Case

A 38-year-old female with history of longstanding non-ischemic cardiomyopathy underwent orthotopic heart transplantation (OHT). Her past medical history was significant for factor V leiden and methylenetetrahydrofolate reductase (MTHFR) heterozygous deficiencies with chronic pulmonary embolism, sickle cell trait, atrial flutter, type 2 diabetes mellitus, and hypertension. The patient had a long and complicated course post-transplantation. Immediately after OHT, she was noted to have donor-specific human leukocyte antigen (HLA) antibodies treated with 5 cycles of plasmapheresis. On further biopsies it was noted that she had acute cellular rejection requiring pulse-dose parenteral steroids on multiple occasions. Her immunosuppression therapy consisted of tacrolimus, mycophenolate and prednisone. Six months post-transplant she was noted to have a spontaneous 4cm right calf muscle hematoma based on lower extremity ultrasound that was felt to be due to her underlying hematologic disease. At 7 months post-transplant the patient was hospitalized twice. The first admission was for multifocal necrotizing pneumonia. Although sputum cultures were non-diagnostic, the patient improved with 2 weeks of antibiotic treatment. The second admission occurred after a routine right heart catheterization that showed hemodynamic parameters concerning for rejection. At that time, the patient received empiric parenteral pulse steroids while waiting for final pathology results; these were negative for rejection and the patient’s immunosuppressants were continued at previous doses.

The newest hospitalization was 8 months post-transplant, when she was admitted with a chief complaint of worsened right-sided calf pain for a month. On physical exam the patient was noticed to have an area of warmth, induration and palpable tenderness. Patient denied any other symptoms, and specifically denied fevers, chills, respiratory symptoms or trauma. Imaging studies on admission included a lower extremity ultrasound that showed the hematoma had increased in size to 9 cm from previous study 2 months prior. Lab studies to assess any acute hematologic cause of recurrent spontaneous hematoma were negative. The differential diagnosis on admission included a leg abscess; however the absence of fever, leukocytosis and loculations made it seem unlikely. A calf MRI performed 4 days later showed the collection had increased to 13 cm. It was complex but still compatible with hematoma, although superimposed infection could not be ruled out. At this point it was decided for the patient to undergo an ultrasound guided fluid aspiration for diagnostic and therapeutic purpose, given the patient’s continuing pain and rate of growth. Fluid aspiration yielded 50 cc of pus. Broad spectrum antibiotics were started, and that evening the patient went to the operating room for an incision and drainage. The following day the wound culture grew a modified acid fast gram positive bacilli (by modified Kinyoun method) that immediately raised the concern for infection with nocardia species, especially given patient’s immunosuppression and recent treatment with pulse-dose parenteral steroids. Patient’s antibiotics were narrowed to intravenous ceftriaxone and patient was discharged home on this regimen, to convert to oral trimethoprim-sulfamethoxazole (TMP-SMX) 4 weeks later for at least a 6

Figure 1. Gram stain from our patient showing gram positive bacilli bacilli.

Figure 2. Modified Acid Fast (Kinyoun) Stain showing acid fast bacilli.
Discussion

Nocardia bacteria are weakly acid-fast (by modified Kinyoun, Ziehl-Neelsen, and Fite-Faraco methods) gram positive bacilli that grow slowly in aerobic culture. Nocardia species are saprophytes that are found worldwide in soil. There are various nocardia species that cause human disease, most commonly *N. brasiliensis*, *N. otsidiscaviarum*, *N. farcinica*, *N. nova*, *N. transvalensis*, and *N. pseudobrasiliensis*. 

Our patient’s pathogen, *N. cyriacigeorgica*, is the most common cause of nocardiosis in the southern United States. 

Nocardia infections are rare among the general population of the United States, with an approximate incidence of 0.35-4 cases per 100000 people. Infections are concentrated to people with depressed cellular-mediated immunity, including patients with HIV, solid organ transplants, bone marrow transplants, cancer, and rheumatologic disease on immunosuppressive medications. In these patients, nocardia infections can have significant mortality, described as 11-67% (in case series with sample sizes of greater than or equal to 10). 

Nocardia infections most commonly affect the lungs, central nervous system (CNS) system and skin. Nocardia pneumonia has a tendency for nodularity, cavitation and empyema. One half of patients present with extrapulmonary disease. CNS disease is most commonly an abscess. Therefore, patients with Nocardia skin infections may have primary cutaneous infection, or may have disseminated infection. Among immunocompetent persons, there are case reports of primary cutaneous infection. 

Primary nocardia skin and soft tissue infections are divided into three main categories: mycetomas, lymphocutaneous nocardiosis and primary cutaneous nocardiosis. Some form of traumatic skin opening classically precedes all three types, although iatrogenic cases have been reported. In tropical countries where mycetomas (Madura foot) are highly prevalent, nocardia is an alternative cause (after the more common fungal pathogens), resulting in non-painful chronic suppurrative infection with draining sinuses and discharging granules. 

Primary cutaneous nocardiosis may include soft-tissue abscess, cellulitis, bulla or ulcer, but is classically acute and painful. Lymphocutaneous nocardiosis consists of an acute primary cellulitis with lymphangitic spread and causes lymphadenitis. 

Medical treatment of cutaneous nocardia infections is largely empiric and based on experience with treatment of invasive disease. Historically, oral TMP-SMX has been used for treatment of nocardiosis, with minocycline as an alternative. Given the high mortality of serious or invasive infections, an empiric regimen of TMP-SMX, amikacin, and ceftriaxone or imipenem is recommended. Of note, more recent data suggests growing TMP-SMX resistance. 

Treatment in our patient was difficult given her chronic kidney disease and nephrotoxic immunosuppressive medication; therefore we empirically treated her with ceftriaxone and TMP-SMX alone. 

Particularly in the heart transplant population, primary cutaneous nocardiosis remains a rare disease, with our online literature search yielding only three reported cases. All the three cases had an identifiable cause: cardiac catheterization, intramuscular injections, and an insect bite. Our patient had no such identifiable cause, either iatrogenic or traumatic. 

In conclusion, nocardiosis is a rare but deadly disease that mainly affects immunocompromised patients. Cutaneous nocardiosis results from traumatic invasion and has three different manifestations, with the primary cutaneous and lymphocutaneous versions common in the developed world. Treatment with TMP-SMX is often overlapped with intravenous antibiotics for serious infections.

References


