Pseudomonas cepacia Empyema Necessitatis After Lung Transplantation in Two Patients With Cystic Fibrosis*

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Lung transplantation is an accepted modality for patients with cystic fibrosis (CF) who have end-stage respiratory failure. The postoperative course of these patients is often complicated by serious infections with organisms such as Pseudomonas aeruginosa and Pseudomonas cepacia that may be multiply resistant to conventional antimicrobial agents. We describe two patients with CF who, after double lung transplantation, developed the unusual complication of empyema and empyma necessitatis due to P cepacia that was resistant to all tested antibiotics. (Chest 1994; 105:1888-91)

CF=cystic fibrosis; CMV=cytomegalovirus; TBBx=transbronchial biopsy; TMP-S=trimethoprim-sulfamethoxazole

Lung transplantation has become an accepted mode of treatment for children with end-stage pulmonary disease from a variety of causes, including cystic fibrosis (CF).1,2 Infection in the transplanted lung remains a major cause of morbidity after lung transplantation3 and is a particular problem in patients with CF, who are often colonized with organisms such as Pseudomonas cepacia at the time of the transplant4 that are resistant to multiple antibiotics. Empyema, the accumulation of purulent material in a cavity, usually pleural, but also subdural or mediastinal, occurs infrequently in the modern antibiotic era and has not been a major problem after lung transplantation. Similarly, empyma necessitatis, the extension of pus from an empyema cavity into cutaneous soft tissues, is distinctly unusual. We describe here two patients with CF who developed empyma necessitatis as a result of antibiotic resistant P cepacia after double lung transplantation.

CASE REPORTS

CASE 1

An 18-year-old man, whose tracheobronchial secretions were previously colonized with P cepacia resistant to all tested antibiotics, underwent double lung transplantation for end-stage CF lung disease. His initial postoperative course was complicated by pulmonary vein thrombosis, which required reoperation on postoperative day 4. Perioperative antibiotic treatment consisted of tobramycin, clindamycin, and ceftazidine for 6 days. Immunosuppressive therapy consisted of FK506, azathioprine, and prednisone. He was discharged 28 days after transplantation with resolution of the pulmonary vein thrombosis.

Two months later he developed fever accompanied by roentgenographic evidence of a left lower lobe nodule. At surgery, a left lower lobe abscess was drained and cultures revealed Aspergillus

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the bronchial epithelium and invaded the overlying pleura. The lymph nodes were free of tumor. Nearly all malignant cells displayed prominent intranuclear staining following in situ hybridization with the HPV 11 probe only (Fig 1).

Serial sections for in situ hybridization, using cloned HPV DNA labeled with biotin, were cut from a formalin-fixed, paraform-embedded block of carcinoma. Single probes to HPV 6, 11, 16, 18, 31, 33, and 35 were employed. Positive and negative control tissues, fixed in a similar manner, were run simultaneously with the test samples. The sensitivity of this method is one to two viral copies per cell. Full details of the method have been published previously.5

**DISCUSSION**

Bronchogenic squamous cell carcinoma is a rare complication of RRP in the absence of a history of irradiation or smoking. In previous cases, it arose as a complication of RRP that extended into the tracheobronchial tree before diagnosis of the malignancy. In some cases, the malignancy was an incidental finding at autopsy of patients with RRP dying of pneumonia or respiratory failure.5

The unique feature of this case was the development of a bronchogenic squamous cell carcinoma in a patient in whom RRP had remained clinically localized to the larynx for 45 years. Distal involvement would not have been surprising in view of the recognized subglottic involvement, disease duration, previous tracheostomies, and numerous endoscopic excisions.2

Steinberg et al7 demonstrated that HPV is present in normal-appearing mucosa in patients with RRP. Therefore, the development of a bronchogenic carcinoma in apparently uninvolved mucosa is not surprising.

This case represents an important caveat. Squamous cell carcinoma of the lung can develop in the absence of obvious RRP extension into the tracheobronchial tree, indicating the importance of considering this possibility in patients with RRP who present with cough or other lower respiratory tract symptoms.

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Pseudomonas cepacia Empyema Necessitatis (Noyes et al)
and cytomegalovirus (CMV). Bronchoalveolar lavage (BAL) fluid and sputum cultures were processed as per our routine; fluid was cultured quantitatively onto blood, MacKonkey, and chocolate agar, as well as calcium nutrient agar plates. Antibiotic susceptibility testing was performed on purified cultures by the minimal inhibitory concentrations method (Sensititre, Radiometer American Inc). In this case, BAL fluid yielded CMV and Aspergillus but no Pseudomonas species. Ganciclovir and amphotericin were begun. FK506 immunosuppression was reduced, and he was eventually discharged to complete a 4-week course of ganciclovir and an 8-week course of antifungal therapy. He was readmitted, however, 1 week later because of recurrent fever. A repeat BAL culture grew no organisms but a sputum culture revealed a light growth of P cepacia. Histologic examination of tissue from a transbronchial biopsy (TBBx) revealed acute cellular rejection, and he was treated with a 3-day course of methylprednisolone. The patient improved only slightly and subsequently developed fevers exceeding 39.5°C accompanied by shaking chills and rigors.

