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Pulmonary Nocardia: A Single-center Experience

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Introduction

Nocardiosis is an uncommon but serious infectious disease caused by gram-positive branching filamentous bacilli. It belongs to the Actinomycetales order and is a weak acid-alcohol-fast bacterium. It inhabits the telluric environment where they contribute to the degradation of organic matter and its transmission generally occurs through inhalation or direct inoculation of spores [1,2]. Seven species of the genus Nocardia are considered as human pathogens (*N. asteroides*, *N. brasiliensis*, *N. otitidis-caviarum*, *N. farcinica, N. nova, N. transvalensis, and N. pseudobrasiliensis*) and at least eleven additional species have been linked to disease in humans. *N. farcinica*, a less common but more virulent specie than *N. asteroides,* and more prone to disseminated forms. *N. pseudobrasiliensis* often leads to invasive disease and *N. brasiliensis* usually causes a disease limited to the skin.

Although cases have been reported in healthy people, it mainly affects immunocompromised patients, mostly men. The most frequent form of presentation is pulmonary nocardiosis representing 40% of all infections caused by Nocardia. Organs other than the lung frequently affected in Nocardia infections are the Central Nervous System (CNS), skin, kidneys, bones and soft tissues. Disseminated nocardiosis is defined as the Nocardia infection affecting two or more noncontiguous organs or the CNS [3]. The site of entry is the lung where it primarily affects patients with severe immunosuppression, worsening its prognosis. Treatment will be prolonged and the antibiotics of choice are sulfonamides. Second choice treatments are minocycline, levofloxacin, amoxicillin clavulanate or linezolid [3,4]. In the case of disseminated Nocardiosis or subcutaneous and CNS abscesses, surgical drainage will be required.

Here we will focus on pulmonary Nocardiosis since it is the most common presentation in our clinical practice and experience gained at our center.

Pulmonary Nocardiosis

Pulmonary Nocardiosis is considered an opportunistic disease with high morbi-mortality. It occurs by inhalation of aerial pseudomycelium fragments. Between 80-90% of pulmonary Nocardiosis are caused by the Nocardia asteroides complex (*N. asteroides sensu stricto*, *N. farcinica* and *N.nova*). The disease can be either local or disseminated. Its onset is subacute with non-specific respiratory manifestations (cough, fever and dyspnea being the most common symptoms) however cases of acute or chronic pulmonary Nocardiosis have also been described. Radiologically it may manifest in various ways, with the most characteristic manifestation being multiple infiltrates with tendency to cavitation [2] (Figures 1 and 2). One third of pulmonary Nocardiosis presents with empyema [1]. Nocardia is not transmitted from person to person so it does not require patient isolation. It does not belong to the commensal flora so isolation should be considered as infection. As described earlier, Nocardiosis is considered an opportunistic disease. Several risk factors have been described such as cellular immunodeficiency, chronic treatment with corticosteroids (both systemic and inhaled) and structural lung disease (bronchiectasis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis being among the most frequent) [1]. Given the non-specific clinical presentation and radiology, it is an under diagnosed disease with slow microbial growth (from 48 hours to 3 weeks) [5]. Diagnosis is made by clinical suspicion and confirmatory microbiology tests. Selective culture media such as modified Agar Tayer-Martin or Agar BCYE-α are used and for the weak acid-alcohol resistance, the Kinyoun stain will be helpful. The Polymerase Chain Reaction (PCR) and RNAr 16s sequencing will also help. The main samples used for diagnosis are sputum, blood culture and in case of empyema, pus. Series have been described in which up to 44% of cases have required invasive techniques for diagnosis such as fiberoptic bronchoscopy for Bronchioalveolar Lavage (BAL) and bronchial aspirate, or CT-guided fine-needle aspiration (CT-FNA). In these cases the sample performance improves, being positive between 85 and 95% of the cultures.

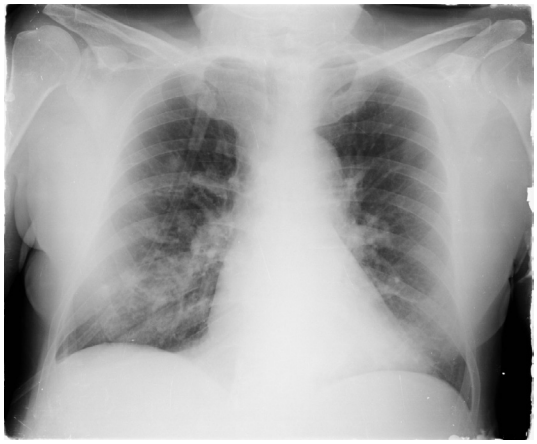

Figure 1: Chest X-ray showing consolidation of right lower lobe.

