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Nocardia cyriacigeorgica Septicemia

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We report two cases of *Nocardia cyriacigeorgica* septicemia and disseminated infection in the setting of profound immunodeficiency. In both instances, diagnosis was rapidly facilitated by 16S rRNA gene sequencing of blood culture isolates. These constitute the first confirmed reports of *Nocardia cyriacigeorgica* bloodstream infection in humans.

CASE REPORTS

Case 1. The patient was a 69-year-old woman with type 2 diabetes mellitus, chronic lymphocytic leukemia, and hypogammaglobulinemia who presented to hospital "A" with a 3-week history of malaise, right-sided flank and pleuritic chest discomfort, left leg weakness, and an ataxic gait. She denied any fever, chills, cough, or weight loss. Baseline laboratory studies revealed neutrophilia, lymphocytosis, anemia, and hyponatremia. Radiologic studies demonstrated patchy and nodular infiltrates in the right lung, bilateral pleural effusions, multiple ring enhancing lesions in the cerebellum and cerebrum, and a right adrenal mass. Upon the patient's admission to hospital, three sets of BacT/Alert FAN (bioMerieux Inc., Durham, N.C.) aerobic and anaerobic blood cultures were collected, while the adrenal mass was biopsied to rule out infectious and noninfectious etiologies. After 2.5 days of incubation, the aerobic bottle of one of the blood culture sets demonstrated the presence of a partially acid fast, branching, rod-shaped bacterium that formed dry white colonies after overnight growth on 5% sheep blood and Sabouraud dextrose agar media. Respiratory samples were not collected for microbiological analysis. A diagnosis of disseminated nocardiosis was subsequently made, after which the patient received empirical therapy with intravenous meropenem (1 g every 8 h) and oral trimethoprim-sulfamethoxazole (TMP-SMX) (160 and 800 mg, respectively, twice daily). Using Microseq 500 kits and an ABI Prism 3100 genetic analyzer (Applied Biosystems, Foster City, CA), partial sequencing (first 500 bp) of the 16S rRNA gene of the blood culture was successful. A BLAST search (http://www.ncbi.nlm.nih.gov/BLAST/) of the GenBank database revealed 100% homology of our patient's sequence with that of five strains of *Nocardia cyriacigeorgica* (GenBank accession numbers AB094578, AB115955, AY244782, AY262326, and AB094580) and 98.1% and 97.9% homology with two other *N. cyriacigeorgica* strains (GenBank accession numbers AF430027 and AF282889, respectively). The adrenal biopsy culture was also positive for *N. cyriacigeorgica*. The isolate was susceptible to TMP-SMX (MICs, ≤2/38 μg/ml), imipenem (MIC, 2 μg/ml), and amikacin (MIC, ≤16 μg/ml) based on Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) broth microdilution susceptibility testing (13). The patient's clinical condition gradually improved over the course of her stay in the hospital, but she remained on intravenous meropenem and oral TMP-SMX for several weeks thereafter through the regional home intravenous therapy program. Follow-up radiologic investigations 2 months post-hospital discharge demonstrated complete resolution of the pulmonary abnormalities, persistent but significantly resolved cerebral and cerebellar lesions, and decreased size of the right adrenal mass. Sequelae included mild to moderate speech impairment and generalized weakness.