A repeat BAL, performed 1 week after his steroid bolus contained a few neutrophils and on culture yielded a heavy growth of P cepacia that was resistant to all tested antibiotics. Blood cultures on three occasions also grew antibiotic resistant P cepacia. Treatment with meropenem, an imipenem derivative, was begun. The patient improved slightly, but intermittant fevers continued, and 2 weeks after meropenem was begun, a 6- by 7-cm fluctuant, warm, tender mass was noted at the left anterior axillary line at the site of the patient's thoracotomy scar. A chest computed tomography (CT) showed a pleural empyema with communication to the chest wall (Fig 1). During surgical exploration, 7 ml of thick creamy material was expelled from the pleural and abscess cavities. Cultures of this material, of blood, and of BAL fluid from the left lower lobe at the time of surgery all grew P cepacia that was resistant to all antibiotics tested, including meropenem. Clinofosaxin, a fluoroquinolone, was obtained and the patient gradually improved on a regimen of meropenem, clinofosaxin, rifampin, and high-dose (600 mg three times a day) aerosolized tobramycin. Six weeks later, meropenem was discontinued because of manufacturing problems and increased drainage was subsequently noted from the abscess cavity. A drainage tube was placed and a sinogram revealed direct communication with the left lung. Meropenem was restarted and was continued for an additional 12 weeks with no further positive blood, abscess, or BAL cultures. Subsequently, a repeat sinogram showed communication with a small abscess cavity. The patient is currently doing well at home, 14 months after transplant, with no recent evidence of P cepacia in BAL cultures and no further abscess drainage.

CASE 2

This 9-year-old boy with CF was previously colonized with P cepacia sensitive to several antibiotics and had received double lung transplantation for end-stage lung disease. On the afternoon after transplant, a blood culture grew P cepacia sensitive to ceftazidime, piperacillin, mezlocillin, and trimethoprim/sulfamethoxazole (TMP-S). A previous allergic reaction to cephalosporins prompted the use of piperacillin; tobramycin and intravenous TMP-S were added when blood cultures remained positive. Immune suppression consisted of FK506, azathioprine, and prednisone. The patient became afebrile, and subsequent blood cultures were sterile. He completed a 14-day regimen of piperacillin, tobramycin, and TMP-S. He had no other problems and was discharged on the 29th postoperative day.

The patient returned 1 week later for a regularly scheduled outpatient BAL, and TBBx and a blood culture was obtained, prompted by the presence of low-grade fever (38.6°C) the previous evening. He was admitted to the hospital and received a 3-day course of methylprednisolone after the TBBx revealed acute rejection. He became afebrile rapidly, but at 72 h the blood culture became positive for P cepacia, resistant to all antibiotics tested.

Piperacillin and tobramycin were begun and he underwent flexible endoscopic sinus surgery to irrigate and ablate the sinuses in an effort to prevent further P cepacia colonization. When fever returned and blood cultures remained positive, aztreonam was substituted for tobramycin, and within three days, his blood cultures became negative. He was discharged after 13 days of aztreonam and piperacillin, but he was readmitted again a week later with fever to 38.6°C. A chest radiograph showed right middle and lower lobe infiltrates with bilateral pleural effusions. The BAL fluid cultures yielded Pseudomonas aeruginosa and P cepacia, the latter resistant to all antibiotics tested. Piperacillin, tobramycin, and aztreonam treatment were reintstituted, but the patient remained febrile to as high as 39.6°C. Over a span of 48 h, a fluctuant, tender, erythematous expanding chest wall mass was noted in the midclavicular line medial to the nipple and superior to the surgical scar (Fig 2). A chest CT showed a large mass of mixed attenuation involving the chest wall and mediastinum with consolidation of adjacent lung (Fig 3). At surgery, thick, creamy fluid was drained from the abscess cavity which communicated with the mediastinum. Cultures of blood, abscess cavity, and of BAL fluid grew multiply antibiotic resistant P cepacia with P aeruginosa also growing from BAL fluid. The patient was treated with piperacillin, rifampin, aztreonam, and clinofosaxin, and he improved clinically and radiographically over the ensuing 3 weeks. Bronchoscopy subsequently showed moderate to severe stenosis of the right mainstem bronchus at the anastomotic site.

