Brain Abscess Caused by *Nocardia cyriacigeorgica* in a Patient with Human Immunodeficiency Virus Infection

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*Nocardia cyriacigeorgica* is a recently characterized species within the genus of *Nocardia*. We report a brain abscess, following a primary pulmonary colonization, due to this species in a human immunodeficiency virus-infected patient. This case confirms that isolation of *Nocardia* in sputum is associated with a high risk of disseminated infection in immunocompromised patients.

CASE REPORT

A sub-Saharan 33-year-old human immunodeficiency virus (HIV)-infected woman was admitted for a generalized seizure in April 2004. Six months prior to admission, HIV infection had been diagnosed when she presented with weight loss, fever, cough, dyspnea, and chest pain. The CD4 lymphocyte count was 20 cells/mm³. Diagnosis of cavitary pneumonia due to *Actinomyces* sp. was established by culture of a bronchoscopic sample. She received oral treatment with amoxicillin at 150 mg/kg of body weight per day and minocycline at 100 mg twice a day. She also received primary prophylaxis for pneumocystosis with co-trimoxazole (one double-strength tablet per day) and highly active antiretroviral therapy with didanosine, lamivudine, and lopinavir-ritonavir. The patient was compliant with this regimen, which was associated with a global improvement of her clinical status, and the pneumonia was cured. Five months later, a new sputum sample grew *Nocardia cyriacigeorgica*. At that time she was asymptomatic, with no evidence of active pneumonia. The immune condition of the patient had also improved with a CD4 lymphocyte count at 80 cells/mm³. No change in therapy was made, based on a presumption of respiratory tract colonization by *Nocardia*. The follow-up sputum cultures did not grow the pathogen. On the day of her admission, she suddenly presented a grand mal seizure. A brain computed tomography scan showed a single ring enhancing nodular hyperdensity, surrounded by an edema, in the right frontal lobe which was confirmed by magnetic resonance imaging. A biopsy was first considered hazardous to perform. The diagnosis of toxoplasmosis abscess was unlikely because of primary prophylaxis with co-trimoxazole with good compliance, negativity of toxoplasmosis serology, and negativity of toxoplasmosis cerebrospinal fluid PCR assay. Because of a presumptive diagnosis of *Actinomyces* brain abscess, amoxicillin and minocycline therapy was continued, but oral amoxicillin was switched to intravenous administration at a dose of 200 mg/kg per day. However, the patient presented a progressive right arm paresis and new episodes of generalized seizure despite anticonvulsant therapy. Two weeks later, the follow-up brain magnetic resonance imaging showed a progression of the right frontal abscess and three new abscesses in the left cerebral hemisphere. A stereotaxial brain biopsy of the frontal abscess was performed. Direct sample examination by microscopy showed many polymorphonuclear leukocytes without any bacteria, but the culture grew a branched gram-positive rod organism, which was further identified as *N. cyriacigeorgica*. Antimicrobial therapy was changed to imipenem, amikacin, and ciprofloxacin, and the patient made a clinical and neurological recovery. After 1 month, the antibiotic treatment was replaced by oral treatment with co-trimoxazole (two double-strength tablets three times daily) and amoxicillin (150 mg/kg per day), associated with an anticonvulsant drug and highly active antiretroviral therapy. Three months after onset of therapy, she was asymptomatic and the brain computed tomography scan showed a major improvement. She was discharged in stable condition without neurological deficit. Six months later, she showed no recurrence of the brain abscess and no recurrence of the neurological signs and symptoms.

Microbiology. Examination of the sputum by direct microscopy showed multiple gram-positive branched rods. A culture on chocolate agar, incubated at 37°C in an atmosphere enriched with 5% CO₂, yielded 10⁵ CFU/ml of white colonies with a typical earthy smell, among commensal flora, after 4 days of incubation. Growth was also obtained in a Mycobacteria Growth Indicator tube (Becton Dickinson, Sparks, Maryland) after 2 days of incubation. The organism was strictly aerobic. The catalase production and the nitrate reductase activity were noted. The morphology of the colonies and the typical Gram stain led to the presumptive identification of *Nocardia* species. The isolate was further identified by the API ID 32C yeast identification system (BioMérieux, Marcy l’Etoile, France) as recommended by Muir and Pritchard (12). A presumptive identification of *Nocardia asteroides* was obtained after 7 days of incubation (esculin hydrolysis, assimilation of gluconate and levulinate as carbon sources, and acid

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production from the oxidation of glycerol). Culture of the stereotaxial biopsy specimen on chocolate agar yielded colonies with the same morphological Gram stain characteristics. For both isolates, species identification was completed by sequencing a 5'-end 606-bp fragment of the 16S rRNA gene and gave Nocardia cyriacigeorgica. It was based on the search of the phylogenetically closest known species inferred from the database of the Observatoire Français des Nocardioses (Laboratoire de Mycologie Fondamentale et Appliquée aux Biotechnologies Industrielles, Université Claude Bernard, Lyon, France). This database included 16S rRNA gene sequences from reference strains of all validated nocardial species, and the database comparison used BIBI software (1) (http://pbil.univ-lyon1.fr). The two strains formed a phylogenetically individualized cluster with N. cyriacigeorgica DSM 44484T (data not shown) and showed 99.3% similarity with this strain.

