Case Report

Disseminated nocardiosis masquerading as metastatic malignancy

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ABSTRACT

Nocardiosis is an uncommon gram-positive bacterial infection caused by aerobic actinomycetes of the genus Nocardia. It can be localized or systemic and is regarded as an opportunistic infection that is commonly seen in immunocompromised hosts. We report a case of disseminated nocardiosis caused by Nocardia cyriacigeorgica in a patient with underlying malignancy in whom the clinical presentation was highly suggestive of a metastatic disease.

KEY WORDS: Disseminated, metastatic disease, Nocardia cyriacigeorgica, nocardiosis

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INTRODUCTION

Nocardiosis is caused by Nocardia, a group of strictly aerobic, partially acid-fast, branching, often beaded, filamentous, and weakly gram positive bacteria that typically fragment into nonmotile rod- or coccoid-shaped elements.¹⁰ Nocardiosis may be localized or disseminated infection, and the usual modes of transmission are by inhalation or through the cutaneous route. The pulmonary infection in humans may be self-limited, subclinical, or may progress to an acute, subacute, or chronic process mimicking tuberculosis, fungal infection, or even malignancy. Hematogenous dissemination spreads particularly to the nervous system, skeletal and soft tissue structures.

Disseminated nocardiosis is defined as involvement of two noncontiguous sites that may or may not include a pulmonary focus. From a pulmonary or cutaneous focus, Nocardia can disseminate to virtually any organ.

CASE REPORT

A 61-year-old man presented to our clinic with complaints of cough with mucopurulent expectoration and blood streaking since 3 weeks and low grade intermittent fever for the past 1 week. He had no history of dyspnea, chest pain, or aspiration. He was not a diabetic and did not have any underlying lung disease or tuberculosis in the past. He had no history of close contact with anyone having tuberculosis either. He had no pets or any significant travel history. He had no addictions. Twenty months before this admission, he was diagnosed with adenocarcinoma of the lower end of the esophagus for which he underwent esophagogastrectomy and gastric pull through surgery. He received 6 months of chemotherapy and radiotherapy and was under regular follow-up of the oncologist. A follow-up contrast-enhanced computed tomography (CT) of the abdomen and chest and an upper gastrointestinal (GI) endoscopy done 6 months later did not show any evidence of recurrence. One year later, he developed altered sensorium and was evaluated with magnetic resonance imaging (MRI) of the brain.

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resonance imaging (MRI) of the brain, which showed multiple heterogeneously enhancing lesions involving the precentral gyrus of the right high frontal lobe, parietal and temporal lobes, with mass effect and perilesional edema suggestive of metastasis [Figure 1]. He was started on dexamethasone 8 mg twice daily, levetiracetam, and cranial irradiation.

Two weeks later, he developed fever, cough, and hemoptysis and was referred to our clinic. On examination, his vital signs were stable. He was pale, febrile, emaciated, and had clubbing of the fingers and toes. The lymph nodes were not palpable. Examination of the respiratory system revealed bilateral scattered wheezes. He appeared confused but there were no focal neurological deficits. The rest of the systemic examination was unremarkable.

A chest radiograph showed a cavity in the left upper zone, a nodular lesion in the right middle zone, and left-sided pleural effusion [Figure 2]. His complete blood count was 9500 µl with polymorph predominance (95%), hemoglobin was 10 g%, platelet count was normal, and the C-reactive protein level was 360 mg/L. The human immunodeficiency virus (HIV) test was negative. Sputum smear for acid-fast bacilli (AFB), gram stain, cultures, Xpert MTB, and fungal stain were sent and the patient was started on parenteral amoxicillin-clavulanic acid. A contrast-enhanced CT of the thorax showed a thick-walled cavitary lesion in the left upper lobe, left pleural effusion, and multiple bilateral nodular lesions, some of which were cavitating [Figures 3–5]. These features were suggestive of multiple lung metastases or a new onset cavitating lung malignancy (second primary). He continued to have pyrexial spikes and hence, the antibiotics were escalated to piperacillin-tazobactam and levofloxacin after sputum smears for AFB were reported as negative. In view of fever with lung and brain lesions in an immunocompromised patient, his brain and lung images were reviewed and the differential diagnoses that were thought of were tuberculosis, bacterial pneumonia and brain abscess, lung and brain metastasis with secondary infection, invasive fungal infections and other uncommon infections such as nocardiosis.

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**Figure 1:** Magnetic resonance imaging of the brain’s right parasagittal section T1-weighted contrast image showing well-defined focal ring enhancing lesion with eccentric enhancing dot within, involving the precentral gyrus of the right high frontal lobe.

**Figure 2:** Chest x-ray posteroanterior view showing cavity in the left upper lobe, left-sided pleural effusion, and a nodular lesion in the right mid-zone.

