonia but caused drug-induced renal failure. Because many centers are willing to transplant candidates who are on mechanical ventilation or extracorporeal life support, the incidence of XDR *A. baumannii* colonization of pretransplant lungs is expected to increase. Further studies are needed to examine pre-transplant management strategies in patients colonized with XDR *A. baumannii*.

Key Words: *Acinetobacter baumannii*; drug resistance; lung transplantation.

In recent decades, the indications for lung transplantation (LT) have been extended, and favorable outcomes in patients diagnosed with chronic graft-versus-host disease-associated bronchiolitis obliterans syndrome (BOS) after bone marrow transplantation (BMT) have been published.[1-3] With the progress in immunosuppressant modulation and antibiotics, successful LT has been performed in patients colonized with drug-resistant pathogens, although colonization with highly resistant bacteria is generally considered to be a relative contraindication to LT.[4] Extensively drug-resistant (XDR) *Acinetobacter baumannii* is a nosocomial pathogen frequently associated with prolonged ventilation in the intensive care unit or the long-term use of broad-spectrum antibiotics.[5] In recent years, acquired infections of the transplanted lung with multidrug-resistant *A. baumannii* in the postoperative period have had devastating outcomes.[6,7] In the pretransplant setting, however, there are no reports describing the impact of colonization by multidrug-resistant *A. baumannii* on the post-transplant outcomes.[8] We herein report a case of pretransplant colonization of XDR *A. baumannii* in a patient who underwent bilateral lung transplantation for BOS after stem cell transplantation that was complicated by a severe infection.

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Case Report

A 23-year-old man was admitted to the hospital with dyspnea. He had been diagnosed with BOS in 2010 after allo-BMT for acute lymphoblastic leukemia. The hematological malignancy had shown a complete response since 2009. The patient developed recurrent pneumothorax in 2012 and 2014 and recovered after chest tube drainage. Pulmonary function tests performed in 2012 showed evidence of BOS with severe obstructive lung disease, a reduced ratio of the forced expiratory volume in one second (FEV_1) to forced vital capacity (50% of expected), FEV_1 (0.62 L, 15% of expected), diffusion capacity (33% of predicted), and increased residual volume (3.26 L, 238% of expected). He had been taking an inhaled corticosteroid to treat the BOS and low-dose mycophenolate mofetil (MMF) for extensive chronic oral, eye, and lung graft-versus-host disease for 5 years. Before admission, he had been treated for a nontuberculous *Mycobacterium intracellulare* lung infection with rifampin, ethambutol, and clarithromycin for 3 months with sputum converting to negative after 1 month of treatment. At the time of admission, the patient had a cough and whitish sputum, but did not have a fever; his lungs were clear with no wheezing on auscultation. The white blood cell count was $4,770/\text{mm}^3$

with 62% segmented neutrophils; the high-sensitivity C-reactive protein (hs-CRP) level was 2.67 mg/dL (reference range, <0.47 mg/dL). Chest computed tomography showed heterogeneously decreased lung attenuation with bronchial dilatation, suggesting advanced BOS (Fig. 1) without evidence of pneumothorax or progressive acute infection. An initial arterial blood gas examination showed a pH of 7.381, PaCO_2 of 72.5 mmHg, PaO_2 of 48.7 mmHg, HCO_3^- of >40 mmol/L, and SPO_2 of 93.8% on 2 L/min oxygen support via nasal prongs; the PaCO_2 was higher than it had been 3 months previously. Four days after admission, an endotracheal tube was inserted and mechanical ventilation was started due to progressive hypercapnia. After intubation, the arterial blood gas examination showed hypercapnic respiratory acidosis on ventilatory support (pH, 7.192; PaCO_2 , 116 mmHg; PaO_2 , 401 mmHg; HCO_3^- , 40 mmol/L; and SpO_2 , 99%). With ventilatory support and inhaled corticosteroids, the acute hypercapnic respiratory failure was partly relieved. However, ventilator weaning 9 days after admission failed, and a tracheostomy was performed for long-term mechanical ventilation. XDR *A. baumannii* had been isolated from the sputum and bronchial washing fluid cultures 10 times since the fourth day of admission. All isolates were resistant to all cephalosporins, quinolones, aminoglycosides, and

Fig. 1. Chest computed tomography taken before lung transplantation showed heterogeneously decreased lung attenuation with bronchial dilatation, suggesting advanced BOS.

