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Sepsis, Multiple Organ Failure, and Death Due to *Pandoraea pnomenusa* Infection after Lung Transplantation

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A 30-year-old man died with *Pandoraea pnomenusa* sepsis after lung transplantation. *Pandoraea* species are gram-negative rods, closely related to, and commonly misidentified as, *Burkholderia cepacia* complex or *Ralstonia* species. Heretofore considered soil bacteria and colonizers that infect patients with chronic lung diseases, *Pandoraea* species can produce severe infections.

CASE REPORT

A 30-year-old African-American man was referred for transplantation evaluation owing to end-stage pulmonary sarcoidosis complicated by nocardiosis and mycetomas. Upon admission for transplantation, he was oxygen dependent and was receiving prednisone, 50 mg daily, and itraconazole, 100 mg twice daily. There was no history of recent fever or change in his cough, sputum production, or severe dyspnea. Gram-negative rods had not previously been recovered from respiratory samples, nor had he received antibacterial therapy in the previous 2 months.

The patient underwent bilateral cadaveric lung transplantation. Ceftazidime, vancomycin, and amphotericin B lipid complex (ABLC) were given systemically immediately before transplant surgery and were continued thereafter; inhaled ABLC and intravenous ganciclovir were added postoperatively. His immunosuppressive regimen included FK506 (Tacrolimus) and methylprednisolone. Immediately postoperatively, the patient's temperature rose to 41°C, and hypotension requiring high doses of vasopressors ensued. His low peripheral vascular resistance and high cardiac output were consistent with septic shock. A chest radiograph showed mild edema, small bilateral pleural effusions, and tiny pneumothoraces. Laboratory values included a white blood cell count, 20,600 per μl with 96% neutrophils; fibrinogen, 308 mg per dl (normal value, 183 to 434 mg per dl); international normalized ratio, 1.3; and activated partial thromboplastin time, 32.8 s (normal value, 23.6 to 33 s). Blood cultures subsequently grew a non-lactose-fermenting gram-negative rod from both aerobic and anaerobic FAN bottles at 48 h (BacT/Alert blood culture system; bioMérieux, Inc., Durham, N.C.). By postoperative day 3 the patient had defervesced, and vasopressor support was discontinued on postoperative day 4; however, he had progressive bilateral pulmonary infiltrates, and a computed tomography scan of the chest showed extensive bilateral airspace disease, consistent with the adult respiratory distress syndrome. Deteriorating renal function led to continuous venous-venous hemodialysis on postoperative day 5.

On postoperative day 8, the patient again developed fever and hypotension (again requiring vasopressors), and blood cultures were repeated. These blood cultures also turned positive for a gram-negative rod similar to that isolated on the day of transplantation. The gram-negative rod grown from blood obtained on the day of transplantation grew well on *B. cepacia* Selective Agar (7) and was presumptively identified as *Burkholderia cepacia* (similarity index of 0.639 for *B. cepacia*) by analysis of cell wall fatty acid composition (Microbial Identification System, version 4; MIDI, Inc., Newark, Del.), although the biochemical profile (negative for oxidase and lysine decarboxylase activity; failure to oxidize sucrose and lactose) was not consistent with the *B. cepacia* complex species. Meropenem was substituted for ceftazidime, since the isolate was susceptible to imipenem but resistant to aminoglycosides, ceftazidime, ciprofloxacin, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole by disk diffusion testing. Despite therapy with meropenem, vancomycin, ABLC, and ganciclovir, the patient remained febrile, was dependent on vasopressors for circulatory support, and required mechanical ventilation with increasing oxygen demands. Diffuse bilateral infiltrates persisted.

Multiple diagnostic procedures, including repeated bronchoscopies with bronchoalveolar lavage (BAL) and a transbronchial biopsy submitted for viral, bacterial, mycobacterial, and fungal cultures, failed to disclose an alternative pathogen to the gram-negative rod recovered from his blood initially and on postoperative day 8 as well as from a BAL sample obtained on day 10. No ulcers or pseudomembranes were seen at anastomotic sites. Tests for cytomegalovirus DNA by hybrid capture were negative. Histopathology showed diffuse alveolar damage, but no microorganisms were seen on special stains. Imipenem was substituted for meropenem based on repeat susceptibility testing (33-mm zone of inhibition by disk diffusion testing versus 6-mm zone size, respectively) of the gram-negative rod grown from his blood. Nonetheless, the patient developed progressive adult respiratory distress syndrome, coagulopathy, refractory hypotension, leukopenia (white blood

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cells, 2,600 per μl), and thrombocytopenia (platelets, 64,000 per μl). The patient died on postoperative day 17 with refractory shock and multiple organ failure.

