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

O'Neil Green[a], Patrick Murray[b,*], Juan C. Gea-Banacloche[c]

[a]*Department of Internal Medicine, New York Hospital Queens/Weill-Cornell Medical College, Flushing, NY 11355, USA*
[b]*Department of Laboratory Medicine, National Institutes of Health Clinical Center, MD 20892, USA*
[c]*Department of Infectious Diseases, National Institutes of Health Clinical Center, Bethesda, MD 20892, USA*

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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 1st reported case of human disease caused by this organism.
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1. Introduction

Elizabethkingia miricola, a Gram-negative, nonmotile, non–spore-forming rod was 1st described in 2003 when it was isolated from condensation water on the space station Mir (Li et al., 2003). Initially named *Chryseobacterium miricola*, it was reclassified along with *Chryseobacterium meningosepticum* into the new genus *Elizabethkingia* (Kim et al., 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 after relapse in January 2007. The chemotherapy consisted of mini-BEAM (carmustine, etoposide, arabinoside C, and melphalan). After chemotherapy, the patient experienced a relapse of his graft versus host disease of the skin and prolonged neutropenia. During neutropenia, he developed an episode of fever that resolved after 24 h of empirical ceftazidime and vancomycin. Physical examination was unrevealing except for his graft versus host disease of the skin; blood and urine cultures were negative, and the chest computed tomography (CT) was normal. Two weeks later, a 2nd 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 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 intensive care unit (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 postadmission 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 3510 cells/μL, with 75% neutrophils. Blood culture on day 18 was negative.

* Corresponding author. Tel.: +1-301-402-9559; fax: +1-301-402-1886.
E-mail address: pmurray@cc.nih.gov (P. Murray).

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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 *C. meningosepticum* susceptible to ciprofloxacin and levofloxacin (MIC ≤1 and 2 μg/mL, respectively) but resistant to all other antibiotics tested (aminoglycosides; 1st-, 2nd-, and 3rd-generation cephalosporins; carbapenems; trimethoprim/sulfamethoxazole; and colistin). Subsequent E-test showed the MIC for tigecycline is 2 μg/mL. One of 2 blood cultures collected on day 19 was positive for vancomycin-resistant *Enterococcus 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 1 of 4 blood cultures obtained on day 21 grew a Gram-negative rod that seemed identical to the one isolated 3 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, 3rd-generation cephalosporins, trimethoprim/sulfamethoxazole, aminoglycosides, and colistin. E-test was performed for tigecycline (2 μg/mL) and rifampin (0.5 μg/mL). Tigecycline was used initially to treat simultaneously the *E. faecium* bacteremia (avoiding linezolid toxicity) and the *E. miricola* pneumonia. The fever resolved after 48 h 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 days 29 and 32 remained positive for *E. miricola*. The subsequent clinical course of the patient was complicated by worsening graft versus host disease, a 2nd 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 days 75, 91, and 111. These later isolates were resistant to levofloxacin and susceptible to tigecycline (2 μg/mL) and were not clearly associated with new pulmonary infiltrates or bacteremia.

2.1. 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, that is, GenBank National Center for Biotechnology Information (NCBI) and the Ribosomal Database (RDP) of Michigan State University (East Lansing, MI).

3. Discussion

This is the 1st reported isolation of *E. miricola* from clinical specimens. Initially, in this patient, the organism was misidentified as *Elizabethkingia meningoseptica* (formerly *C. meningosepticum*); however, the routine procedure of the National Institutes of Health Clinical Center Microbiology Laboratory is to confirm all uncommon bacterial and fungal identifications by gene sequencing. Using full 16S rRNA sequencing, we found that the patient's isolate was most closely related to the type strain of *E. miricola* (99.8% identity, GTC862; Gifu Type Culture Collection, Japan) compared with the type strain of *E. meningosepticum* (98.5%, ATCC 13252; American Type Cell Culture, Manassas, VA).

For comparison, Bloch et al. (1997) reported 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 2 being neutropenic at the time of positive culture. The mean time from admission to infection was 28.2 days, with a range of 6 to 48 days in hospital. All patients had received antibiotic therapy before the positive index culture. In her literature review in the same article, Bloch et al. found that the lung was the most frequent site of infection in postneonatal 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 3 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* establishes 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 3-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. meningoseptica*. 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 Clinical and Laboratory Standards Institute interpretive standards for susceptibility to tigecycline, but our patient had a clinical response after 48 h of treatment with tigecycline (MIC, 2 μg/mL).