Fig. 2. Bronchoscopy performed on POD 7 showed erythematous, inflammatory mucosa with profuse purulent sputum in both bronchi.

carbapenems, but susceptible to colistin (minimum inhibitory concentration [MIC], ≤ 0.5) and tigecycline (MIC = 2). Because there were no signs or symptoms of systemic inflammation, the pathogen was considered to be colonizing and targeted therapy was not planned. To treat the end-stage BOS, the patient was listed for lung transplantation. After mechanical ventilation for 51 days, he underwent bilateral LT from a cadaveric unrelated donor. The postoperative antimicrobial prophylaxis regimen comprised colistin, teicoplanin, trimethoprim-sulfamethoxazole, ganciclovir,

and itraconazole on the day of the operation, with immunosuppression using basiliximab, tacrolimus (trough level 10–15 $\mu\text{g/mL}$), MMF, and corticosteroids. Bronchoscopy on postoperative day (POD) 7 showed that the anastomosis was intact, but the mucosa of the transplanted lung showed erythematous inflammatory changes with profuse, thick purulent sputum in both bronchi (Fig. 2). On POD 13, a fever of 37.7°C occurred with hypotension, an elevated serum hs-CRP level (20.95 mg/dL), and leukocytosis ($20.33 \times 10^9/\text{L}$). A chest X-ray showed extensive infiltration of both

Fig. 3. Chest x-ray taken on POD 1 (A), POD 13 (B), POD 18 (C), and POD 27 (D), respectively. On POD 13, extensive bilateral infiltrations developed along with hypoxemic respiratory failure, which improved on POD 18. Chest x-ray on POD 27 showed almost complete regression of the pneumonic infiltrations.

Fig. 4. Bronchoscopy performed on POD 18 showed improved mucosal inflammation and purulent secretion.

lung fields; the $\text{PaO}_2/\text{FiO}_2$ ratio was decreased at 65 (Fig. 3). Due to the progressive hypoxemic respiratory failure, venous-venous extracorporeal membrane oxygenation was started. XDR *A. baumannii* with the same resistance pattern was isolated from bacterial cultures of the bronchoscopic washing fluid recovered on POD 7 and sputum on POD 8. At that time, the serum *Aspergillus* antigen result was negative (0.16) and the cytomegalovirus RQ-PCR result was <500 copies/mL. Because the same XDR *A. baumannii* was recovered repeatedly from the sputum and bronchial washing fluid and there was no evidence of combined bacterial, mycobacterial, or fungal infection, pneumonia aggravated by XDR *A. baumannii* was strongly suspected. The antibacterial treatment regimen was changed to meropenem (3 g/day), intravenous (IV) colistin (4.5 mg/kg), and colistin nebulizer (4.5 mg/kg) to achieve a synergistic effect on the XDR *A. baumannii*. The target tacrolimus level was adjusted to 5 to 7 $\mu\text{g/mL}$, and the MMF dose was decreased from 2 to 1 g/day. With the change in the antibacterial regimen and reduced immunosuppression, the elevated hs-CRP level and leukocytosis regressed on POD 18 (7.51 mg/dL and $10.97 \times 10^9/\text{L}$, respectively), and the bilateral lung infiltrations resolved (Fig. 3). Follow-up bronchoscopy on POD 18 showed improved mucosal inflammation and decreased purulent sputum in the allograft lung (Fig. 4). After POD 19, no XDR *A. baumannii* was cultured in sputum samples

retrieved from the tracheostomy site. The combined therapy with meropenem and IV colistin was continued for 2 weeks, with the IV colistin used for 40 days and colistin nebulizer for 86 days in total. Drug-induced acute renal failure developed on POD 16, with a serum creatinine level twice as high as the initial value and decreased urine output. However, the decreased renal function recovered after continuous renal replacement therapy for 23 days. At the time of this writing, the patient was still hospitalized (POD 128) while undergoing a respiratory rehabilitation program to promote generalized buildup.