Case 2. The patient was a 47-year-old woman with follicular non-Hodgkin's lymphoma who eventually underwent an allogeneic stem cell transplant. She presented to hospital "B" (approximately 7 months prior to the presentation of the case 1 patient) 6 months posttransplantation, with a 2-week history of a productive cough and dyspnea. A chest X ray revealed a right lower lobe infiltrate, after which she was admitted with a diagnosis of community-acquired pneumonia. She was treated with intravenous levofloxacin but without clinical improvement; her dyspnea worsened, and she later developed hemoptysis. A computed tomography scan of the chest was performed, which demonstrated a cavity in the right lower lung lobe. Bacterial, fungal, and other etiologies were considered in the differential diagnosis of her pulmonary process, and her antibiotic therapy was later modified to include levofloxacin, piperacillin-tazobactam, and amphotericin B. Bronchoscopy was subsequently performed to rule out these considerations, although Gram staining and culture of bronchoalveolar lavage specimens did not reveal the presence of any microbial pathogen. Two sets of BacT/Alert FAN (bioMerieux Inc., Durham, N.C.) aerobic and anaerobic blood cultures were collected shortly upon admission to hospital. After 3.5 days of incubation, the aerobic bottle from one of the blood culture sets was positive for a partially acid fast, branching, gram-positive rod-shaped bacterium, which grew very well as a dry white colony on 5% sheep blood and Sabouraud dextrose agar media. A diagnosis of disseminated nocardiosis was subsequently made, after which the patient received empirical therapy with intravenous meropenem (1 g every 8 h for 1 week) followed by TMP-SMX (70 and 350 mg, respectively, given intravenously

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every 8 h for 2 weeks, followed by 160 and 800 mg given orally twice daily thereafter). Sequencing of the 16S rRNA gene of the blood culture isolate was successful, resulting in the identification of the organism as *Nocardia cyriacigeorgica*, with a sequence and an antimicrobial susceptibility profile identical to those of the case 1 isolate. Almost 2 months later (while on oral TMP-SMX), the patient developed *Klebsiella pneumoniae* bacteremia, for which intravenous ceftriaxone was started. She also suffered from graft-versus-host disease, which required tapering of her immunosuppressive (100 mg of cyclosporine twice daily and 50 mg of prednisone once daily) medications. However, she developed new pulmonary nodules and underwent a repeat bronchoscopy that revealed an *Aspergillus* sp. from bronchoalveolar lavage fluid cultures. The *Aspergillus* sp. was treated with amphotericin B, but the patient's clinical condition gradually deteriorated despite all efforts, and she died 5 months after admission. An autopsy revealed the presence of central nervous system and pulmonary aspergillosis without evidence of disseminated nocardiosis, although autopsy tissue specimens for microbiological culture were not submitted.

The genus *Nocardia* comprises a group of obligately aerobic, weakly gram positive, partially acid fast, branching, often beaded, filamentous bacteria that typically fragment into nonmotile rod- or coccoid-shaped elements (4). The name of the genus originated from the work of Edmond Nocard, who in 1888 reported the isolation of an aerobic actinomycete from cattle with bovine pleuropneumonia (16), although Eppinger reported the first case of human *Nocardia* infection 2 years later (16). At least 44 species of *Nocardia* are officially recognized to date, of which 24 are considered to be of medical importance, while an additional 4 newly proposed species (all of medical importance) are being considered for taxonomic inclusion in the genus (4, 7). Nocardiae are found ubiquitously in the environment worldwide, including various soil, freshwater, marine-water, and organic-matter habitats, where they are believed to maintain a saprophytic existence (3, 4, 12). *Nocardia* species may also be present in domestic environments such as house dust, garden soil, beach sand, and swimming pools (12). Occasionally, they may be found as transient colonizers of the skin and upper respiratory tract (12).

Human infections caused by this group of organisms typically involve the lungs or skin and occur via inhalation of contaminated airborne dust particles or cutaneously via traumatic implantation, respectively (3, 4, 12, 16). About 1,000 cases of infection are estimated to occur annually in the United States (11). Pulmonary nocardiosis, the most common form of human nocardial infection in developed countries, is an acute, subacute, or chronic necrotizing suppurative infection usually caused by members of the *Nocardia asteroides* complex (11, 12, 16). Cutaneous nocardiosis typically presents as a mycetoma or a sporotrichoid infection, is more common in the tropics and subtropics, including Central and South America and the deep southern United States, and is usually caused by *Nocardia brasiliensis* but may also be caused by other *Nocardia* species (4, 11, 12, 16). Hematogenous dissemination to the central nervous system, bone, joint, eyes, kidney, spleen, liver, thyroid, adrenal, heart, and/or prostate may occur (4, 10–12, 16), although central nervous system infection without apparent lung or skin involvement has commonly been reported (2, 16). While nocardial infections may occur in individuals with intact immune systems, disease (particularly disseminated infection) is more commonly seen in patients with marked immunodeficiency such as those with bone marrow or solid-organ transplants, lymphoreticular malignancy, or AIDS or in the setting of chronic corticosteroid therapy (3, 4, 6, 10–12, 16).

