Disseminated Nocardiosis: an unexpected diagnosis

Nocardiosis diseminada: un diagnóstico inesperado

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ABSTRACT

Nocardiosis is a rare opportunistic infection caused by the bacteria Nocardia spp. It may present as a localized cutaneous infection or as an invasive infection (pulmonary, central nervous system or disseminated). The authors describe a 65-years-old woman, without a known cause of immunosuppression, admitted with fever, respiratory and constitutional symptoms. After an exhaustive etiological study, it was diagnosed a disseminated nocardiosis (pulmonary and central nervous system), in a probable context of immunosuppression secondary to a previously undiagnosed systemic lupus erythematosus. Nocardiosis is a serious infection with a variable and non-specific presentation making its diagnosis a challenge.

Palabras clave: Nocardia; Nocardiosis diseminada; Inmunosupresión.

Keywords: Nocardia; Disseminated nocardiosis; Immunosuppression.

INTRODUCTION

Nocardiosis is a rare infection caused by *Nocardia spp.*, an aerobic gram-positive bacteria, saprophytic of the soil and aquatic environments.[1-6] Nocardiosis is often classified as an opportunistic disease being more frequent and severe in immunocompromised individuals.[1-8]

The main risk factors for the development of nocardiosis are corticotherapy, organ or bone marrow transplant, chemotherapy, neoplasia, diabetes mellitus, chronic obstructive pulmonary disease, sarcoidosis, tuberculosis, human immunodeficiency virus (HIV) infection, autoimmune diseases, nephrotic syndrome, alveolar proteinosis, dysgammaglobulinemia, alcoholism and intravenous drug use.[1,2,4-7,9] Nocardiosis is acquired by inhalation or direct inoculation of the bacteria into the skin and soft tissues.[2,4,9] Clinically, it manifests as a localized cutaneous infection or as an invasive infection (pulmonary, central nervous system or disseminated). When the infection occurs in two or more noncontiguous sites, it is considered disseminated.[3,10] The main route through which *Nocardia spp.* can be acquired is by inhalation, which explains why pulmonary nocardiosis is the most common clinical presentation.[1-5,9] The standard method for the diagnosis of *Nocardia spp.* is isolation in culture medium. The first-line therapy for nocardiosis is Trimethoprim/Sulfamethoxazol (TMP/SMX) and in cases of disseminated disease or CNS involvement a second antibiotic (imipenem, amikacin or ceftriaxone) is associated.[1-5,8] The duration of treatment should vary between 6 and 12 months.[1,8]

CASE PRESENTATION

A 65-years-old woman was admitted to the emergency department due to a one week history of fever and productive cough. The patient also reported asthenia, anorexia, night sweats and weight loss of about 10% within the previous three months. The patient had been medicated with amoxicillin/clavulanic acid and azithromycin for community acquired pneumonia less than three months before. She had past medical history of gastric adenocarcinoma submitted to gastrectomy, eight years before the current episode and without history of recurrence. On admission the patient was pale, dehydrated and febrile. Blood tests showed anemia and thrombocytopenia (Hemoglobin 9.9 g/dL, Platelets 82000 U/L) and an elevation of C reactive protein (37.2 mg/L). Thoraco-abdomino-pelvic computed tomography (CT) showed two foci of cavitated pulmonary consolidations in the anterior segment of the right upper lobe and in the inferior segment of the lingula and pericardial and bilateral pleural effusions. Serologic tests for human immunodeficiency virus, B and C hepatitis, Cytomegalovirus and Epstein-Barr virus were negative. Antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) were positive (ANA 1/1000, anti-dsDNA 800 UL/ml). Sputum smear microscopy, sputum *Mycobacterium tuberculosis* nucleic acid amplification test and sputum culture in Lowenstein medium were negative. A bronchofibroscopy was preformed, collecting bronchial and bronchoalveolar lavage (LBA) to anatomopathological, microbiological, mycological and mycobacteriological analyses.

A performed ultrasound-guided needle biopsy of a cavitated lung lesion was compatible with necrotizing pneumonia. Empiric antibiotic treatment with piperacillin/tazobactam and clindamycin was introduced. Itraconazole was associated after the identification of fungi with characteristics of *Aspergillus fumigatus* in the anatomopathological analyses, and isolation of *Aspergillus fumigatus* in BAL culture. After 5 day therapy with itraconazole, chest CT showed an increased bilateral pleural effusion, a new opacity in the left upper lobe and an increased nodular cavitation of the lingula, suggestive of an ongoing infectious process without the characteristics of aspergillosis. (Figure 1)

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Pleural fluid was classified as an exudate (pH 7.21, Lactate Dehydrogenase 975 U/L, Glucose 58 mg/dl; cytological analyses with predominance of polymorphonuclear cells), negative for malignant cells and with a negative microbiological exam. On the 16th day of hospitalization *Nocardia spp.* was isolated in the blood and BAL cultures, confirmed by polymerase chain reaction in both samples. TMP/SMX (320 mg/1600 mg intravenous, three times a day) and imipenem (500 mg intravenous, four times a day) were then started. Transthoracic echocardiogram excluded endocarditis. The patient presented deterioration of consciousness, conjugate deviation of the gaze and right hemiplegia 3 days afterwards. Cranio-encephalic CT revealed rounded formations, compatible with abscesses, within a massive left hemorrhagic lesion at the caudate-lentículo-capsular level, associated with perilesional edema, compression of the ipsilateral ventricle, deviation of the midline structures, and subfalcine and left transtentorial uncal herniation. (Figure 2) The patient died on the 21st day of hospitalization.

