Rare Gram-Negative Sepsis in a Non-Ventilated Neutropenic Patient with AML

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Case Report

A 57-year-old man with history of hypertension, hyperlipidemia, and gout presented for evaluation of both a perioral infection and an infection in his right great toe from an injury on the beach at his shore house. The toe trauma was complicated by a massive hematoma and phlebitis, which required antibiotics. His primary care physician ordered basic laboratory studies that showed an anemia and thrombocytopenia. He was sent to a Hematology and Oncology specialist and subsequently directly admitted to Thomas Jefferson University Hospital for blood transfusion and further work-up. Upon further questioning, the patient admitted to chills starting 2 weeks prior to admission, elevated temperatures, rigors, dizziness, weakness, shortness of breath and a weight loss of about 16 pounds over 1 month. He denied prolonged bleeding or easy bruising, but did admit to recurrent upper respiratory infections.

On admission, the patient's white blood cell count was 8.9 x103 / μL, hemoglobin was 4.1 g/dL, and platelets were 5,000 /μL. There was a lymphocytic predominance on the manual differential. On physical exam, the patient was in no acute distress. He was awake, alert and oriented to person, place, and time. Vitals signs at that time showed the patient to be afebrile at 99.5 F and tachycardic at 112 beats per minute, with a respiratory rate of 16 breaths per minute, a blood pressure of 155/90 mm Hg, and an oxygen saturation 100% on room air. The patient's heart and lung exams were both unremarkable. The only significant finding on exam was edema and tenderness over the entire right great toe.

Following admission, the patient underwent a bone marrow biopsy that revealed acute myeloid leukemia (AML) with markedly decreased background maturing trilineage hematopoiesis. Upon discussion with the patient, his family, and the medical team, it was determined that the patient would be initiated on induction chemotherapy with 7 days of cytarabine and 3 days of daunorubicin (7+3). Initiation of the induction therapy however, was delayed due to the infection in his right 1st toe. Radiography and magnetic resonance imaging of the right 1st toe revealed extensive osteomyelitis involving the right first proximal and distal phalanges; cultures of the toe fluid eventually grew *Pseudemonas aeruginosa. Vascular surgery was promptly consulted and the patient underwent amputation of the right 1st toe. Chemotherapy was initiated a week after amputation to allow for a period of treatment of the Pseudomonas and wound healing prior to inducing further immunosuppression.*

Before and during chemotherapy, the patient had intermittent fevers with a peak at 102 F. Blood and urine cultures were obtained with the fevers, but the cultures were sterile. It was deemed likely that the fevers were due to tumor burden, but cultures were continually sent with each elevated temperature as a precaution. The patient tolerated his 7+3 chemotherapy and required several packed red blood cell and platelet transfusions during his stay. He had been doing quite well after chemotherapy and was almost 1 month post-treatment when he developed severe rigors and had temperatures up to 103 F during a platelet transfusion. Blood cultures were again sent, though all blood cultures prior to that day had been negative. It was initially thought that antibodies to foreign material in the platelet transfusion that the patient was receiving caused the rigors.

During his second episode of rigors, the patient had episodes of desaturations to as low as 80% while on 6 L nasal cannula. His saturations improved with bronchodilators and increased oxygen therapy via a non-rebreather facemask. A computed tomographic scan of the chest revealed pulmonary infiltrates in bilateral lower lung segments with developing pleural effusions and mild pulmonary edema. The patient continued to have rigors and elevated temperatures despite initiation of broad-spectrum antibiotics and desaturated to an oxygen saturation percentage in the high 80s and low 90s. He was quickly transferred to the medical respiratory intensive care unit for further care and management. On the next day, blood cultures grew *Acinetobacter baumannii that was pan-resistant to the patient's current broad-spectrum antibiotic regimen of aztreonam, ciprofloxacin, tobramycin, and vancomycin. He was intubated for respiratory distress and started on vasopressors. His clinical picture continued to deteriorate, and on the morning of hospital day 30 he expired.*

Discussion

Acute Myeloid Leukemia and Neutropenic Fever

AML is a hematologic cancer characterized by an elevated number of myeloid cells in the bone marrow. This disease often causes arrested maturation of hematopoietic cells, leading to anemia, thrombocytopenia, leukopenia with neutropenia specifically, and sometimes a leukocytosis with poorly functioning or diminished granulocytes.[1] Patients initially present with symptoms of fatigue due to anemia, bleeding from thrombocytopenia, and infection or fever due to inadequately functioning white blood cells.[1,2] Patients may also present with pallor, shortness of breath, or as in this patient's presentation, with non-healing wounds. Additionally, leukemic cell abnormalities may affect a variety of other tissues and organs, causing various other organ-specific symptoms.[1,2]

Diagnosis of AML is routinely done via bone marrow biopsy and examination of the aspirate under microscopy. Detection of at least 30% myeloblasts with round or irregular nuclei, little cytoplasm and the presence of cytoplasmic Auer rods

(azurophilic granules within lysosomes) confirms the diagnosis of AML.[1,2]

The primary objective in treating AML is inducing remission and preventing recurrence of disease. Remission in AML is defined by finding less than 5% of myeloblast cells in the bone marrow aspirate and by having the recovery of hemoglobin, platelet, and white blood cells levels to normal ranges in peripheral blood. The standard of treatment for AML is daunorubicin and cytarabine. Daunorubicin is typically given for 3 days, while cytarabine is given for 7 days, thus giving the commonly used name of "7+3 induction therapy."[1,2] Remission rates for patients under the age of 60 on this combination therapy is as high as 80%, but as with all chemotherapy agents, neutropenia is a common and severe side effect which may lead to morbidity and mortality from infections.[1,2]