Nocardiosis in our Center

From 2007 to 2011, positive samples for Nocardia spp at our institution were reviewed, with a total of 12 patients of whom 75% were male and 25% female. The variables taken into account were; sample type, presence of immunosuppression, underlying lung disease, previous colonization by *Pseudomonas aeruginosa*, chronic treatment with corticosteroids, types of Nocardia infection and the treatment they received. The results in form of descriptive summary are shown here: Of the 12 positive samples for Nocardia spp, 10 were sputum (83%) and 2 blood cultures (17%). Of the 10 sputums, 6 were unimicrobial (only Nocardia spp was isolated) and 4 polymicrobial (isolated with Nocardia spp, in order of frequency; *Aspergillus, Candida albicans*, *S. aureus* and *S. maltophila*). Of the 12 patients, 1 had immunodeficiency disease (hypogammaglobulinemia), 1 had pharmacological immunosuppression (cyclophosphamide as treatment of vasculitis) and

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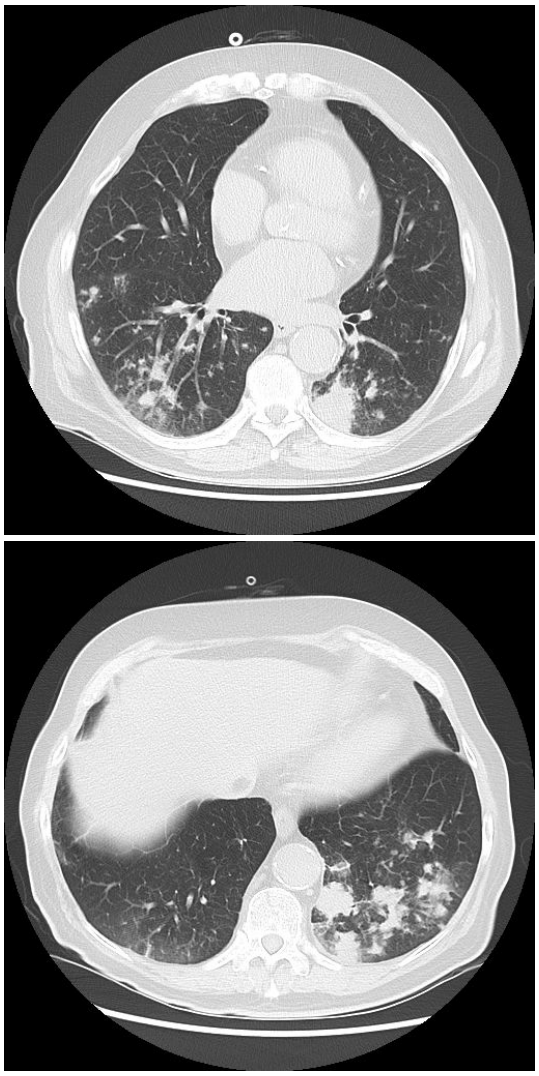

Figure 2: Pulmonary nocardiosis. Thoracic CT: multiple bilateral nodular infiltrates.

2 patients were diagnosed with Systemic lupus erythematosus (SLE) but were not receiving any immunosuppressant. We did not found any patient infected by the Human Immunodeficiency Virus (HIV). Of these 12 patients, 10 (83%) had structural lung disease; 6 chronic obstructive pulmonary disease (COPD) (2 patients were classified as GOLD II and 4 as GOLD III), 3 bronchiectasis and 1 possible COPD (no lung function tests were performed at diagnosis). Half of these 10 patients were previously colonized by *Pseudomona aeruginosa*. Of all patients, 9 (75%) received chronic treatment with corticosteroids: 4 systemic treatment (3 with prednisone and 1 with methylprednisolone) and 5 inhaled treatment (4 with fluticasone and 1 with budesonide both at medium doses). Of these 12 positive samples for Nocardia spp, 8 corresponded to pulmonary nocardiosis (66%), 2 disseminated nocardiosis (17%) and 2 were considered as chronic colonization (they were incidental findings in control sputums of patients without any kind of symptoms who shared bronchiectasis as a common feature). A mortality of 47% (5 passed away) was recorded. In 8 cases they received cotrimoxazole, the treatment of choice. The 4 remaining cases received alternative treatments: levofloxacin due to sulfonamides and penicillin allergy (1 case), amoxicillin clavulanic due to cotrimoxazole allergy (2 cases) and imipenem due to altered liver function (1 case).

Conclusions

Nocardiosis is an uncommon disease with a high morbi-mortality whose diagnosis is limited by low clinical suspicion, nonspecific clinic and radiological findings and slow growth of the microorganism. The most frequent form of presentation is pulmonary and its principal risk factors are immunosuppression, chronic treatment with corticosteroids and structural lung disease. The first line treatment is cotrimoxazole and its duration depends on the presentation and risk factors, ranging between 6 and 12 months. Chronic colonization has also been seen in patients diagnosed with structural lung disease, most commonly bronchiectasis [3]. The question of whether or not isolation of Nocardia in sputum is a colonization or is an infection is difficult to answer. In a review of 42 isolates, Rosset et al. found only 47% of the isolates corresponded to real infection. Ferrer et al. found real infection on 63% of patients [5,6]. Factors as bronchiectasis, corticoesteroids (inhaled or systemic), antibiotic therapy, polymicrobial sputum (in our data base *P. aeruginosa*, Aspergillus spp, *S. maltophila*, *S. aureus* and Candida spp) and the specific findings on chest X-Ray are factors that difficult the identification of infections caused by Nocardia [9]. In our patients, specific treatment for Nocardia improved symptomatology; this fact would suggest a real infection by Nocardia in those cases.

In conclusion, despite the small sample size, we have observed that the main risk factor was structural lung disease (specifically COPD), especially in those patients with advanced disease treated with long term corticosteroids [7,8]. Nocardia spp should be suspected as the etiologic agent in slowly resolving pneumonia, mainly in these types of patients [9]. Notifying the microbiology laboratory for culture in specific media, while performing bronchoscopy to obtain bronchial samples may also be indicated. As part of protocol a cranial CT scan should also be performed in any patients with pulmonary nocardiosis in order to rule out CNS infection and therefore disseminated nocardiosis [2].

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