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Case Report

Nocardiosis of the Lung with Hematogenous Spread to the Brain in Post-Transplant Patient: A Case Report and Review of the Literature

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Abstract

Nocardiosis is a potentially lethal complication of organ transplantation. Each year, approximately 500 to 1000 cases of nocardiosis are diagnosed in the United States. Nocardiosis commonly occurs in the lung, brain, and heart of transplant recipients. This case describes a 63-year-old male who presents with a solitary brain and multiple pulmonary lesions. Nocardiosis represents a problematic diagnosis due to non-specific symptoms and imitation of more common differentials. Nocardiosis should always be included in the differential diagnosis of any patient who presents with brain, soft tissue, or cutaneous lesions and a concurrent or recent pulmonary lesion. Early detection combined with empiric antibiotic therapy is considered the current standard of care in patients with nocardiosis. We present a case of nocardiosis of the lung with hematogenous spread to the brain in post-transplant patient who responded well to treatment with complete recovery.

Keywords: Nocardiosis, Organ Transplant, Pulmonary Lesion, Immunocompromised, brain

ABBREVIATION

CNS: Central nervous system, **TMP-SMX**: trimethoprim-sulfamethoxazole

INTRODUCTION

Nocardia spp are weakly Gram-positive, catalase-positive, rod-shaped bacteria that form acid-fast branching filaments and are not members of normal human flora [1]. *Nocardia* spp are found in soil, decomposing vegetables, and marine environments and have the potential to become airborne on dust particles to be inhaled, entering the body through the lungs.[5] Nocardiosis is a common infection in transplant or immunocompromised patients; however, approximately one-third of infected patients are immunocompetent [2].

Nocardia spp can inhibit phagocytosis, inhibit the phagosome-lysosome fusion, as well as produce superoxide dismutase and catalase [21]. The majority of patients diagnosed with nocardiosis are immunocompromised, commonly due to cell-mediated abnormalities frequently due to glucocorticoid therapy, organ transplantation, HIV infection, hematopoietic stem cell transplantation and malignancy [2,8,18].

Nocardiosis can be a problematic diagnosis due to the number of more common differentials and the variability of presentation. Pulmonary nocardiosis may imitate or present as worsening pulmonary sarcoidosis or chronic obstructive pulmonary disease, which may lead to a delay in diagnosis [10,11]. Image findings of pulmonary nocardiosis have demonstrated great variability; findings including single nodules, multiple nodules, reticulonodular infiltrates, lobar consolidation, pleural effusions, lung masses with consolidation, lung masses without consolidation, and subpleural plaques. Due to the variability of imaging studies and the fact that *Nocardia* spp is weakly acid-fast, nocardiosis is often mistaken for fungal disease, tuberculosis infection or malignancy [2,14]. Furthermore, patients prescribed glucocorticoids may not exhibit signs and symptoms of infection as plainly, due to reduction in inflammatory responses and inhibition of cytokine release.

There are no specific preventative measures for nocardiosis. People who have weakened immune systems are advised to wear clothing covering the skin, wear shoes and cover open wounds and cuts when working in soil to prevent cutaneous infections. Organ transplant recipients may be prescribed antibiotics to prevent bacterial infections, which may prevent nocardiosis.

CASE PRESENTATION

A 63-year-old man presented with a solitary brain and multiple pulmonary lesions during his hospital stay following renal transplant for end stage renal disease. The patient was placed on steroid therapy following the transplant.

Head magnetic resonance imaging (MRI) showed a sharply defined lesion measuring 3.2 cm in the left temporal lobe of the brain, in addition to long T1-weighted and T2-weighted signals

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shadows and a circular equisignal. Enhanced diffusion-weighted imaging signals were observed in the center of lesion. CT of the lung showed multifocal lung consolidation as a predominant finding. Foci of decreased attenuation were present within consolidated lung and were more conspicuous on contrast-enhanced CT. Occasional cavitation was also noted in some of the lung nodules. There was no evidence of mediastinal or hilar lymphadenopathy. An infectious process was suspected, likely an opportunistic infection in an immunocompromised patient on steroid therapy.

The patient underwent a CT-guided fine needle aspiration biopsy from one of the lung consolidated areas. The cytology specimen was cellular enough to produce adequate cellblock preparation for ancillary studies. Cytology slides and cell block slides showed scattered viable clusters of epithelioid histiocytes in a background of severe acute necrotizing inflammatory process (**Figure 1A**). Branching filamentous organisms were noted in the DQ stained cytology slides (**Figure 1B**) Special stains including GMS (**Figure 1C**) and AFB showed branching filamentous bacteria, indicative of Nocardia. The diagnosis was consistent with lung Nocardiosis in an immunocompromised patient, with hematogenous spread to the brain. Culture results confirmed the presence of N. brasiliensis, and it was also sensitive to amikacin, ceftriaxone, trimethoprim, and gentamycin.