The effects of prolonged neutropenia have been well described for nearly 40 years. The risk of infection substantially increases when the absolute neutrophil count (ANC) is less than 500 cells/mm3. Many acquired infections in the neutropenic host are related to skin and mucosal breakdown that commonly manifests as mucositis or typhlitis. Translocation from the gastrointestinal tract with gram-negative and anaerobic pathogens is a common cause of febrile illness in neutropenic patients. It is has been hypothesized that mucositis that often accompanies chemotherapy can provide an entry to the blood stream for enteric pathogens. Other predisposing factors for developing infections include rapidly declining ANC, increasing duration of neutropenia, unresponsiveness of cancer to chemotherapy, and use of peripheral or central venous catheters.[3]

Gram-negative bacilli, particularly *Pseudomonas aeruginosa, are the pathogens of particular concern. Monotherapy with beta-lactams, carbapenems, and 3*rd generation cephalosporins are common initial therapies for patients with febrile neutropenia.3,4 Typically, gram-positive antimicrobial therapy is not empirically started at initial presentation, unless the patient has obvious mucosal barrier breakdown. Vancomycin and linezolid are common gram-positive antimicrobials prescribed in this setting. It is recommended however, that cessation of gram-positive coverage should occur if cultures remain negative for 72 hours.4 Fungal pathogens are also of concern, particularly after one to two weeks of neutropenia. *Candida albicans is often implicated in central venous catheter infections, and Aspergillus species commonly cause invasive pneumonias, sinusitis, and skin ulcers. As a result, antifungals are typically added after the patient has had four or more days of neutropenia and fevers.*[5]

Our patient had several risk factors for developing life-threatening infection. He was functionally neutropenic on the day of admission, and remained profoundly neutropenic for his entire hospitalization, as his neutrophil percentage remained below 10% of the leukocyte differential. Additionally, he also had a peripherally inserted central catheter in his right upper extremity, although this never appeared indurated or erythematous. Our patient was also on all the appropriate antimicrobial therapies given the duration and severity of his neutropenia. On the day the patient developed rigors and positive blood cultures, he received aztreonam, caspofungin, ciprofloxacin, acyclovir, metronidazole, tobramycin, vancomycin, and voriconazole. Despite these broad-spectrum, potent combinations of antimicrobials, he still had fevers and eventually the positive blood cultures speciated out a strain of *Acinetobacter baumanii that was highly resistant to all of the patient's current antibiotics.*

Acintobacter Baumannii:

Acinetobacter species are aerobic, gram-negative bacilli commonly found in aquatic environments and in soil, and have become an increasingly important pathogen in nosocomial infections. Unfortunately, strains of acinetobacter are becoming increasingly resistant to common antimicrobials leading to a higher incidence in mortality. A 2005 study from Korea aimed to identify mortality risk factors in patients with Acinetobacter baumannii bacteremia. Their results identified an association with neutropenia as well as with an elevated Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The authors point to a mortality rate between 17-52%.[6] Additional studies have shown resistance patterns in Acinetobacter baumannii infections. In a 3-month study by Landman, et al. from Brooklyn, NY, it was found that 53% of the 419 strains isolated in 15 hospitals were resistant to meropenem and/or imipenem and of these, 12% were resistant to all standard antibiotics.[7]

Given the multi-drug resistant patterns of *Acinetobacter baumannii, it has been proposed that colistin may be one of the few antibiotics capable of combating these infections. Colistin, a polymyxin antibacterial, was first available for use in 1959. It is a bactericidal medication that binds to lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria. This causes a disruption in the membrane leading to bacterial lysis and spillage of intracellular contents.*[8] Colistin fell out of favor in the 1980's largely due to concerns of nephrotoxicity, neurotoxicity, and neuromuscular blockade. It has had a comeback of sorts recently due to demonstrated in-vitro bactericidal activity against gram-negative bacilli and relatively low resistance patterns. A small study from Brazil showed treatment with colistin resulted in a "good outcome," defined by negative blood cultures, cessation of fever, and prevention of mortality for 35 out of 59 cases of Acinetobacter infections. This study does, however, report that 22 of the 59 patients died, although of unreported causes. One could argue that a "good outcome" is not an objective measurement and that no parameters were discussed regarding said outcome. Additionally, further quantification of so-called "good outcomes" should be clarified, especially when 22 of the patients in this small study died. Additionally, the authors describe an increase in the baseline serum creatinine in 32% of patients in the study due to colistin.[8]

Conclusion

The complications of AML and neutropenia are a daily challenge to physicians caring for patients with this disease. The diseases itself, as well as all treatments for the disease predispose these patients to unique pathogens that can cause catastrophic harm or death. In an era of multi-drug resistant pathogens, clinicians must remain hyper vigilant for newly emerging resistance patterns and know how to combat these lethal microbes with appropriate antibiotics. If drug resistant bacteria are considered, swift action must be undertaken with aggressive antibiotics and potential infectious disease specialist consultation. Acinetobacter infections, although less common, have proven to be notoriously difficult to treat and potentially deadly.

Our patient in the intensive care unit did undergo a change in antibiotic coverage from aztreonam to meropenem, but he did not receive colistin. It is unlikely that using colistin would have helped given his clinical picture of profound gram-negative septic shock. Had our patient received colistin in the first hours of his rigors his outcome may have been different. Although it is impossible to predict, the astute clinician must always be aware of the multitude of resistant organisms and the arsenal of potential life-saving treatments against them. The challenge remains to develop new antimicrobials to keep up with the ever-changing patterns of bacterial disease.

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