**FIGURE 1.** Chest CT scan demonstrates bilateral pleural effusions with left lower lobe consolidation and a sinus tract extending to the subcutaneous tissues.

**FIGURE 2.** Warm, fluctuant, tender cutaneous abscess noted in patient 2 in the midclavicular region slightly superior to his transthoracic surgical scar.

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site. A BAL and TBBx showed a light growth of *P. cepacia* and
moderate acute rejection. He received 3 days of methylprednisolone. Seven
days later, he became tachypneic with increased respiratory distress and
temperature to 39.7°C. Bronchoscopy and TBBs showed no evidence of
rejection but worse narrowing at the right anastomotic site. The BAL fluid once again grew *P. cepacia* that
was resistant to all antibiotics tested. Increasing respiratory distress over
the next several days prompted the insertion of a silastic stent at the site of
the right bronchial narrowing. The patient remained intubated after surgery, developed *P. cepacia* sepsis,
worsening respiratory failure with clinical and radiographic evidence
of adult respiratory distress syndrome, and subsequently died 114 days after transplant. Postmortem examination revealed
a necrotizing *P. cepacia* right lower lobe pneumonia.

**DISCUSSION**

In the antibiotic era, empyema complicating bacterial pneumonia is relatively uncommon, occurring in 1 percent of
cases. Empyema necessitatis is an extremely unusual complication of empyema, with scattered case reports appearing
for the past 30 years, most occurring in patients with underlying tuberculosis. In fact, it has been more than 50 years since empyema necessitatis was last reviewed
in the literature.

Pneumonia caused by *Pseudomonas* species accompanied by bacteraemia occurs predominantly in immunocompromised
patients and has been observed rarely in patients with CF, usually in infants and usually in the setting of severe respiratory disease. To our knowledge, empyema has not been reported as a complication of *Pseudomonas*
bronchitis in immunocompetent individuals with CF, although there have been reports of *P. aeruginosa* pneumonia complicated by empyema in patients without CF. The Toronto Lung Transplant Group reported
recently their experience with lung transplantation in CF, noting the poor outcome in patients who were colonized
with *P. cepacia* before transplant. Fifteen of their 24 patient-recipients of lung transplants had sputum or BAL fluid cultures positive for *P. cepacia*, 7 of whom died. Five patient deaths were directly attributable to *P. cepacia* infections. Fourteen of 15 patients ever colonized with *P. cepacia* had significant postoperative infections with this organism and 4 were complicated by *P. cepacia* empyema.

The two patients described here are noteworthy for several reasons. We believe this is the first report of *P. cepa-

cia* empyema accompanied by empyema necessitatis in CF or in immunocompromised patients. The lung transplant
recipients described here posed unique treatment problems in that they were receiving immunosuppressive drugs
and were known to have respiratory tracts colonized with organisms against which most or all conventional antimicrobial agents were ineffective. *Pseudomonas* pneumonia occurring in patients with CF after lung transplant has been a frequent problem, presumably from seeding of the allograft by contaminated upper respiratory airway secretions, arising either from the trachea or sinuses. It has been
our experience that the pneumonia in these patients tends to be difficult to treat since, with exposure to multiple
courses of intensive IV antibiotics, the organisms cultured from these patients at the time of transplant tend to be
resistant to most or all antibiotics.

In the first patient described, a left lower lobe pneumonia caused by *P. cepacia* that was resistant to all antibiotics tested
was accompanied by a pleural effusion and, presumably, an empyema. In the second patient, we speculated that the *P. cepacia*
bacteraemia noted on the day of transplant seeded his mediastinal wound and the latter remained the nidus of subsequent bacteraemic events that were partially suppressed by relatively ineffective antimicrobial coverage. As the resistance pattern of his *P. cepacia* emerged, a mediastinal empyema
developed with erosion into the chest wall.

In summary, we have described empyema necessitatis due to multiply antibiotic resistant *P. cepacia* in two patients with
CF after lung transplant. This complication led to the death of one patient and significant morbidity in the other. We now
consider the presence of multiply antibiotic resistant *P. cepacia* in the sputum of CF patients to be a contraindication to lung
transplantation. It has also prompted us to alter our handling of subsequent CF transplant patients in an effort to eliminate
or reduce these infectious complications. First, we have avoided "triple" immunosuppressive therapy by using FK506 and
corticosteroids alone and rapidly tapering the latter in the first several weeks after transplant. Second, we view the use of antimicrobial agents specifically tailored to results from pretransplant sputum cultures as treatment of a contaminated wound and continue antibiotics for 10 to 14 days after the
transplant procedure. Third, we now monitor the patient closely with random blood cultures intraoperatively and
postoperatively. Finally, we consider meticulous handling of the airways intraoperatively and avoidance of cross-contamina-
tion during the sequential bronchial transplant procedure crucial.