The patient reported Sulfa allergy, so Trimethoprim-sulfamethoxazole was not used, and he was treated with amikacin and ceftriaxone, the brain abscess was cleaned ad removed with craniotomy. After 4 months of treatment, the pulmonary lesions resolved completely, and repeat MRI brain also revealed resolving lesions. A 6 months follow up showed no evidence of recurrence or complication after which the patient was lost to follow up as he returned to his country of origin.

DISCUSSION

Nocardia spp are weakly Gram-positive, catalase-positive, rod-shaped bacteria that form acid-fast branching filaments and are not members of normal human flora [1]. *Nocardia* spp are found in soil, decomposing vegetables, and marine environments and have the potential to become airborne on dust particles to be inhaled, entering the body through the lungs [5]. Nocardiosis is a common infection in transplant or immunocompromised patients; however, approximately one-third of infected patients are immunocompetent [2]. Common characteristics of nocardiosis are its propensity of recurrence or progression despite therapy as well as its capability to disseminate to any organ. Classification of nocardiosis is based upon the extent of the infection as well as the location of the disease, including central nervous system (CNS), pulmonary, cutaneous and disseminated ailments [3,4].

Cell-mediated immunity is important in containing *Nocardia* spp infection. The initial response to nocardiosis involves macrophages and neutrophils to inhibit the bacteria to limit the spread until a more specific response can begin [2]. Gamma delta T-lymphocytes are thought to play a crucial role in host defenses, enhancing phagocytosis and stimulating cellular response [20]. *Nocardia* spp has multiple abilities to oppose the host immune system. *Nocardia* spp can inhibit phagocytosis, inhibit the phagosome-lysosome fusion, as well as produce superoxide dismutase and catalase [21]. The majority of patients diagnosed with nocardiosis are immunocompromised, commonly due to cell-mediated abnormalities frequently due to glucocorticoid therapy, organ transplantation, HIV infection, hematopoietic stem cell transplantation and malignancy [2,8,18].

There are no pathognomonic signs or symptoms in patients who have nocardiosis so it should be suspected in any patient who presents with brain, soft tissue, or cutaneous lesions and a concurrent or recent pulmonary lesion. Most often, *Nocardia* spp infection is associated with vague symptoms such as night sweats, fatigue, anorexia, fever, dyspnea, cough, hemoptysis or chest pain [3,4]. Studies have shown that pulmonary nocardiosis is the most common form; followed by systemic nocardiosis, CNS only, and

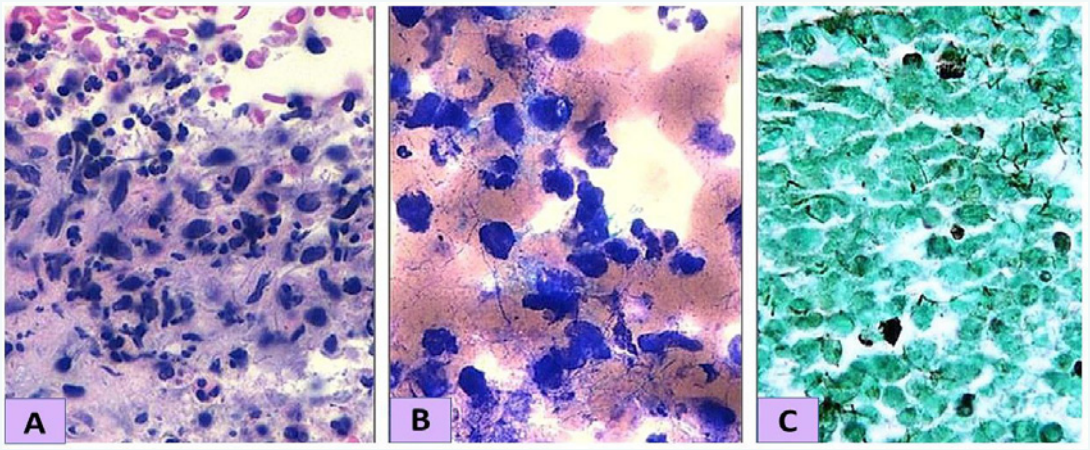

Figure 1 Examination of the Fine Needle Aspiration Sample from the lung
1A: Epithelioid histiocytes (H&E 20x)
1B: Branching filamentous organisms (DQ 40X)
1C: Branching filamentous bacteria, indicative of Nocardia (GMS 20x)

