Case report

Pulmonary nocardiosis: A Single Center Study

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ABSTRACT

Objectives: Nocardiosis is a rare infection caused by Nocardia spp., a gram-positive bacteria non-commensal of the human flora. Nocardiosis usually presents with lung infection but may disseminate to other organs, most frequently the brain. The major risk factor is immunosuppression, but lung diseases also increase the risk of infection. Treatment with antibiotics is usually prolonged. In this study, we made a retrospective analysis of pulmonary nocardiosis cases and a review of the available literature.

Methods: We made a retrospective analysis of all pulmonary nocardiosis cases from 13 years (January 2005 to December 2017) in our institution, selecting patients from pulmonology and infectious diseases consultation.

Results: We found four patients diagnosed with pulmonary nocardiosis, three males (patients 1, 2 and 3) and one female (patient 4). Median age was 71 ± 15 years old. Different specimens were identified (N. cyriacigeorgica, Nocardia spp., N. nova, and N. wallacei/transvalensis). Bronchofiberoscopy with bronchoalveolar lavage culture was the most frequent diagnostic procedure (patients 1 and 4). Only patient 2 presented an unfavorable response to treatment and died from septic shock.

Conclusions: Pulmonary nocardiosis has a good prognosis if diagnosed early and treated adequately. It should always be considered in the differential diagnosis of pulmonary infections concomitant with brain or other soft tissue lesion, especially in immunocompromised patients.

1. Introduction

Nocardiosis is an infection caused by Nocardia spp., a gram-positive aerobic bacteria non-commensal of the human flora, usually found in soils, decomposing organic matter, water or air. Hence, its microbiological identification in human samples is highly suggestive of infection [1–9]. The prevalence of the disease is currently unknown, due to the scarce reported cases. However, it appears to be gradually increasing, mostly due to higher clinical suspicion and improvement of diagnostic methods. Despite this, pulmonary nocardiosis remains a rare infection [10].

The main risk factor for infection is immunosuppression (prolonged corticosteroid therapy, malignancy, organ transplantation, or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)). However, nocardiosis may also affect immunocompetent individuals, in 33% of cases, and should not be considered an opportunistic infection. Other important risk factors include male gender (3:1 ratio), diabetes mellitus, alcohol abuse, alveolar proteinosis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, tuberculosis and Mycobacterium avium complex (MAC) infections [2–6,8,9,11–13]. It can be caused by inhalation of dust particles or result from nosocomial infection in patients with injured skin, such as catheterized patients or those submitted to surgical procedures. There is no evidence of human-to-human transmission [3].

Nocardia spp. may cause focal or systemic infections. The main form of presentation is pulmonary disease, in 73–77% of cases [2–4,7]. Exclusive pulmonary forms of infection occur in 39% of all cases, and up to 50% disseminate to other organs, usually the brain [1]. Nocardia asteroides complex (N. asteroides, N. farcinica, N. nova, and N. transvalensis complex) is responsible for 85% of nocardiosis and most of pulmonary cases [1–3,7]. There are no pathognomonic signs or symptoms of the disease, but they usually include fever, cough, chest pain, nocturnal
sweating and/or weight loss. For these reasons, nocardiosis should be suspected in the presence of cerebral or skin lesions, concomitant with recent pulmonary radiological changes [3,6].

Common radiographic findings include nodules, diffuse reticulonodular infiltrates or, sometimes, pleural effusions. Some cases present with empyema. Thorax computed tomography (CT) scan usually shows multifocal consolidations, but also solitary or multiple nodules (more common in the disseminated disease), abscess or cavitary lesions (33% of patients). Upper lung lobes are usually more affected and the combination of these findings with unspecific clinical manifestations commonly lead to misdiagnosis with tuberculosis, fungal disease or malignancy [1,6,9].

The microbiological identification of the bacteria is usually a difficult and slow process [8]. However, faster molecular methods are available: polymerase chain reaction (PCR), polymorphisms analysis, 16S ribosomal RNA or DNA sequencing, which is, currently, the favorite technique [2,3,5-7].

There is no consensual treatment in nocardiosis, and so, antibiotic susceptibility test (AST) is required [11]. In most cases, empiric treatment with trimethoprim-sulfamethoxazole (TMP-SMX), 5–10 mg/kg (TMP) and 25–50 mg/kg (SMX), divided in 2–4 daily doses, is preferred until further adjustment based on AST results [2,3,5,9,11]. Higher doses can be used in extensive disease. In severe cases, imipenem/meropenem and/or amikacin may be added to the antibiotic regimen [2,11]. Treatment duration is prolonged and depends on the severity of the disease, immunocompromise and clinical evolution. Usually it is recommended a total of 6–12 months of treatment, but it can be extended in immunocompromised patients or in cases of central nervous system involvement [9,11]. Some cases of abscess and empyema may need surgical intervention for drainage and debridement [1].