**Figure 3:** Contrast-enhanced computed tomography (CT) of the chest showing large thick-walled cavity in the left upper lobe.

**Figure 4:** Contrast-enhanced CT of the chest showing multiple nodular lesions bilaterally.
Sputum gram stain showed occasional gram positive cocci, modified AFB stain showed branching beaded filamentous bacteria [Figure 6], and the bacterial culture after 72 h did not show any growth. Since all the tests were inconclusive, a flexible fiberoptic bronchoscopy was performed and lavage was taken from the left upper lobe for microbiologic examination and cytopathology. The results of bronchoalveolar lavage reports including Gram stain, bacterial culture, fungal smear, culture, Xpert Mycobacterium tuberculosis (MTB)/rifampin (RIF), AFB smear and culture, and periodic acid-Schiff (PAS) stain were negative and no malignant cells were noted. He was continued on parenteral antibiotics but still continued to have temperature spikes. Five days later, the sputum culture grew dry chalky white colonies, which were identified as Nocardia species and the same grew in the lavage fluid also [Figure 7]. Species identification was done with MALDI-TOF (BioMérieux, France) as *Nocardia cyriacigeorgica*. It was sensitive to ceftriaxone, trimethoprim, tetracycline, amikacin, and imipenem. Piperacillin-tazobactam, and levofloxacin were discontinued and was initiated on intravenous imipenem 500 mg 6 hourly, intravenous amikacin 1 g once daily, oral trimethoprim-sulfamethoxazole double strength two tablets thrice daily in view of the disseminated disease. A brain biopsy was advised but the patient declined the same. After getting the drug susceptibility reports, imipenem was deescalated to ceftriaxone. He became afebrile after starting a specific therapy for nocardiosis, and his respiratory symptoms resolved. His mental status improved and he became alert and well-oriented. Since his clinical status improved, he was discharged with advice to continue the parenteral antibiotics as outpatient via a peripherally inserted central catheter line. After an initial 4 weeks of intensive intravenous therapy, he was switched to cotrimoxazole and minocycline in the maintenance phase and this was planned to be continued for 6–12 months. A follow-up chest X-ray demonstrated near-total resolution of the pulmonary infiltrates [Figure 8].

The patient continued to have clinical improvement but 3 months later; he developed features of progression of the primary malignancy, anorexia, and electrolyte imbalance. The family opted for comfort care and the patient expired 1 month later.
DISCUSSION

Nocardiosis is a rare gram-positive bacterial infection caused by aerobic actinomycetes of the genus *Nocardia*. It can be localized or systemic. Nocardiosis is considered to be an opportunistic infection, but approximately one-third of the infected patients are immunocompetent. Infection by members of the *Nocardia asteroides* complex (NAC) represents the most common cause of nocardiosis worldwide.[2]

The aerobic *Actinomycetes* are a large and diverse group of gram-positive bacteria that appear on microscopy as branching filamentous cells and includes *Mycobacterium, Corynebacterium, Nocardia, Gordona*, and *Tsukamurella*. All the members also have mycolic acid in addition to other components, which is responsible for the acid-fastness. The genus is named after Edmond Nocard who in 1888 described the isolation of an aerobic actinomycete from cattle with bovine farcy. Although traditional laboratory methods can identify *Nocardia*, molecular methods are needed for accurate species determination.[3] Species determination is important as antibiotic susceptibility varies among different species.

*Nocardia* species are ubiquitous environmental saprophytes occurring in the soil, organic matter, and water. Protective immune responses to *Nocardia* are primarily T-cell mediated; hence, impaired cell mediated immunity is a risk factor.[3] Human infection is usually from direct inoculation of the skin or soft tissues or by inhalation. The risk of nocardial infection is increased in immunocompromised patients, particularly those with defects in cell-mediated immunity such as glucocorticoid therapy, malignancy, organ transplant recipient, HIV infection, diabetes, and alcoholism.[4]

Presentation of nocardiosis depends on organ involvement. The lungs are the primary site of nocardial infection, occurring in more than 40% of reported cases and 90% of these are due to members of NAC. Clinical manifestation of the established disease includes endobronchial inflammatory masses, pneumonia, lung abscess, cavitary disease, effusion, and empyema. Radiologic manifestations include irregular nodules, cavitation, reticulonodular diffuse pneumonia, and pleural effusions. Progressive fibrotic disease may develop following inadequate therapy. Pulmonary nocardiosis may be a fatal disease in advanced HIV infection.[5]