cutaneous [6-9]. *Nocardia* spp isolation from respiratory sputum is indicative of infection as *Nocardia* is not normally found in the respiratory tract [1]. In up to 50% of respiratory cases, there is dissemination to extra-respiratory sites, with the most common site being the brain [3]. Other complications of nocardial infection include superior vena cava syndrome and pericarditis [12,13]. *Nocardia* spp has a disposition for neural tissue and can cause CNS nocardiosis [2,3]. The defining characteristic of CNS nocardiosis is the formation of a parenchymal abscess that has the ability to arise in any zone of the brain [15].

Nocardia spp diagnosis often requires invasive procedures to gather an adequate specimen. When *Nocardia* infection is suspected, specific staining procedures and media are used, with care taken to avoid sodium hydroxide, N-acetylcysteine, and benzalkonium chloride, as they are toxic to this bacterium [3]. Gram stain, modified acid-fast (Kinyoun) stain or auramine-rhodamine fluorescent stain are commonly staining techniques used to identify *Nocardia.* Histologically, tissue specimens show necrosis with abscess formation. There may also be a mixed cellular infiltrate of lymphocytes, plasma cells, polymorphonuclear leukocytes, and hemosiderin-laden macrophages [22]. Granulomas with central necrosis in respiratory tissue have been infrequently noted.

The risk of nocardiosis is highest in the first year after organ transplantation, seemingly due to the amount of immunosuppressants given to prevent transplant rejection [18]. The rate of *Nocardia* infection is highest in lung and heart transplant recipients and lowest in kidney and liver transplant recipients.[19] Risk factors for *Nocardia* infection in transplant patients include high-dose glucocorticoids, high serum calcineurin-inhibitor concentration, advanced patient age, length of stay in intensive care and recent cytomegalovirus infection [8].

Nocardiosis can be a problematic diagnosis due to the number of more common differentials and the variability of presentation. Pulmonary nocardiosis may imitate or present as worsening pulmonary sarcoidosis or chronic obstructive pulmonary disease, which may lead to a delay in diagnosis [10,11]. Image findings of pulmonary nocardiosis have demonstrated great variability; findings including single nodules, multiple nodules, reticulonodular infiltrates, lobar consolidation, pleural effusions, lung masses with consolidation, lung masses without consolidation, and subpleural plaques. Due to the variability of imaging studies and the fact that *Nocardia* spp is weakly acid-fast, nocardiosis is often mistaken for fungal disease, tuberculosis infection or malignancy [2,14]. Symptoms and signs of nocardial brain abscess are non-specific and variable; they include fever, seizures, headache, focal neurological deficits, and meningismus [2,16]. CNS nocardiosis is often misdiagnosed as a primary or metastatic neoplasm due to the presentation of symptoms suggesting a mass lesion and the possibility of the lack of symptoms association with an infection. The average time from the onset of symptoms to the definitive diagnosis has ranged from 42 days to 12 months in numerous studies, which is due to the patient's blood cultures needing to be incubated for 4 weeks to attain maximum yield [2,17,18]. Furthermore, patients prescribed glucocorticoids may not exhibit signs and symptoms of infection as plainly, due to reduction in inflammatory responses and inhibition of cytokine release.

There are no specific preventative measures for nocardiosis. People who have weakened immune systems are advised to wear clothing covering the skin, wear shoes and cover open wounds and cuts when working in soil to prevent cutaneous infections. Organ transplant recipients may be prescribed antibiotics to prevent bacterial infections, which may prevent nocardiosis.

Nocardia spp are usually resistant to penicillin and numerous other antibiotics. As a result, the standard of therapy is empiric coverage with three agents in patients whom have severe infection. Most studies recommend trimethoprim-sulfamethoxazole (TMP-SMX) [23]. Other antibiotics that demonstrate activity against *Nocardia* include amikacin, imipenem, meropenem, third generation cephalosporins, linezolid, tigecycline, dapsone and extended spectrum fluoroquinolones [24].

This case and literature review seek to shed light on the variability, diagnostic and treatment challenged in patients diagnosed with nocardiosis. Delay in early detection due to numerous factors poses a threat to patients who are immunocompromised. The definitive diagnosis is made through laboratory cultures, specific staining, and microscopic imaging, which aids in the correct diagnosis of *Nocardia* infections.

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