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outcomes for this population. In view of the very large size of the surgical population, such measures might lead to a substantial reduction in the number of deaths.

We declare that we have no conflicts of interest.

*Rupert Pearse, Andreas Hoeft, Rui P Moreno, Paolo Pelosi, Andrew Rhodes
r.pearse@qmul.ac.uk

Adult Critical Care Unit, Barts and the London School of Medicine and Dentistry, Queen Mary's University of London, Royal London Hospital, London E1 1BB, UK (RP); Department of Anaesthesiology, University of Bonn, Bonn, Germany (AH); UCINC, Hospital de São José, Centro Hospitalar de Lisboa Central, EPE, Lisbon, Portugal (RPM); IRCCS AOU San Martino-IST, Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy (PP); and St George's University of London, London, UK (AR)

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E anophelis outbreak in an intensive-care unit

We read with interest Jeanette Teo and colleagues' report (Sept 7, p 855)[1] of the first outbreak of *Elizabethkingia anophelis* identified by 16SrRNA sequencing and whole-genome alignment. The subgroup of isolates had been previously identified as *Elizabethkingia meningoseptica* on the basis of matrix-assisted laser desorption-ionisation time-of-flight (MALDITOF) mass spectrometry analysis.

The history of this microorganism starts with its description as a cause of infant meningitis by Elizabeth O King at the US Centers for Disease Control and Prevention (CDC). She first isolated an organism referred to as CDC group IIa in 1959 and named it *Flavobacterium meningosepticum*. It was subsequently renamed *Chryseobacterium meningosepticum*, and classified in the new genus *Elizabethkingia*, in 2005.[2]

We believe that modern techniques (such as MALDITOF and sequencing) might generate more and more pseudo first outbreaks. Outbreaks of *F meningosepticum*, *C meningosepticum*, and *E meningoseptica* have been described in several patient settings, including intensive-care units.[3–5] Thus, what is new here, except the name? To be considered as new outbreaks, future reports should describe a new source or pathway of transmission and not merely one that appears new because of the diagnostic methods presently used.

We declare that we have no conflicts of interest.

*Andreas Voss, Jan Kluytmans, Eli Perencevich
vossandreas@gmail.com

Radboud University Nijmegen Medical Centre and Canisius-Wilhelmina Hospital, Department of Medical Microbiology and Infectious Diseases, 6500 GS Nijmegen, Netherlands (AV); VU University Medical Center Amsterdam and Amphia Hospital Breda, Department of Medical Microbiology, Breda, Netherlands (JK); and University of Iowa, Carver College of Medicine Department of Internal Medicine, Iowa City, IA, USA (EP)

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Authors' reply

Andreas Voss and colleagues have alluded to the fact that 16SrRNA sequencing in the early 2000s allowed *Elizabethkingia* to be placed separately from the genus of *Chryseobacterium*. Next-generation sequencing has facilitated a higher level of differentiation between two very distinct species of *Elizabethkingia*, namely *Elizabethkingia meningoseptica* and *Elizabethkingia anophelis*.[1,2] Our analyses identifying the intensive-care unit outbreak strain as *E anophelis* is not just a reclassification of an old species as Voss and colleagues suggest. *E anophelis* is an entirely separate species with infection potential. *E anophelis* is presently understudied but should not be considered irrelevant in the clinical setting. Our sequencing data suggest the presence of a substantial number of virulence determinants, and studies to assess *E anophelis*' virulence potential in animal are in progress.

Investigation of novel outbreaks when paired with comparative genome sequencing data provides important information to understand transmission of a pathogen, and especially so for rare organisms. Comparative genomics is a crucial approach in the discovery of virulence determinants and genetic markers of uncharacterised bacterial species. Genome-based approaches can be associated with other omics-based approaches (eg, transcriptomics and proteomics)[3] to analyse bacterial physiology and pathogenesis mechanisms.

An intriguing and important issue is the transmission pathway of *E anophelis*. We speculate that malaria carriage in patients might be at the origin of *E anophelis* transmission in the hospital setting, which we are investigating.

We declare that we have no conflicts of interest.

*Sean Yang-Yi Tan, Jeanette Teo, *Liang Yang
yangliang@ntu.edu.sg