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Sepsis caused by *Elizabethkingia miricola* successfully treated with tigecycline and levofloxacin

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Abstract

Elizabethkingia miricola is a gram-negative rod that was initially isolated from condensation water of the space station Mir. This is the first reported case of human disease caused by this organism.

1. Introduction

Elizabethkingia miricola, a gram-negative, non-motile, non-spore-forming rod was first described in 2003 when it was isolated from condensation water on the space station Mir (Li, 2003). Initially named *Chryseobacterium miricola*, it was reclassified along with *Chryseobacterium meningosepticum* into the new genus *Elizabethkingia* (Kim, 2005). To date, *E. miricola* has not been isolated from other environmental or clinical sources. We report the isolation of *E. miricola* from the sputum and blood of a man with mantle cell lymphoma who had undergone stem cell transplant and chemotherapy and required ventilator support.

2. Case

A 55-year-old man with stage IV mantle cell lymphoma who had received allogeneic stem cell transplant in August 2007 was admitted for salvage chemotherapy and stem cell reinfusion following relapse in January 2007. The chemotherapy consisted of mini-BEAM (carmustine, etoposide, arabinoside C and melphalan). Following chemotherapy, the patient experienced a relapse of his graft versus host disease of the skin and prolonged neutropenia. During neutropenia, he developed a first episode of fever that resolved after 24h of empirical ceftazidime and vancomycin, Physical exam was unrevealing except for his graft versus host disease of the skin; blood and urine cultures were negative and the chest CT was normal. Two weeks later, a second episode of fever prompted substituting meropenem for ceftazidime. The chest CT at this point showed pulmonary nodules in the right upper and right lower lobes which later evolved into diffuse infiltrates. A bronchoalveolar lavage (BAL) showed pulmonary hemorrhage. The galactomannan antigen index in the BAL fluid was 10. The BAL cultures

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were negative, but subsequent sputum and tracheal aspirate grew *Aspergillus terreus* and *Aspergillus ustus*. Treatment with voriconazole and caspofungin was administered. His aspergillosis resulted in repeated episodes of hemoptysis that required admission to the ICU and several episodes of intubation and mechanical ventilation. The patient was treated with granulocyte colony stimulating factor until the absolute neutrophil count improved to greater than 1000 cells/mm^3 on day 14 post-admission to ICU. On day 17 post-ICU admission he had a new fever (38.7 C). At this point his total white cell count was 3,510 cells/mcL with 75% neutrophils. Blood culture on day 18 was negative. Respiratory specimens from day 18 (tracheal aspirate and sputum) showed few neutrophils and mixed oral flora, and the culture grew a gram-negative rod initially misidentified as *Chryseobacterium meningosepticum* susceptible to ciprofloxacin and levofloxacin (MIC ≤ 1 and 2 mcg/ml, respectively) but resistant to all other antibiotics tested (aminoglycosides, first, second and third-generation cephalosporins, carbapenems, trimethoprim/sulfamethoxazole and colistin). Subsequent E-test showed MIC for tigecycline = 2 mcg/mL. One of two blood cultures collected on day 19 was positive for vancomycin-resistant *E. faecium*; therefore, linezolid was added to the antibiotic regimen. However, the fever persisted. A chest radiograph on day 21 showed a new consolidation behind the heart, and one of four blood cultures obtained on day 21 grew a gram-negative rod that seemed identical to the one isolated three days earlier from the tracheal aspirate. Biochemical testing and sequence analysis of the 16S rRNA gene was used to identify the isolates as *E. miricola*. The blood isolate was susceptible to levofloxacin and resistant to all other antibiotics tested, including carbapenems, third-generation cephalosporins, trimethoprim/sulfamethoxazole, aminoglycosides and colistin. E test was performed for tigecycline (2 mcg/mL) and rifampin (0.5 mcg/mL). Tigecycline was used initially to treat simultaneously the *E. faecium* bacteremia (avoiding linezolid toxicity) and the *E. miricola* pneumonia. The fever resolved after 48h of tigecycline; levofloxacin was subsequently added to complete 2 weeks of total therapy. The interpretation of the alveolar infiltrates present on chest radiograph was complicated by subsequent episodes of pulmonary hemorrhage and fluid overload. Repeat blood cultures were persistently negative although respiratory specimens collected on day 29 and day 32 remained positive for *E. miricola*. The subsequent clinical course of the patient was complicated by worsening graft versus host disease, a second episode of bacteremia with vancomycin-resistant Enterococcus, aspergillosis refractory to medical treatment (including voriconazole, anidulafungin and liposomal amphotericin B) that required resection of the right upper lobe and part of the right lower lobe, *Bacteroides fragilis* bacteremia and sepsis, and finally adenovirus pneumonia with respiratory insufficiency and death on day 120 of his ICU admission. *E. miricola* was isolated again in tracheal aspirates obtained on day 75, day 91 and 111. These later isolates were resistance to levofloxacin and susceptible to tigecycline (2 mcg/mL) and were not clearly associated with new pulmonary infiltrates or bacteremia.