In this study we aimed at making a retrospective analysis of all cases from our institution and review the available literature on pulmonary nocardiosis.

2. Materials and methods

2.1. Study design

We performed a retrospective single center analysis of all cases of pulmonary nocardiosis, between January 2005 and December 2017. We used our institutional software SClinico and SAM to obtain clinical data.

2.2. Data collection

We collected relevant clinical information, including age, gender, smoking habits, previous lung disease and risk factors for immunosuppression, clinical manifestations, analytical findings (C-reactive protein (CRP), leukocytes, neutrophils, arterial blood gases), radiological findings (chest radiograph and CT scan), presumptive diagnosis, length of stay, identified microorganisms and respective diagnostic procedure, treatment and follow-up, to analyze and compare between patients.

Diagnostic procedures included bronchoalveolar lavage, sputum, blood cultures or tissue biopsy. Diagnostic molecular techniques included genetic sequencing procedures for microorganism identification.

2.3. Patient eligibility

In this study, all cases of nocardiosis were selected for analysis. Patients with no pulmonary involvement were excluded.

2.4. Data analysis

Patients’ characteristics and clinical data were summarized for comparison. Mean and median values were calculated with IBM SPSS Statistics v23.

2.5. Ethics approval

This study was approved by our Hospital Ethics Commission and Administrative Council.

3. Results

3.1. Study population

A total of four patients were diagnosed with pulmonary nocardiosis: three men (patients 1, 2 and 3) and one woman (patient 4). Median age was 71 ± 15 years old. Patients characteristics are summarized in Table 1 for comparison.

3.2. Cases description

3.2.1. Clinical case 1

Male patient, 75 years old, former smoker (20 pack-year units (PYU)), with clinical background of idiopathic lymphopenia, bronchiectasis and previous MAC infection (completed 11 months of treatment with clarithromycin and ethambutol). Due to new onset of constitutional symptoms with 6-months evolution, a thorax CT scan was performed. It showed bilateral consolidations and micronodules with tree-in-bud pattern in the left upper lobe (Fig. 1). He was submitted to bronchofibroscopy with bronchoalveolar lavage, which allowed the identification of *Nocardia cyriacigeorgica* in microbiological culture. The patient was hospitalized with the diagnosis of pulmonary nocardiosis. Extrapulmonary sites of infection were excluded by cranial magnetic resonance imaging (MRI), lumbar puncture with cerebrospinal fluid analysis, abdominal CT scan and ophthalmologic examination. He was treated with intravenous imipenem and TMP-SMX for 4 weeks, with good clinical evolution. At hospital discharge, he kept follow-up in infectious diseases consultation, completing 12 months of oral TMP-SMX, with good clinical and radiological evolution.

3.2.2. Clinical case 2

Male patient, 77 years old, former smoker (40 PYU), with clinical background of COPD and bronchiectasis. He was admitted in the Emergency Room (ER) for dyspnea, non-productive cough and fever. Chest radiograph revealed increased cardiothoracic ratio with nodular opacities predominant in the lower lung fields (Fig. 2). It was assumed a COPD exacerbation due to acute tracheobronchitis with congestive heart failure exacerbation. He started treatment with amoxicillin-clavulanate, for 10 days, with good analytical response, but with no clinical resolution of symptoms. Due to the persistence of fever, antibiotic treatment was changed to piperacillin-tazobactam and vancomycin. Thorax CT scan was performed, showing bilateral consolidations with air bronchogram, suggestive of nosocomial bilateral pneumonia (Fig. 2). *Nocardia* spp, was identified in blood cultures, and TMP-SMX added to antibiotic regimen. However, the patient presented unfavorable evolution, development of septic shock with multiorgan dysfunction, refractory to all therapeutic measures, and died.