Secondary cerebral localization and clinically silent destructive infection are sufficiently common, accounting for 44% of systemic nocardiosis in one large survey. Hence, cerebral imaging should be performed in all cases of pulmonary and disseminated nocardiosis. Clinical manifestation of cerebral disease is usually neurologic deficit or behavior abnormalities depending on the localization in the brain. Nocardiosis of the brain commonly produces granuloma or abscess. Tissue diagnosis of a cerebral mass in the setting of a proven pulmonary nocardiosis is not always necessary.[5]

Other extrapulmonary manifestations include the kidney, bone, muscle, and skin involvement causing cellulitis, abscess, lymphocutaneous syndrome, or actinomycetoma and eye infections such as acute keratitis and endophthalmitis.[3] Concurrent involvement of the lung and skin mimicking bronchogenic carcinoma with cutaneous metastasis has also been reported.[5]

Respiratory and disseminated infections are most often due to members of NAC.[3] Isolation and identification of the organism from a clinical specimen gives a definite diagnosis of nocardiosis. Examination of the sputum or pus for crooked, branching, beaded, gram-positive filaments is the first step in diagnosis. *Nocardia* is acid-fast in direct smears if a weak acid is used for discolorization (e.g., in the modified Kinyoun, Ziehl-Neelsen, and Fite-Faraco methods). *Nocardia* retains fuchsinse less tenaciously and so, the modified Kinyoun stain that discolores is better for demonstrating the variable and transient acid-fast property of *Nocardia* species.[6] *Nocardia* can be supported on most routine aerobic bacterial, fungal, and mycobacterial culture media. Selective media include buffered charcoal yeast extract (the media used for the isolation of *Legionella* spp.) and modified Thayer-Martin agar. In routine aerobic cultures, *Nocardia* spp. form chalky white to pigment-producing orange, yellow, or brown colonies and requires 5–21 days for growth. Molecular diagnostic testing for identification of *Nocardia* spp. is more accurate and rapid.

Sulfonamides have been considered as the standard for therapy. Trimethoprim-sulfamethoxazole (TMP-SMX) (10–20 mg of TMP per kg and 50–100 mg of SMX per kg are given each day in two divided doses and later, the daily doses can be decreased to 5 mg/kg and 25 mg/kg, respectively) is used most frequently. Alternatives to sulfonamides include minocycline (100–200 mg twice a day), amikacin (5–7.5 mg/kg every 12 h or 15 mg/kg every 24 h), imipenem (500 mg IV every 6 h), and linezolid.[3]

In a severe infection that does not involve the CNS, the recommended treatment regimen is intravenous (IV) induction therapy with TMP-SMX (15 mg/kg IV of the trimethoprim component per day in two to four divided doses) plus amikacin (7.5 mg/kg IV every 12 h). Alternatively, imipenem (500 mg IV every 6 h) plus amikacin can also be given.[2,3] In severe infection with central nervous system (CNS) disease, IV induction therapy with TMP-SMX (15 mg/kg IV of the trimethoprim component per day in two to four divided doses) plus imipenem (500 mg IV every 6 h) is the preferred regimen. For disseminated nocardiosis, IV amikacin is added to the above regimen. Selected patients who clinically improve with the induction of IV therapy and do not have CNS disease may be switched to oral monotherapy (usually after 3–6 weeks) based on susceptibility results. In patients with
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Nocardia cyriacigeorgici and was first reported from a patient with chronic bronchitis in 2001.[7] Although this organism was originally thought to belong to NAC, due to differences in antibiotic susceptibility pattern and molecular techniques, it is now considered to be a separate entity.[8,9] With the advent of newer molecular diagnostic techniques such as 16S rRNA gene or matrix-assisted laser desorption/ionization time of flight (MALDI TOF) invasive infection by Nocardia Cyriacigeorgica is being increasingly reported. The literature review showed that among 765 Nocardia isolates submitted to the United States Centers for Disease Control and Prevention between 1995 and 2004, 13% were Nocardia cyriacigeorgica.[9] Of the 303 nocardiosis cases in Japan from 1992 to 2001, 10% again belonged to this species.[10] There are case reports of septicemia, disseminated infection as well as endocarditis due to Nocardia cyriacigeorgica.[11,12]

This case is being reported to highlight two unique aspects. First, a rare subtype of Nocardia was isolated both in the sputum and bronchoalveolar lavage specimen—Nocardia cyriacigeorgica. The second point worth emphasizing is the clinical presentation of this unique infection in the background of malignancy, mimicking metastatic disease in the lungs and brain. Nocardiosis is often overlooked since the presentation is insidious and nonspecific and often lacks the clinical findings and laboratory evidence of bacterial infection.[13] Nocardia should always be considered in the differential diagnosis as a possible pathogen causing infection in patients with malignancy as well as other immune-compromised states.

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**Conflicts of interest**

There are no conflicts of interest.

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