Microbiology Testing

Blood cultures were processed in the Bactec 9240 system (Becton Dickinson & Co, Sparks, MD) using the Standard Aerobic/F and Anaerobic/F bottles with all bottles incubated for a minimum of 7 days. Respiratory specimens were inoculated onto trypticase soy agar with sheep blood, chocolate agar, and MacConkey agar (Remel, Lenexa, KS) and incubated at 37°C in a 5% CO_2 atmosphere. Initial microbial identification and antimicrobial susceptibility testing were performed in the MicroScan System (Siemens Healthcare Diagnostics, Deerfield, IL) using the Neg Combo Type 30 panel. Definitive identification of the gram-negative rod recovered from our patient was performed by sequence analysis of the 16S ribosomal RNA gene. Genomic DNA was extracted from the bacterium and amplified, and the complete 16S rRNA gene was sequenced using Applied Biosystems BigDye Terminator v1.1 chemistry (Foster City, CA). The sequence was analyzed and aligned using Lasergene DNA Star software

and compared with public databases, i.e., GenBank (NCBI) and the Ribosomal Database (RDP) of Michigan State University.

3. Discussion

This is the first reported isolation of *E. miricola* from clinical specimens. Initially in this patient the organism was misidentified as *E. meningosepticum* (formerly *Chryseobacterium meningosepticum*); however the routine procedure of the NIH Clinical Center Microbiology Laboratory is to confirm all uncommon bacterial and fungal identifications by gene sequencing. Using full rRNA 16S sequencing, the patient's isolate was most closely related to the type strain of *E. miricola* (GTC862, Gifu Type Culture Collection, Japan; 99.8% identity) compared with the type strain of *E. meningosepticum* (ATCC13252, American Type Cell Culture, Virginia; 98.5%).

For comparison, Bloch et al reported in 1997 a small series of 15 patients with *C. meningosepticum* infections. Eighty percent of the patients had nosocomially-acquired infections and 20% were colonized with *C. meningosepticum* without evidence of infection. Of special note, all infected patients were significantly immunocompromised with two being neutropenic at the time of positive culture. The mean time to from admission to infection was 28.2 days with a range of 6–48 days in hospital. All patients had received antibiotic therapy before the positive index culture. In her literature review in the same article, Bloch found that the lung was the most frequent site of infection in post-neonatal patients. Although we are unable to make any definitive conclusions regarding the epidemiology of *E. miricola* in the patient reported herein, the respiratory tract is the most likely initial site of infection because positive respiratory cultures preceded bacteremia by three days.

Confirmation of the pathogenic role of uncommon isolates in severely immunocompromised patients with multiple problems is challenging; however, in this case the combination of new fever, newly identified pulmonary infiltrate and positive respiratory and blood cultures for *E. miricola* establish it as a potential cause of nosocomial pneumonia. The resistance to antibiotics reported for *E. meningosepticum* held true for this particular isolate that became progressively resistant to all classes of antibiotics over a three month period.

In summary, *E. miricola* might have the potential to cause ventilator-associated pneumonia and bacteremia in immunocompromised patients. It can be misidentified as *E. meningosepticum*. Antibiotic resistance may be common so antimicrobial susceptibility tests should guide selection of therapy. The role of tigecycline remains to be defined. There are no CLSI interpretive standards for susceptibility to tigecycline, but our patient had a clinical and microbiologic response after 48h of treatment with tigecycline (MIC, 2 mcg/mL).

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