**REFERENCES**

Diffuse Alveolar Hemorrhage Associated With Mycoplasma hominis Respiratory Tract Infection in a Bone Marrow Transplant Recipient*

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An 18-year-old woman developed respiratory distress and diffuse pulmonary infiltrates after allogeneic bone marrow transplantation. Bronchoalveolar lavage findings indicated diffuse alveolar hemorrhage. Cultures of the lavage fluid and the pharynx grew Mycoplasma species; the pharyngeal isolate was identified as Mycoplasma hominis. Mycoplasma hominis infection may have an etiologic role in diffuse alveolar hemorrhage. (Chest 1994; 105:1891-92)

Diffuse alveolar hemorrhage is a syndrome of unknown etiology characterized by dyspnea, hypoxia, cough, and diffuse infiltrates on chest radiograph. In this syndrome, aliquots of lavage fluid recovered from sequential bronchoalveolar lavage typically contain hemosiderin-laden macrophages and progressively increasing concentrations of blood.1 Routine microbiologic studies of bronchoalveolar lavage fluid are generally negative. This condition occurs in 5 to 35 percent of bone marrow transplant recipients and is fatal in 80 to 100 percent of cases.2,3 Although anecdotal reports suggest that corticosteroid therapy may be beneficial,2 no specific therapy has proved effective. We describe a bone marrow transplant recipient who recovered from diffuse alveolar hemorrhage associated with Mycoplasma hominis respiratory tract infection.

CASE REPORT

An 18-year-old woman with acute myeloblastic leukemia in remission received an HLA-matched sibling bone marrow transplant following a preparatory regimen of cytarabine, cyclophosphamide, and fractionated total body irradiation with delivery of 1,400 cGy. The patient was participating in a pilot study to evaluate the effect of pentoxifylline administered in conjunction with cyclosporine on the incidence and severity of graft-vs-host disease. The first month of the posttransplantation course was complicated by grade 3 graft-vs-host disease of the skin (managed with methylprednisolone and cyclosporine), mild elevations of liver enzyme levels, hemorrhagic cystitis, hypertension, pseudomembranous colitis, and fever that was unresponsive to empiric antimicrobial therapy (vancomycin, cefazidime, metronidazole, trimethoprim sulfamethozaxole, amphotericin B, and ganciclovir). Thirty-seven days after transplantation, the patient developed progressive tachypnea, hypoxia, and respiratory distress, and diffuse alveolar infiltrates appeared on chest radiographs. At this time, the absolute neutrophil count was 5,000 cells per microliter, platelets were 30,000 per microliter, and results of coagulation studies were normal except for a slightly prolonged partial thromboplastin time (patient, 40 s; control, 31 s). Bronchoscopy was performed. The airways were erythematous and friable. Sequential instillation and aspiration of normal saline solution produced progressively bloodier lavage fluid. Hemosiderin-laden macrophages were found on cytologic examination. The corticosteroid therapy was continued, and platelet transfusions and erythromycin (for diffuse lung infiltrates) were administered empirically. The patient defervesced the following day and remained afebrile thereafter. The lung infiltrates improved steadily, almost completely clearing in 5 days.

Mycoplasma species with identical colony morphologic features were isolated from cultures of the lavage fluid, the pharyngeal mucosa, and the urine. The pharyngeal and urinary isolates were passaged in culture and were identified as M hominis. In vitro antibiotic susceptibility testing indicated that the isolates were resistant to erythromycin and tetracycline, and susceptible to doxycycline (identification and susceptibility testing were performed at the Mycoplasma Diagnostic Laboratory, University of Alabama, Birmingham). Attempts to pass the bronchoalveolar lavage fluid isolate were not successful. Routine and special bacterial, viral, and fungal cultures of the bronchoalveolar lavage fluid had no growth other than the Mycoplasma colonies, and Gram stain revealed no organisms. The patient's respiratory symptoms resolved over a 5-day period. A few days later, gross hematuria recurred. A course of tetracycline was administered (prior to the availability of antibiotic susceptibility tests) and the hematuria abated. The patient was discharged from the hospital 54 days after transplantation.

One week later, the patient was readmitted to the hospital with gross hematuria. Culture of the urine was now negative for Mycoplasma, but positive for adenovirus. During this hospital admission, the patient developed progressive renal, marrow, respiratory, and cardiovascular failure. She died 91 days after transplantation. Permission for autopsy or bone marrow aspiration was not granted and the underlying cause of death was not determined.

DISCUSSION

To our knowledge, this is the first report of an apparent