

Fatal *Citrobacter farmeri* Meningitis in a Patient with Nasopharyngeal Cancer[∇]

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We describe the case of an adult male with nasopharyngeal carcinoma who had meningitis caused by *Citrobacter farmeri*. The isolate was confirmed as *C. farmeri* by two commercial identification systems and 16S rRNA gene analysis. The patient developed multiorgan failure and died despite antibiotic treatment with *in vitro* active agents (ceftriaxone and meropenem).

CASE REPORT

A 54-year-old man who had been treated with radiotherapy for nasopharyngeal cancer 4 years earlier presented with fever and progressive drowsiness for 2 days. He reported developing headaches, a poor appetite, and general malaise 2 weeks before this visit. On examination, vital signs were as follows: temperature, 38.8°C; pulse rate, 105 min/min; respiratory rate, 22/min; and blood pressure, 152/96 mm Hg. Physical examination was unremarkable except for neck stiffness. The results of laboratory tests were as follows: white blood cell (WBC) count, 17,430 cell/mm³ (neutrophils, 77%; lymphocytes, 17%); hematocrit value, 41%; platelet count, 236,000 cell/mm³; serum creatinine, 0.8 mg/dl; aspartate aminotransferase, 50 U/liter (normal, <37 U/liter); and C-reactive protein, 16.24 mg/dl (normal, <0.8 mg/dl). Brain computed tomography disclosed dilated ventricles with diminished sulci. Cerebrospinal fluid (CSF) study revealed the following: initial pressure, 245 mm H₂O; WBC count, 725 cells/ml (neutrophils, 91%; lymphocytes, 9%); protein level, 532.7 mg/dl; and glucose level, 25 mg/dl (blood glucose level, 148 mg/dl).

Microbiological studies of CSF, including Gram staining, acid-fast staining, Indian ink assay, and cryptococcal antigen assay, all yielded negative results. Due to suspicion of acute bacterial meningitis, intravenous vancomycin (1 g every 12 h) and ceftriaxone (2 g every 12 h) were administered; however, fever persisted, and consciousness deteriorated. Repeated lumbar puncture on the seventh hospital day yielded a pus-like fluid aspirate. CSF study still disclosed pleocytosis, with a WBC count of 15,900 cells/ml (neutrophils, 92%; lymphocytes, 3%), a protein level of 131 mg/dl, and a glucose level of 7 mg/dl. Bacterial culture of the CSF was negative. The antibi-

otic regimen was switched to meropenem (2 g every 8 h); however, the patient's condition worsened, and respiratory and renal failure developed. The patient died 1 month later.

Microbiology. Two CSF specimens both grew oxidase-negative and Gram-negative bacilli. The organisms were initially identified as a rare *Citrobacter* species, *Citrobacter farmeri*, by the Phoenix automated system PMIC/ID-30 (Becton Dickinson Diagnostic Systems, Sparks, MD) (confidence value, 99%) and the Vitek 2 system (bioMérieux Inc., La Balme les Grottes, France) (probability of identity, 95%). These organisms were further confirmed to the species level by 16S rRNA gene sequence analysis using two primers, 8FPL (5'-AGAGTTTGAT CCTGGCTCAG-3') and 1492RPL (5'-GGTTACCTTGTTA CGACTT-3'). The sequences obtained (1,399 bp) were compared with published sequences in the GenBank database using the BLASTN algorithm (<http://www.ncbi.nlm.nih.gov/blast>). The closest match observed was obtained with *C. farmeri* (accession number AF025371.1; maximal identity, 99% [1390/1399]). The isolates were susceptible to cefotaxime (MIC, ≤1 μg/ml), ceftriaxone (≤1 μg/ml), cefepime (≤2 μg/ml), ciprofloxacin (≤0.5 μg/ml), imipenem (≤1 μg/ml), and meropenem (≤1 μg/ml) by the Phoenix automated system PMIC/ID-30 (Becton Dickinson Diagnostic Systems). The organism was negative for extended-spectrum β-lactamase (ESBL) production, as determined by comparing the MIC of cefepime alone with the MIC of cefepime plus clavulanic acid (10 μg) by using the agar dilution method (no decrease in the cefepime MIC [1 μg/ml] when tested in combination with clavulanic acid versus in the absence of clavulanic acid) (7). The organism was also negative for *Klebsiella pneumoniae* carbapenemase (KPC) production, detected by the modified Hodge test as recommended by the Clinical and Laboratory Standards Institute (3).

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Citrobacter species are opportunistic pathogens in humans and can cause urinary tract infection, superficial wound in-

fections, respiratory tract infection, bacteremia, endocarditis, and intra-abdominal infection (1, 4, 5, 8, 11). Central nervous system infection due to *Citrobacter* is an uncommon condition which is more frequent in neonates and young children. In adults, *Citrobacter* meningitis is extremely unusual and has been reported to be caused by *Citrobacter koseri* and *Citrobacter freundii* (9, 10). *C. farmeri* was first recognized by Farmer et al., who defined this new biogroup of *Citrobacter amalonaticus* (biogroup 1) based upon the ability of these strains to ferment sucrose, raffinose, α -methyl-D-glucoside, and melibiose (6). However, little is known about the clinical importance of *C. farmeri* (2). Although *C. farmeri* was reported as the cause of bacteremia in a child with short-bowel syndrome requiring total parenteral nutrition, the condition resolved without further sequelae after antibiotic treatment (2).

This is the first report of *C. farmeri* as a human pathogen causing fatal meningitis. *C. farmeri* was isolated in pure culture twice from the CSF specimen of this immunocompromised patient with symptoms or signs of meningitis, and the identification of *C. farmeri* was confirmed by molecular methods in addition to conventional biochemical study. Thus, *C. farmeri* should be considered as a possible cause of meningitis.

The portal of entry of *C. farmeri* could not be determined in this patient. Although most *Citrobacter* meningitis was assumed to occur via hematogenous spread, facial trauma and neurosurgery procedures were also routes for this organism to reach the leptomeninges (2, 9). This patient had negative blood cultures for *C. farmeri*, no recent history of head trauma or surgery, and no symptoms and signs associated with gastrointestinal diseases (2). This clinical scenario might suggest that the organism colonized the preexisting nasopharyngeal lesion and subsequently gained access to the leptomeninges, resulting in meningitis.

Because of the very limited clinical experience with *C. farmeri* infection, the optimal antimicrobial treatment is not known. Our patient's clinical condition deteriorated despite appropri-

ate antibiotic treatment with *in vitro* active agents (ceftriaxone and meropenem) against the ESBL-negative and KPC-negative *C. farmeri* isolate. This outcome is consistent with previous findings that the outcome of *Citrobacter* meningitis is usually poor with a mortality rate of almost 50% (9). Further *in vitro* and *in vivo* studies are needed to define the appropriate management for *Citrobacter* meningitis.

In conclusion, *C. farmeri* should be considered as a possible cause of fatal meningitis in cancer patients.

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