3.2.3. Clinical case 3

Male patient, 60 years old, with clinical background of idiopathic thrombocytopenic purpura treated with long-term corticosteroid therapy. He was admitted in the ER for hemoptysis and pleuritic chest pain. He was hospitalized and underwent a thorax CT scan that showed a consolidation in the lung lingula and diffuse nodules (Fig. 3). He was diagnosed with community-acquired pneumonia (CAP) and ceftriaxone with azithromycin was initiated empirically. Considering the patient was immunocompromised, bronchofibroscopy was performed and showed no evident endobronchial lesions. Bronchoalveolar lavage analysis revealed inflammation, no evidence of malignant cells, and the
In the ER, the following month, with abdominal pain, vomiting and fever, the patient was admitted. Abdominal CT scan revealed a retroperitoneal adenopathy conglomerate. In the suspicion of a metastatic lung cancer, excisional biopsies of chest and cervical nodules were performed, with no identification of malignant cells or microbiological agent. Sputum samples, however, allowed the identification of Nocardia nova, and so, treatment with TMP-SMX, ceftriaxone and amikacin was initiated (after the AST results), for 6 weeks. To confirm the possibility of disseminated disease, the patient underwent a forearm subcutaneous nodule biopsy. Microbiological analysis identified the same microorganism, confirming the diagnosis of a disseminated nocardiosis, affecting lung, skin and retroperitoneal regions. After hospital discharge, with clinical improvement, he completed maintenance treatment with oral TMP-SMX, for 12 months.

### Table 1

| Characteristics                  | Patient 1          | Patient 2          | Patient 3          | Patient 4          | Median ± IQR |
|----------------------------------|--------------------|--------------------|--------------------|--------------------|--------------|
| Age (years)                      | 75                 | 77                 | 60                 | 66                 | 71 ± 15      |
| Gender                           | Male               | Male               | Male               | Female             |              |
| Smoking habits                   | Former smoker      | Former smoker      | None               | None               |              |
| Lung disease                     | Bronchiectasis, MAC infection | COPD, bronchiectasis | None | Bronchiectasis |              |
| Immunosuppression                | Idiopathic lymphopenia | Constitutional symptoms | None | None |              |
| Clinical manifestations          |                    |                    |                    |                    |              |
| Analytical findings              |                    |                    |                    |                    |              |
| CRP (mg/L)                       | 157.4              | 40                 | 23,2               | 3,8                | 31.6 ± 119.4 |
| Leuk (EXP3/µL)                   | 11.4               | 8.6                | 2                  | 7.39               | 8 ± 7.4      |
| Neutr (%)                        | 89.5               | 71.1               | 74.5               | 47.1               | 72.8 ± 32.7  |
| Blood gases                      | No RF              | Hypoanemic RF      | No RF              | No RF              |              |
| Chest radiograph                 | Nodular opacities (right middle lung field) | Bilateral nodular opacities | No RF | NA |              |
| Thorax CT scan                   | Bilateral consolidations, micronodules, tree-in-bud pattern | Diffuse consolidations with air bronchogram | Consolidation with air bronchogram in the lingula, diffuse nodules | Bilateral micronodules, tree-in-bud pattern |              |
| Presumptive diagnosis            | Infected bronchiectasis | Acute tracheobronchitis, heart failure | CAP | CAP/Infected bronchiectasis |              |
| Hospitalization (days)           | 30                 | 28                 | 49                 | 30 ± 12            |              |
| Microorganism                    | N. cyriacigeorgica | Nocardia spp.      | Nocardia nova      | N. wallacei/N. transvalensis |              |
| Diagnostic procedure             | BFC with BAL       | Blood cultures     | Sputum culture, nodule biopsy | BFC with BAL |              |
| Definite diagnosis               | Pulmonary nocardiosis | Pulmonary nocardiosis with sepsis | Disseminated nocardiosis | Pulmonary nocardiosis |              |
| Treatment                        | Imipenem + TMP-SMX (iv, 4w), TMP-SMX (po, 12m) | TMP-SMX (iv) | TMP-SMX + Ceftriaxone + Amikacin (iv, 6w), TMP-SMX (po, 12m) | Favorable | 13 ± 4(m) |
| Outcome                          | Favorable          | Unfavorable        | Favorable          | Favorable          |              |

IQR, Interquartile range; PYU, Pack-year units; MAC, Mycobacterium avium complex; COPD, Chronic obstructive pulmonary disease; ITP, Idiopathic thrombocytopenic purpura; CST, Corticosteroid therapy; CRP, C-reactive protein; Leuk, Leukocytes; Neutr, Neutrophils; RF, Respiratory failure; NA, not available/applicable; CAP, Community-acquired pneumonia; BFC, Bronchofibroscopy; BAL, Bronchoalveolar lavage; TMP-SMX, Trimethoprim-sulfamethoxazole; PCR, Protein-chain reaction; iv, intravenous; po, oral dosing; w, weeks; m, months.

### Fig. 1. Patient 1 radiological findings. A: Chest radiograph (posteroanterior incidence) shows bilateral nodular opacities, more evident in the right middle lung field. B: Thorax CT scan shows bilateral ground-glass and consolidations (posterior segment of right upper lung lobe), centrifibulous micronodules with tree-in-bud pattern (apicoposterior segment of left upper lung lobe).

