Recurrent *Nocardia* Sepsis in a Patient With Sickle Cell Anemia Receiving Continuous Deferoxamine

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Received March 25, 2013; accepted April 25, 2013; electronically published July 23, 2013.

*Nocardia* species are ubiquitous soil-borne organisms that most commonly cause invasive disease in patients with defective cell-mediated immunity. We report a case of recurrent *Nocardia* sepsis in a patient with sickle cell disease and chronic iron overload, who was undergoing high-dose infusions of deferoxamine through a central venous catheter.

**Key words.** hemoglobinopathies; iron chelation; *Nocardia*; sickle cell disease.

*Nocardia* sp are ubiquitous saprophytic organisms that cause localized or disseminated infections in both animals and humans. Humans are infected through traumatic inoculation of the organism, leading to a superficial wound infection; or through inhalation, leading to pulmonary disease or dissemination to the central nervous system, retina, kidneys, joints, bone, skin and subcutaneous tissue, or heart [1]. *Nocardia* bacteremia, although reported in patients with central venous catheters, is an uncommon manifestation of this disease [2, 3].

In more than 60% of nocardiosis cases, there is an underlying disease process such as chronic pulmonary disease, diabetes, organ transplantation, or acquired immunodeficiency syndrome that causes an impaired cell-mediated immune response or immune dysregulation [4].

Although patients with sickle cell disease are usually functionally asplenic and have associated deficits in humoral immunity and opsonization, they have normal cell-mediated immunity, and as a group they have not been shown to carry a higher risk for nocardiosis. As a result of frequent blood transfusions, many patients with sickle cell disease require chelation therapy for iron overload. We report a case of recurrent *Nocardia* sepsis in a patient with chronic transfusional iron overload receiving high-dose intravenous deferoxamine infusions. Given the use of siderophores by *Nocardia* species for iron scavenging, we hypothesize that deferoxamine, a siderophore made by a related bacteria, *Streptomyces*, provided sufficient nutritional iron for rapid bacterial growth leading to *Nocardia* sepsis [5].

**CASE REPORT**

An 18-year-old female with a history of Hemoglobin SS disease and cerebral infarction, receiving high-dose intravenous deferoxamine infusions every 4 weeks via an implanted central venous catheter, presented to a local emergency room with acute onset of fever, cough, and pleuritic chest pain 3 weeks after her last scheduled transfusion/infusion. Blood cultures were drawn and she was started on empiric ceftriaxone and vancomycin. The blood cultures drawn both from her peripheral blood and central venous catheter became positive in less than 24 hours with beaded gram-positive branching rods that were modified acid-fast, consistent with *Nocardia* sp, prompting the addition of sulfamethoxazole/trimethoprim. Computerized tomography (CT) scans of the chest and abdomen showed multiple pulmonary nodules (Figure 1) and several renal lesions, respectively. The organism was speciated as *Nocardia nova* prompting the addition of amikacin. Her central line was not removed; however, within a few days, she had clinically improved and was discharged home to complete a total of 3 weeks of intravenous amikacin and a planned 6-month course of oral sulfamethoxazole/trimethoprim. Her presumed exposure to
Nocardia occurred while gardening and spreading mulch around her house.

Two months later, while still taking sulfamethoxazole/trimethoprim, she developed fever and altered sensorium during a home infusion of continuous intravenous deferoxamine. This progressed to septic shock and acute respiratory distress syndrome requiring vasopressor support and mechanical ventilation. A CT scan of the head was performed and showed no abnormalities. Blood cultures again grew N. nova with the same susceptibilities as that previously isolated. Her central line was removed, she was treated with intravenous sulfamethoxazole/trimethoprim and ceftriaxone, and over the next 2 weeks she made a marked recovery. She was discharged on intravenous ceftriaxone and amikacin as well as oral sulfamethoxazole/trimethoprim. She had no lasting sequelae from her infection. Chronic deferoxamine infusions were stopped as a result of these repeat infections.

DISCUSSION

In 1888, a French veterinarian named Edmond Nocard was the first to describe a usually fatal illness in cattle caused by the aerobic actinomycete, now called Nocardia [6]. Nocardia is a slow-growing, gram-positive, filamentous, branching, weakly acid-fast organism that is found worldwide in soil, water, and organic matter. When traumatically inoculated, the organism can cause a superficial wound infection in an immune competent host. More commonly reported is an opportunistic infection in patients with impaired cell-mediated immunity in which Nocardia organisms are inhaled or ingested and lead to pulmonary disease or dissemination [1].