DISCUSSION

The authors present a case of disseminated nocardiosis with pulmonary and central nervous system (CNS) involvement. Pulmonary nocardiosis is the most common clinical presentation but its varied and nonspecific clinical and radiological presentation mimics other infections making its diagnosis challenging. The imagiological findings are varied and nonspecific, ranging from nodules, and abscesses to pulmonary cavitations.[1,3-5,9] In this case radiological and histological findings compatible with necrotizing pneumonia and the subsequent isolation of *Aspergillus fumigatus* in BAL baffled the diagnosis. Extrapulmonary nocardiosis can occur through hematogenous dissemination or a contiguous spread of necrotizing pneumonitis into the pleura, pericardium, mediastinum, and vena cava.[1,9] Hematologic dissemination is present in 50% of the cases of pulmonary nocardiosis and the CNS is the most common secondary site once *Nocardia spp.* presents neurotropism.[1,4] The formation of abscesses at the embolization sites is frequent as this is a pyogenic bacteria.[1,4,9] The most severe form is the disseminated disease that occurs more frequently in immunocompromised patients, in cases of delayed diagnosis or antibiotic resistance.[3,4] In this case the patient presented arthralgias and malar rash with several months of evolution which in association with positivity for ANAs and anti-dsDNA raised the suspicion of a possible non diagnosed systemic lupus erythematosus. The immunosuppression underlying this autoimmune disease may be associated with an increased risk for nocardiosis.[5]

The isolation of the bacteria from a clinical specimen is crucial for the diagnosis.[2,4,5] Bacteremia by *Nocardia spp.* is rare and other biological specimens should be collected.[1,4] Specimens collected through invasive procedures (e.g. bronchofibroscopy and biopsies) have an increase diagnostic profitability.[1,4,5] The incubation period of the culture media should be extended to 2-3 weeks since *Nocardia spp.* is a slow growing microorganism.[4,5,9] Molecular biology

Figure 1. Chest computed tomography – Bilateral pleural effusion and a nodular cavitation of the lingula.

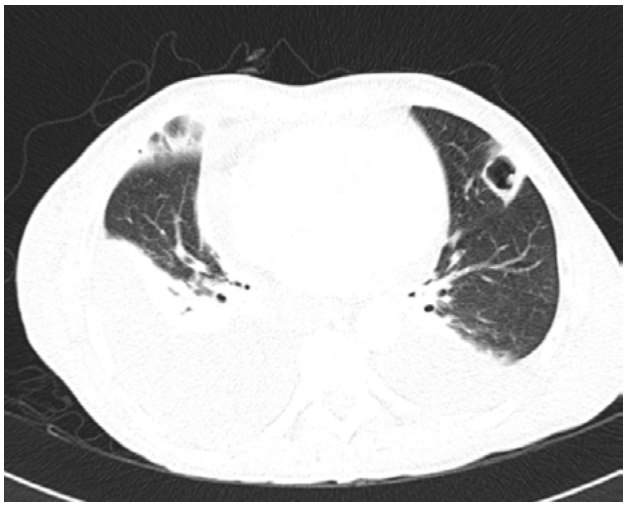
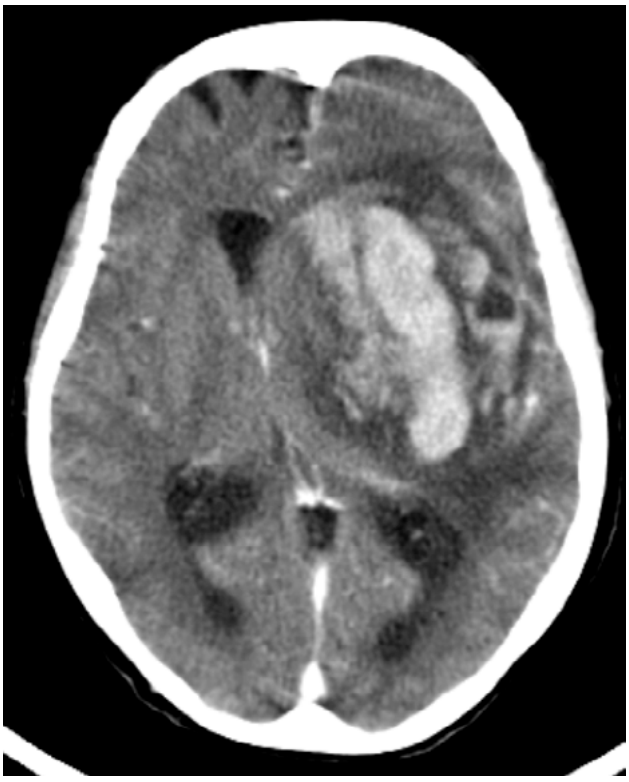


Figure 2. Cranioencephalic computed tomography – Rounded formations, compatible with abscesses, within massive left hemorrhagic lesion at the caudate-lentículo-capsular level, with perilesional edema, compression of the ipsilateral ventricle, deviation of the midline structures, and a subfalcine and left transtentorial uncal herniation.



techniques are more sensitive and swift adding accuracy to the diagnosis.[4]

The treatment instituted in this case was empirical given that the antimicrobial susceptibility tests for this bacteria were not available at this medical center. In the case presented, because it was a disseminated nocardiosis, a second antibiotic (imipenem) was associated with TMP/SMX.[1-5] In such cases therapy should be maintained for 12 months.[1,3,7]

Although nocardiosis is a rare infection, its incidence has been increasing mainly due to the increasing number of immunosuppressed patients. *Nocardia spp.* slow growth in culture media along with its non-pathognomonic clinical and radiological findings delay the diagnosis of nocardiosis; a high level of suspicion is paramount. Since *Nocardia spp.* is a bacteria capable of developing severe metastatic disease, the early recognition and beginning of appropriate treatment is fundamental to achieve more satisfactory outcomes.

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