### Fig. 2. Patient 2 radiological findings. A: Chest radiograph (posteroanterior incidence) shows increased cardiothoracic ratio and bilateral nodular opacities, in both lower lung fields, more evident in the right lung. B: Thorax CT scan shows bilateral multifocal consolidations with air bronchogram and ground-glass densifications.
COPD and/or bronchiectasis (patients 1, 2 and 4).

Three patients had structural lung disease, including constitutional symptoms (asthenia, anorexia, non-quantified weight loss). Only two patients (2 and 4) presented with fever at hospital admission. Only patient 3 presented extrapulmonary manifestations of nocardiosis. No patient had suspicion of pulmonary nocardiosis at hospital admission. Main presumptive diagnosis were CAP and infected bronchiectasis.

To achieve definite diagnosis of nocardiosis, the isolation of the bacteria was necessary. It was made with bronchofibroscopic bronchial lavage with microbiological culture of the respiratory samples (patients 1 and 4), blood cultures (patient 2), sputum culture and nodule biopsy (patient 3).

The length of hospital stay was 30 ± 12 days. Patient 4, the only patient who didn’t require hospitalization, kept regular follow-up in pulmonology consultations.

All patients began treatment with empiric antibiotic regimen at hospital admission, assuming a diagnosis of CAP, acute tracheobronchitis or infected bronchiectasis.

After the establishment of the correct diagnosis, patients 1 and 3 started intravenous treatment (mean duration of 5 weeks) with TMP-SMX associated with imipenem (patient 1), or ceftriaxone and amikacin (patient 3). At discharge, both kept treatment with oral TMP-SMX for 12 months. Patient 2, who also started intravenous TMP-SMX, presented with unfavorable evolution and did not finish treatment. Patient 4, who didn’t require hospitalization, was treated with TMP-SMX and amoxicillin-clavulanate, orally, for 6 months.

Globally, antibiotic treatment time was 13 ± 4 months. Excluding patient 2, all cases presented good clinical, analytical and radiological response to treatment.

Patient 2 was the only one who presented unfavorable evolution, dying in the context of septic shock from pulmonary nocardiosis, refractory to all therapeutic measures.

4. Discussion

Pulmonary nocardiosis is a rare infection with a progressively increasing number of reported cases, concomitant with the increasing number of immunocompromised patients. It affects mainly the respiratory system, but may disseminate to any organ. When dissemination occurs, up to 50% of cases, brain tissue is the most frequent site [1–3,5,7]. In this study, all cases had pulmonary nocardiosis and in one case (patient 3) there was also extrapulmonary dissemination, affecting the skin and retroperitoneal region. No patient had central nervous system lesions, excluded by cerebrospinal fluid analysis, brain CT or MRI scans.

Symptoms are unspecific and commonly seen in common disorders like CAP. To achieve early diagnosis it is crucial to have clinical suspicion of pulmonary nocardiosis in the presence of lung infection concomitant with cerebral, skin or other soft tissues lesions, especially in
patients with risk factors for immunosuppression or structural lung disease [3,6]. Two patients in this study had no risk factors for immunosuppression, besides structural lung disease (patients 2 and 4). A higher prevalence of the disease among male individuals has been reported, as seen in this population.

*Nocardia asteroides complex* was predominant in this population (including *N. nova* and *N. transvalensis*, identified in patients 3 and 4, respectively), in accordance with the literature. Patient 2 had *Nocardia* spp. identified in blood cultures, although this diagnostic method only rarely allows the identification of this bacteria.

Pulmonary nocardiosis is commonly misdiagnosed with fungal infection, tuberculosis or malignancy, leading to a delay in the correct diagnosis, treatment and worsening of prognosis, usually favorable [1–3,5,7]. In this study, one of the patients had unfavorable outcome and died. Antibiotic treatment is prolonged, as seen in the described clinical cases (13 ± 4 months). However, relapse or disease progression is frequent, despite the treatment [1,2]. In a review study, the mortality attributed to nocardiosis was 38.7%, increasing to 64% in cases of disseminated disease, or even up to 100% if there was central nervous system infection. Therefore, it is fundamental to search for signs of disseminated disease at the diagnosis [9].

5. Conclusion

In this review of 13 years from our institution, we found only four cases of pulmonary nocardiosis. Nocardiosis is a rare disease with good prognosis, if diagnosed early and treated adequately. It should be suspected in the presence of pulmonary infection concomitant with brain or other soft tissue lesion, especially in immunocompromised patients.

Study institution

This study was conducted in Pedro Hispano Hospital, Matosinhos, Portugal.

Authors contributions

Every author was involved in the conception and planning of the study, analysis and interpretation of the results, redaction and/or revision of the article.

Sponsorship

None to declare.

Declaration of competing interest

None.

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