Nocardia cyriacigeorgica (formerly named *Nocardia cyriacigeorgici*) was first described by Yassin and colleagues in 2001 (1, 19). These researchers recovered, from the bronchial secretions of a patient with chronic bronchitis, a *Nocardia* sp. that did not belong to any previously described members of this genus based on 16S rRNA gene sequence data and biochemical characteristics (19). Other reports of the recovery of *N. cyriacigeorgica* from human clinical specimens have subsequently been documented (2, 8, 9, 14, 18). In several cases, *N. cyriacigeorgica* was identified in retrospect by 16S rRNA gene sequencing of previously biochemically identified presumptive *N. asteroides* clinical isolates from pulmonary and cutaneous sources (9, 14, 15), although *N. cyriacigeorgica* is easily distinguished from other *Nocardia* species by the results of a few phenotypic tests (15). Based on detailed 16S rRNA gene sequence analysis and limited phenotypic data, it appears that *N. cyriacigeorgica* is identical to *N. asteroides* drug susceptibility pattern type VI (14, 15, 17), which appears to account for approximately 60% of the clinical *N. asteroides* complex strains recovered from patients in the United States (14). Hence, it is likely that many clinical isolates previously generically classified as *N. asteroides* would have had the type VI drug susceptibility pattern and therefore would be considered identical to *N. cyriacigeorgica*.

The first confirmed case of invasive human infection caused by *N. cyriacigeorgica* was reported for an immunocompromised patient with central nervous system nocardiosis where the diagnosis was made by 16S rRNA gene sequencing of the bacterium from brain abscess material (8). While the likelihood exists that strains of *N. asteroides* with drug susceptibility pattern type VI have been recovered from human blood, no detailed reports to date have specifically described the recovery of *N. cyriacigeorgica* from this source based on DNA sequence-based identification. Even though disseminated nocardiosis is presumed to occur via hematogenous spread from pulmonary or cutaneous sites, *Nocardia* bacteremia is unusual (10). In a recent review of bacteremic *Nocardia* infections, *N. asteroides* was found to be the predominant pathogen, while bacteremic disease due to *Nocardia nova*, *Nocardia otitidiscaviarum*, and *Nocardia farcinica* was less commonly encountered (10). The mortality rate among patients with *Nocardia* bacteremia is about 50% (10). Occasionally, the recovery of *Nocardia* species from blood cultures may represent contamination, depending on the clinical setting (10). Since our case 2 patient had no evidence of disseminated nocardiosis upon autopsy, the possibility exists that this may not represent a true case of bacteremia.

Successful therapy of *Nocardia* infections requires the prolonged (usually for months) use of effective antimicrobial agents, often in association with appropriate surgical measures. In vitro susceptibility testing methods for the genus *Nocardia*

have only recently been standardized (13). However, most *Nocardia* species appear to be susceptible to TMP-SMX, carbapenems, and amikacin (4, 16). Limited information regarding the susceptibility profile of *N. cyriacigeorgica* clinical isolates is available (8, 15), although it appears that most isolates would be susceptible to the above agents based on their previous designation as *N. asteroides*. Both of our *N. cyriacigeorgica* strains demonstrated in vitro susceptibility to TMP-SMX, imipenem, and amikacin. Linezolid appears to be the most effective agent against *Nocardia* species based on in vitro data, although experience with this drug in the treatment of *Nocardia* infections is limited (4, 5).

In summary, *N. cyriacigeorgica* represents a distinct lineage within the genus *Nocardia* that is now believed to be identical to formerly uncategorized strains within this genus. Molecular methods such as 16S rRNA gene sequencing have demonstrated the propensity of *N. cyriacigeorgica* to cause bacteremic disease in humans, particularly in individuals with compromised immune systems.

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