The gram-negative rod recovered from blood on the day of transplantation was forwarded to the CFF *Burkholderia cepacia* Research Laboratory and Repository at the University of Michigan for definitive identification. PCR-based assays specific for *B. cepacia* complex species (10, 11) were negative. However, a panel of PCR assays specific for species in the genus *Pandoraea* were positive, and the isolate was identified as *Pandoraea pnomenusa* based on *gyrB* gene RFLP analysis (3, 4, 5).

The *Burkholderia cepacia* complex consists of several related species of gram-negative rods that are generally resistant to multiple antibiotics. Certain of these species may colonize and produce severe lung infection, and sometimes bacteremia, in patients with cystic fibrosis and other chronic lung diseases who undergo lung transplantation (1, 2, 9). In 2000, Coenye et al. described a novel genus of gram-negative bacilli closely related to and commonly misidentified as *B. cepacia* complex. The name *Pandoraea*, in recognition of its genomic diversity, was proposed (3). *Pandoraea* species have been recovered from clinical specimens, particularly from patients with chronic lung disease, as well as environmental samples. To our knowledge, there are no previous clinical descriptions of infections caused by the genus *Pandoraea*. The case reported herein describes a severe infection caused by *P. pnomenusa* in a patient who underwent a bilateral lung transplant for terminal sarcoid lung disease.

The genus *Pandoraea* is composed of aerobic, non-spore-forming, non-nitrate-reducing, non-lactose-fermenting, gram-negative rods with polar flagella. Six species of *Pandoraea* have been described: *Pandoraea apista*, *Pandoraea norimbergensis*, *Pandoraea pnomenusa*, *Pandoraea pulmonicola*, *Pandoraea sputorum*, and one unnamed species. The majority of isolates have been recovered from respiratory samples from patients with cystic fibrosis or other underlying chronic lung disease and soil. Organisms previously included in the Centers for Disease Control and Prevention (CDC) weak oxidizer group 2 (WO-2) have since been reclassified as *Pandoraea* species, and four of the nine organisms in this group were recovered from blood, thus suggesting the potential to cause invasive disease (6). *Pandoraea* strains typically have catalase activity, grow at 30 and 37°C and in 0.5 and 1.5% NaCl, assimilate D-gluconate, L-malate, and phenylacetate, and have acid and alkaline phosphatase and leucine arylamidase activity (3). Species in this genus are often misidentified as *B. cepacia* complex or *Ralstonia* species (including *Ralstonia mannitolilytica*, *Ralstonia paucula*, and *Ralstonia pickettii*) owing to overlapping biochemical profiles without differences that reliably distinguish between species (8). Moreover, our *P. pnomenusa* isolate was misidentified as *B. cepacia* by cell wall fatty acid analysis using the current aerobic library (version 4) of the Microbial Identification System. It is because of these limitations that reliable identification requires 16S ribosomal DNA sequence analysis. From a practical standpoint, the earliest clue as to the possible identity of *P. pnomenusa* may be the unusual pattern of antimicrobial susceptibility to carbapenems that appears unique to most *Pandoraea* species (6).

Evidence for the pathogenic potential of *Pandoraea* species is illustrated by our patient's severe sepsis with bacteremia and multiple organ failure. Isolation of *P. pnomenusa* from blood cultures during the time of hemodynamic instability and fever postoperatively, 8 days later, and at the time of death support causality. Furthermore, *P. pnomenusa* was the most common species of the CDC WO-2 isolates to be recovered from blood, which suggests an increased potential for this particular species to cause invasive disease (6). The source of our patient's bacteremia is unclear. However, the presence of the organism in the purulent secretions collected by BAL on postoperative day 10 implicates the lungs as a possible source. It is possible that the patient or donor had pulmonary colonization with the organism prior to the transplantation. However, neither the donor's nor the recipient's respiratory culture at the time of transplantation grew the organism. The possibility of an environmental source for the pneumonia and bacteremia cannot be ruled out. To date, however, we have not identified any other cases of *Pandoraea* infection or colonization in patients at our hospital.

We believe that *Pandoraea* will be increasingly recognized as a pathogen in patients with chronic lung diseases, particularly in those patients with cystic fibrosis. Susceptibility results for *P. pnomenusa* were remarkable for multidrug resistance and a unique pattern of resistance to carbapenems: resistant to meropenem but susceptible to imipenem. This pattern of carbapenem resistance was common in the profiles of WO-2 strains classified as *Pandoraea*, including three isolates of *P. pnomenusa* (6). Because of this organism's unique antibiotic resistance pattern and ability to produce serious infections, caution should be taken when a pathogen cannot be clearly identified as *B. cepacia* complex or *Ralstonia* species, and antibiotic therapy should be based on actual in vitro susceptibility testing. Specifically, susceptibility testing with meropenem should not be used to predict results with imipenem and vice versa; each should be tested individually for *Pandoraea* species.

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