Antibiotic susceptibility testing was performed by disk diffusion on Mueller-Hinton agar plates at the Laboratoire de Mycologie Fondamentale et Appliquée aux Biotechnologies Industrielles. To prepare the inoculum, a preculture was achieved by suspending colonies in Bennett liquid medium at 36°C and by shaking with glass beads for 2 days. The suspension was centrifuged for 10 min at 50 × g, and a 1:10 dilution of the supernatant was used to inoculate the plates. After 48 h of incubation at 37°C in an atmosphere enriched with 5% CO₂, the plates were read and the results were interpreted according to the guidelines of the Antibiogram Committee of the French Society for Microbiology (www.sfm.asso.fr). The two isolates were susceptible to cefotaxime, imipenem, minocycline, amikacin, ciprofloxacin, and linezolid. They were resistant to kacin, ciprofloxacin, and linezolid. They were resistant to amoxicillin-clavulanic acid. Surprisingly, the pulmonary isolate was resistant to co-trimoxazole while the brain biopsy isolate was resistant to co-trimoxazole at a high dosage, considering the presence of nocardiosis, diagnosed between 1995 and 2000, reported an association of approximately 5.7% with HIV infection (8). This apparently low prevalence of HIV-associated nocardiosis could be related to a protective effect of co-trimoxazole given for primary prophylaxis of pneumocystosis and toxoplasmosis and to an underestimated frequency due to the difficulties of clinical and biological diagnosis. In the present study, prophylaxis of toxoplasmosis with co-trimoxazole did not prevent the spread of Nocardia from the site of entry. Nocardia species are not usual saprophytes of humans. Their presence should suggest a careful evaluation of clinical conditions, particularly in immunocompromised patients (4). However, in a retrospective study, 20% of the Nocardia sp. isolates were found not to be associated with clinical disease (3). Diagnosis of nocardial respiratory infection is difficult because of the slow growth of the bacteria and the presence of commensal flora in the culture. Clinically oriented cultures are improved by using a selective medium which inhibits the commensal flora, such as selective media for Legionella or for Mycobacterium after use of a decontamination method. Criteria useful for evaluating the significance of a positive culture from the respiratory tract are direct visualization of the microorganism on a Gram-stained smear, pure or predominant growth in culture, and repeated isolation from serial clinical samples. In the present case, Nocardia was isolated only once from a sputum sample; the following sputum cultures were negative. Therefore, we considered the presence of Nocardia to be a transient colonization. Since the patient had presented a cavitory pneumonia caused by Actinomyces sp. and received co-trimoxazole prophylaxis and minocycline therapy, Actinomyces was the presumptive bacterium causing the brain abscess. Actinomyces belongs to the endogenous flora of the mucous membranes of the oropharynx. Brain infection is rare, accounting for 1% of the actinomycotic localizations (15), and it results from hematogenous dissemination in only 20 to 25% of the cases (10). Conversely, hematogenous dissemination of Nocardia sp. is usually from a pulmonary focus and most commonly involves the central nervous system (9). Thus, the stereotaxial biopsy, which was hazardous to perform, has permitted the diagnosis of nocardiosis.

Of Nocardia species, the most frequently involved in human infections are members of the Nocardia asteroides complex. The members of this complex were subclassified into six different drug susceptibility types. Numerous new species of the Nocardia asteroides complex have been recently described (13, 14), including N. cyriacigeorgica (17). This species corresponds to strains of drug pattern type VI. It has been rarely reported in human infections so far. However, its frequency may be underestimated since it requires molecular techniques for species identification. Thus, the present isolate was initially misidentified as Nocardia asteroides by the API system. In a retrospective work, Kageyama et al. reported that about 10% of the Nocardia strains which were isolated from infection were N. cyriacigeorgica, but its clinical involvement was not mentioned (5). To our knowledge, a single case of cerebral infection caused by N. cyriacigeorgica, in an immunocompromised patient, has been reported so far (2).

The susceptibility to co-trimoxazole was different between the two isolates by disk diffusion method and by Etest. However, the genetic similarity of the two isolates was confirmed by random amplification polymorphic DNA (data not shown) (6).

Intravenous treatment with imipenem plus amikacin, which is usually used in severe infections, was given. After 1 month of intravenous treatment and a clinical recovery, the treatment was switched to co-trimoxazole at a high dosage, considering...
that the brain biopsy isolate was susceptible to this antibiotic and that until now no study has established a correlation between the results obtained in vitro and the clinical outcome of the patients under treatment (7).

In conclusion, although nocardiosis has been considered to be rare, it has been reported recently that the incidence of this infection is increasing (5). Pulmonary infection caused by *Nocardia* may be difficult to diagnose due to nonspecific clinical and histological manifestation and due to the difficulty of isolating the bacteria among commensal flora in respiratory specimens. Traditional identification methods are time-consuming and not discriminating enough to identify new species within the genus *Nocardia*. Identification to the species level requires molecular techniques. This case report indicates that isolation of *Nocardia* in the sputum of patients with HIV infection is associated with a high risk of disseminated infection.

REFERENCES