Nocardia can be isolated from blood cultures, as seen in our patient, but may require prolonged incubation (>2 weeks) for growth. Although Nocardia will grow on nonselective media, it is more easily differentiated from other flora with the use of selective media such as Thayer-Martin agar with antibiotics, paraffin agar, or buffered charcoal-yeast extract medium [1]. Identification of the specific Nocardia species is important because they each have different antibiotic susceptibilities. N. nova, identified as the causative agent of infection in our patient, is part of the Nocardia asteroides complex, which is responsible for most respiratory and disseminated Nocardia infections [2]. Most N. nova isolates have near complete susceptibility to sulfonamides, which are a mainstay of antibiotic therapy, as well as to amikacin, imipenem, and 3rd-generation cephalosporins, which are commonly used in combination with sulfonamides to treat disseminated nocardiosis [1]. Nocardia has a tropism for cerebral tissue, and nearly one quarter of all noncutaneous nocardial disease involves the central nervous system [1]. This fact, along with the development of altered mental status, prompted the head CT scan performed in our patient.

There are 2 facets of this case that make it a very unique presentation of nocardiosis. First, bacteremia, as demonstrated by the patient’s positive blood cultures, is an unusual manifestation of Nocardia infection, reported in only 7% of patients with nocardiosis in 1 series [3]. Although central venous catheter removal is not absolutely indicated in cases of Nocardia bacteremia, and there are reports of successfully treating through these infections, we believe failure to remove the catheter contributed to a recurrent and severe nocardiosis in our patient [8, 9]. Second, as mentioned previously, sickle cell anemia is not a known predisposing condition to Nocardia infection. There is only 1 other report of a patient with sickle cell anemia who developed nocardiosis. However, this case involved a patient with end-stage renal disease on dialysis, which was likely the condition that most predisposed her to Nocardia infection [7].

Two similar cases involving children with thalassemia major, iron overload, and in-dwelling central venous catheters report the development of Nocardia catheter-related blood stream infections. One describes a 12-year-old boy with Nocardia otitidis caviarum bacteremia and the other describes an 18-year-old female who acquired N. asteroides bacteremia, both while undergoing regular iron chelation treatment with deferoxamine [8, 9]. Taken together, these cases raise the following question: could iron chelation treatment with deferoxamine be a risk factor for Nocardia infection?

Chronic transfusions to diminish Hemoglobin S levels are the standard of care for patients with sickle cell disease.
and cerebral infarcts. Managing iron overload in these patients is often a challenge. Deferoxamine, given as an intermittent subcutaneous infusion, is commonly used to treat iron overload in chronically transfused patients [10]. Continuous intravenous infusions of deferoxamine have also been used to treat patients with severe iron overload that has been refractory to other chelation therapies [11, 12].

Deferoxamine is a siderophore, a molecule that forms high-affinity complexes with iron. Siderophores are produced naturally by bacteria, fungi, and yeast to scavenge iron from the environment. *Nocardia* is 1 species of bacteria that will secrete siderophores in an effort to more efficiently obtain iron. Siderophores from *Nocardia* have been shown to have structural similarity to hydroxamate-type siderophores (desferoxamine B) produced by *Streptomyces*, a closely related organism [5].

Because both *Nocardia* and *Streptomyces* species produce these siderophores, providing a high concentration of deferoxamine iatrogenically will provide both of these species with an excellent source of iron for growth.

Mucormycosis has been well documented in iron overloaded patients and in dialysis patients treated with deferoxamine [13]. Furthermore, the pathophysiology of zygomycetes and the interaction with deferoxamine has been studied in some detail. Deferoxamine chelated with iron stimulates the growth of *Rhizopus*, and it abolishes the fungicidal effect of serum. Growth stimulation by deferoxamine-iron chelates was greater for *Rhizopus* than for *Aspergillus* or *Candida*, demonstrating a species-specific effect [13]. Deferoxamine-iron chelates are efficiently used as an iron source by *Rhizopus*, even in the presence of apotransferrin, a human serum protein that normally withstands iron from infecting microorganisms. The consequent promotion of the growth of *Rhizopus* helps explain the increased risk of mucormycosis in deferoxamine-treated patients [14].

Previous work on the biochemistry of siderophores has shown that certain bacteria (*Escherichia coli*, among others) have the ability to ingest siderophores produced by other organisms [15]. This ability allows these organisms to utilize foreign siderophores for their own growth. Although this process has not been specifically tested for *N nova*, we speculate that *N nova* utilized iron bound to iatrogenically provided deferoxamine for rapid growth leading to septicemia.

By providing a source of iron in a form readily available to *Nocardia* species, we hypothesize that deferoxamine contributed to the recurrent *Nocardia* septicemia experienced by our patient and could potentially put susceptible patients at increased risk for *Nocardia* infection. Future studies of patients with nocardiosis should evaluate iron chelation therapy as an independent risk factor for infection.

**Acknowledgments**

**Disclaimer.** The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Departments of the Army or Air Force nor the US Government.

**Potential conflict of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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