Discussion

To date, the impact of colonization of multidrug-resistant organisms in the pretransplant lung has been studied mostly in patients with cystic fibrosis (CF). For example, *Pseudomonas aeruginosa* colonizes up to 80% of patients with CF, increasing the risk of infection after transplant by an odds ratio of 4.7;[9,10] it is also known to be associated with BOS.[11] *Burkholderia* species colonize 15% to 22% of patients with CF, and pretransplant colonization by this organism is associated with increased mortality (hazard ratio, 2.23; $p = 0.04$).[12,13] Additional data have been published; international guidelines for the selection of lung transplant candidates, published in 2006,[4] state that pretransplant colonization with multidrug-resistant or panresistant *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, and *Aspergillus fumigatus* is a relative contraindication to transplantation.

Few papers have examined the impact of *A. baumannii* infection on LT. Most of them reported high short-term mortality due to the severe infection. One case series[6] reported that six patients with transplanted lungs were infected during a hospital outbreak, and four died as a result of this infection with persistent recovery of *A. baumannii* from the respiratory tract despite aggressive treatment. Sopirala et al[14] reported that among the 52 LTs performed in one hospital, 6 patients developed pneumonia in the postoperative period with multidrug-resistant *A. baumannii*, and two died of the infection. Martins et al.[15] described a case of donor transmission of carbapenem-resistant *A. baumannii*, and the patient died 65 days after transplantation. To our

knowledge, no previous case reports have described colonization of the pretransplant lung by XDR *A. baumannii*.

In this case, we continued colistin treatment from the day of the operation because of the infection risk due to colonization. The same organism had been isolated repeatedly from respiratory specimens and caused a severe infection in the early postoperative period. We changed the antibacterial agents after referring to a study reporting the survival benefit of a regimen of carbapenem and colistin (survival, colistin alone vs. carbapenem/colistin: 9% vs. 60%, respectively) in solid organ transplant patients infected with XDR *A. baumannii*. [7] Our patient showed clinical improvement on this combination regimen.

In immunocompromised hosts, *A. baumannii* infections can lead to multiorgan failure and death, but no drug of choice for treatment has been established. Common treatment options are carbapenems, β -lactamase inhibitors, quinolones, aminoglycosides, minocycline, doxycycline, and polymyxins. New treatment options include minocycline derivatives such as tigecycline, new carbapenems such as doripenem, and new-generation cephalosporins such as ceftobiprole and ceftaroline.[16] MDR *A. baumannii* is defined as being resistant to at least three antimicrobial classes. For the treatment of MDR *A. baumannii*, tigecycline has received attention and polymyxin E (colistin) has been widely used. Some recent clinical trials have shown poor clinical outcomes with tigecycline alone,[17,18] and the safety of colistin has been frequently discussed because of its nephrotoxicity. Combination therapy shows synergistic effects when carbapenems, sulbactam, or tigecycline are combined with aminoglycosides, colistin, or rifampin.[19]

Because the major adverse effect of colistin is nephrotoxicity and our patient developed drug-induced renal failure during the hospital course, the continuous use of IV colistin was reconsidered several times. Older studies report an incidence of nephrotoxicity of up to 20% to 50%, while recent clinical studies have found lower rates of nephrotoxicity of 8% to 14%, and the serum creatinine levels decreased at the end of the colistin treatment.[20] In this case, the MIC of tigecycline was high (MIC = 2), while the colistin, which is less toxic than polymyxin B, had to be administered carefully using strict dose modifications according to the daily laboratory results.

Acinetobacter infection is becoming prevalent as more

centers are willing to transplant candidates who are on mechanical ventilation or extracorporeal life support.[8] Colonization of the pretransplant lung by this organism will likely increase with prolonged ventilation, the use of broad-spectrum antibiotics, and intensive care unit care. We should also consider the patient's host factors; he was severely immunocompromised after taking immunosuppressants for several years after BMT, which made him more susceptible to bacterial infection. Strategies for dealing with pretransplant bacterial colonization and the choice of post-transplant prophylactic antibacterial agent for *Acinetobacter* species considering both host factors and the antibacterial spectrum of the organism should be investigated. Furthermore, the impact of the organism on the short-term mortality and long-term morbidity after transplantation, such as BOS, should be analyzed as more case reports are published.

In conclusion, we have reported a case of severe infection by XDR *A. baumannii* that colonized the pretransplant lung. The pretransplantation work-up of patients colonized with *A. baumannii* should consider host immunological factors and the drug resistance pattern of the colonizing *A. baumannii*.

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