Resistant *Raoultella Ornithinolytica* Bacteremia in a Patient with New Acute Myeloid Leukemia

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INTRODUCTION

Members of the *Raoultella* genus were formerly considered to be *Klebsiella* species until they were differentiated based on phylogenetic Deoxyribonucleic acid (DNA) analysis.[1] Since then, *Raoultella ornithinolytica* has been sparsely implicated in clinically-apparent disease, though more case reports are appearing as of late. Here we report the first documented instance of *R. ornithinolytica* bacteremia in a patient with new acute myeloid leukemia (AML).

CASE PRESENTATION

A 71-year-old man was transferred to our hospital for treatment of newly discovered AML. Prior to transfer, he experienced an aching abdominal pain attributed to pancreatitis and daily episodes of watery diarrhea for five days.

On admission, he had an oral temperature of 102.7°F, pulse of 96 beats per minute, blood pressure of 145/70 mmHg, and oxygen saturation of 97% on room air. Physical exam revealed gray-brown granular material along the gum line of the third tooth that was tender to palpation, tender lymphadenopathy in the right submandibular space and right anterior cervical chain, a grade 2/6 systolic murmur, and no peripheral edema. Abdominal exam revealed tenderness and guarding over the left upper quadrant and epigastrium. The remainder of the physical exam was unremarkable.

Lab work revealed a white blood cell (WBC) count of 25.0 x 10^9/L with 52% blasts, hemoglobin of 7.4 g/dL, and platelets of 36,000 x 10^9/L. Lipase, liver enzymes, and creatinine were within normal limits. There was no acid-base derangement. Nucleic acid amplification testing for *Clostridium difficile* toxin was negative.

Since initial imaging was not available, a computed tomography (CT) scan of the abdomen without contrast was performed showing duodenitis—but not pancreatitis. Further diagnostic workup was deferred to expedite the initiation of chemotherapy for the patient's concomitant AML. Ten days of empiric therapy for *Helicobacter pylori* was completed with clarithromycin 500 mg PO every 12 hours, amoxicillin 1 g PO every 12 hours, and pantoprazole 40 g PO daily.

Hydroxyurea was administered due to a steadily increasing WBC count which peaked at 36.4 x 10^9/L. The patient remained febrile during this time and was considered functionally neutropenic due to his malignancy, therefore was treated for neutropenic fever with piperacillin-tazobactam 3.375 g IV every 6 hours.

On day 6 of his hospitalization, induction chemotherapy was begun with a "7+3" regimen of idarubicin and cytarabine. From approximately day 8 to day 35 of his hospitalization, he remained neutropenic with an absolute neutrophil counts (ANC) in the 0.2-0.3 x 10^9/L range and his piperacillin-tazobactam was continued. His abdominal pain and diarrhea persisted over this time.

On day 14, the patient's fever curves shifted from 100-101 °F to 101-103°F. On day 16, a CT scan of the abdomen with contrast was again performed, showing evidence of ongoing duodenitis without additional pathology. Blood cultures were redrawn on days 15, 16, and 17 and were all negative.

On day 19, FilmArray Blood Culture Identification Panel by BioFireDx identified the family *Enterobacteriaceae* from cultures taken that same day and while the patient was still on piperacillin-tazobactam. The test was negative for *Enterobacteriaceae cloacae* complex, *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus,* and *Serratia marcescens*; this is the extent of the genera of *Enterobacteriaceae* included in this particular test.

Overnight on day 20, the patient vomited and aspirated in his sleep, developing acute hypoxia to SpO2 of 74% on room air, respiratory rate of 34 breaths per minute, and pulse of 133 beats per minute. A portable chest x-ray showed a possible consolidation in the right lower lobe. Due to the patient's extended hospital stay and immuno-compromised status, vancomycin was added and piperacillin-tazobactam was changed to meropenem.

On day 21, a lactose-fermenting gram-negative rod was identified from the blood culture obtained two days prior. Our lab reported that this most closely resembled *Raoultella ornithinolytica*. Antibiotic susceptibility patterns were remarkable for resistance to piperacillin-tazobactam with MIC >64/4 mcg/mL. The organism was susceptible to amikacin and meropenem (Table 1).

A single 15 mg/kg dose of amikacin was administered. Surveillance blood cultures from days 21-26 were negative for further gram-negative infection. On day 24, a CT scan of the abdomen with contrast was repeated showing

obstruction despite ongoing diarrhea, thickened and inflamed segments of jejunum, and persisting duodenitis. On day 25, the patient was started on bowel rest, and total parenteral nutrition (TPN) was initiated.

Anidulafungin was administered from days 18-29 for concern of indolent fungal infection. The patient became delirious for the remainder of his hospital course. He received treatment with granulocyte colony stimulating factor to help bolster his leukocyte counts. The patient did not defervesce until day 35, at which point his mental status also improved. On day 37, his ANC surpassed 0.5 x 10^9/L. On day 38, meropenem was stopped; TPN was also discontinued as the patient began tolerating an oral diet. He had no further positive blood cultures. On day 40, a repeat chest x-ray demonstrated improvement of his right lower lobe and he was deemed medically stable for discharge to a rehabilitation facility.

DISCUSSION

A case series and literature review of *R. ornithinolytica* infections from four university hospitals in France found bacteremia to occur only in 5% of cases.[2] In the setting of malignancies, there is a 16-patient case series in which 15 had recent underlying malignancies both solid and hematologic,[3] a three-patient case series of bacteremia with underlying gastric and biliary malignancies,[4] and a report of a patient with acute lymphocytic leukemia (ALL) who died of *R. ornithinolytica* sepsis.[5] The literature thus indicates that *R. ornithinolytica* bacteremia tends to occur in patients with active comorbidities, especially malignancies, as in our patient.

Among more resistant *R. ornithinolytica* isolates, a blood culture isolate in New Jersey was susceptible only to amikacin and gentamicin,[6] a blood culture isolate in Brazil was susceptible only to amikacin, gentamicin, ciprofloxacin, and levofloxacin,[5] and other carbapenemase-producing strains were found in China[7] and Turkey.[8] *R. ornithinolytica* has natural susceptibility to cephalosporins, carbapenems, aminoglycosides; intermediate susceptibility to some penicillins, not usually including piperacillin/tazobactam; and resistance to macrolides.[9]

R. ornithinolytica is susceptible to piperacillin-tazobactam a majority of the time.[2-4, 7, 10-11] This case highlights the importance of antibiotic stewardship to prevent the inducible resistance that likely contributed to the failure of piperacillin-tazobactam in this case. Febrile neutropenia presents an especially difficult challenge as these patient scenarios often necessitate very long courses of very broad antibiotics in the absence of identified organisms. Procalcitonin may be of potential value in guiding antibiotic administration in patients with febrile neutropenia. Some data indicate that procalcitonin may be useful in distinguishing infectious from non-infectious etiologies of neutropenic fever, as well as trending values to monitor for response to therapy.[12-14]

This case also emphasizes the importance of rapid diagnostics. The assay used in this case used multiplex polymerase chain reaction (PCR) technology to identify an organism belonging to the family *Enterobacteriaceae* that was specifically not a member of the *Klebsiella* genus or other genera within *Enterobacteriaceae*. This particular pattern should evoke concern for *Raoultella*, a former member of the *Klebsiella* genus which should be considered as virulent and resistance-prone as *Pseudomonas*. By quickly identifying a new organism, which persisted through piperacillin-tazobactam therapy, the assay prompted the switch to meropenem and prevented the patient from succumbing to his bacteremia.

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