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Pulmonary nocardiosis in Chronic Obstructive Pulmonary Disease: A new clinical challenge

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Abstract

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Pulmonary nocardiosis (PN) is a rare but severe disease caused by *Nocardia* spp. Despite the traditional description as opportunistic infection, case reports and case series of pulmonary nocardiosis have recently been reported in immunocompetent patients too, in particular among people with chronic pulmonary diseases such as advanced Chronic Obstructive Pulmonary Disease (COPD).

PN is characterized by non-specific symptoms and radiological findings; bacteriological culture can be difficult. For the reasons above, diagnosis of PN is challenging, sometimes resulting in a misdiagnosis of tuberculosis.

We report an interesting case of PN in a 75-year-old male with COPD. He complained a 3-months history of fatigue, evening rise in body temperature, night sweats, unexplained weight loss of 5 kg, worsening dyspnea, cough and mucopurulent sputum. The chest X-ray showed multiple nodules with cavitations bilaterally in the apical and subclavian regions. *Nocardia cyriacigeorgica* with 100% identity was identified in three sputum samples.

Since the patient has never undergone a systemic and/or inhaled steroid therapy, and has no respiratory failure and comorbidities entailing immunodepression, it is conceivable that, in this immunocompetent patient, the COPD could represent an isolated risk factor for PN.

Risk factors, clinical presentations, radiographic findings, differential diagnosis and review of the literature of PN cases in COPD, pointing out the similarities and differences, are also described.

Keywords: Pulmonary nocardiosis, Opportunistic infections, Chronic obstructive pulmonary disease, Tuberculosis
Abbreviations: Chronic Obstructive Pulmonary Disease, COPD; Human Immunodeficiency Virus, HIV; High Resolution Computed Tomography, HRCT; Pulmonary Nocardiosis, PN; Tuberculosis, TB; trimethoprim-sulfamethoxazole, TMP-SMX

1. Introduction

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Pulmonary nocardiosis (PN) is a rare but severe opportunistic infectious disease caused by *Nocardia* spp. The microorganism was first isolated by Edmond Nocard in 1888 from cattle with bovine farcy [1]; Eppinger reported the first human case of nocardiosis in 1890 [2]. The bacteria is commonly found in long standing dust, soil and stagnant water. Aerosol route is the main portal of entry into the body; direct inoculation as result of trauma or intravenous drug assumption or, more rarely, ingestion of contaminated food have also been described [3]. Human-to-human transmission has not been documented [4], [5].

The prevalence of PN is not known. Traditionally, PN has been described in immunocompromised patients, with human immunodeficiency virus (HIV) infection, alcohol abuse, diabetes mellitus, organ transplantation and lymphoreticular neoplasm as the most frequently associated conditions [4], [5]; lung transplant patients have the highest frequency of PN among recipients of solid organs [6]. Iatrogenic immunosuppression is a further risk factor, with long-term steroid, chemotherapeutic immunosuppressive and anti TNF-α agents as the most commonly associated drugs [4], [5], [6], [7], [8]; in particular, chronic steroid therapy has been highlighted in 36% [8], 62.2% [9] and 64% [4] PN patients in three reviews. Intravenous drug abuse has also been described [10].

Commonly, PN presents as a subacute or chronic disease, with a marked tendency towards remissions and exacerbations. It is characterized by non-specific symptoms such as low fever, night sweats, weight loss, cough, expectoration, dyspnea and chest pain; radiological findings include areas of consolidation, nodules and cavitations which are not pathognomonic [4]. Bacteriological culture can be problematic too. Therefore the clinical and imaging presentation can be very similar to tuberculosis (TB) which represents one of the differential diagnosis [11], [12]. Mortality is very high, ranging from 14 to 40% and increasing to 60–100% in patients with dissemination to the central nervous system [5], [13]. Life-saving treatments are widely available: trimethoprim-sulfamethoxazole (TMP-SMX) is often used alone, but combination therapy is recommended and should continue until clinical patient improvement occurs and Nocardia species identification and antimicrobial drug susceptibility information can be confirmed; single-drug therapy may suffice thereafter [14].

In recent years, nocardiosis has been described among immunocompetent patients, both as isolated cases and case series, in lungs and other sites [15], [16], [17], [18], [19], [20]. They can represent from 33% to 56% of total cases [21], [22]. In particular, among patients with chronic respiratory diseases, Chronic Obstructive Pulmonary Disease (COPD) and bronchiectasis have been found as predisposing factors [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39]. Despite reports in literature are limited, COPD is considered the third most common risk factor, surpassed only by chronic steroid treatment and solid organ transplantation [4], [33], [40], [41], [42].

Moreover, COPD life expectancy can be strongly affected by PN: a mortality rate of 17% within the first month and 33% within the first year from diagnosis of PN have been reported [42]. In comparison, the mortality rate for acute exacerbation of COPD is 8% during hospital stay and 23% after 1 year of follow-up [43].

Here we present a case of PN mimicking TB in a patient with undiagnosed COPD.

2. Case presentation

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A 75-year-old white male, weighing 65 kg, presented to our center with complaints of a 3-months history of fatigue, evening rise in body temperature, night sweats, unexplained weight loss of 5 kg, worsening dyspnea, cough and mucopurulent sputum. He was a current smoker (30 pack/years) and worked in a stone quarry up to 12 years before; he had a history of chronic catarrhal bronchitis, benign prostatic hypertrophy and an intestinal polypectomy. He denied performing spirometry and taking systemic or inhaled corticosteroids; a chest x-ray of 3 years before showed rarefaction of bronchovascular tree.

On examination, he was afebrile and reduced vesicular murmur and widespread rhonchi were heard on auscultation of the chest. Remainder of the physical examination was unremarkable.

Blood tests showed neutrophilic leukocytosis (white blood cells 16500/mL, 70% neutrophils), mild anemia (hemoglobin 11,4 g/dl), moderate increase in serum inflammatory markers (erythrocyte sedimentation rate 72 mm/h,

C-reactive protein 20 mg/l). Plasma immunoglobulin, liver and renal function were in the normal range and HIV antibody testing was negative.

A spirometry test was performed, revealing a severe obstructive ventilation defect, post b2 agonist Forced Vital Capacity of 72% and Forced Expiratory Volume in one second of 46% predicted. The chest X-ray showed, bilaterally in the apical and subclavian regions, sclerosis and multiple nodules with cavitations (Fig. 1). The chest high resolution computed tomography (HRCT) was reported as following: "Multiple nodular opacities are recognized in the upper lobes, in the apical segments of the lower lobes and in subpleural location; small and regular central cavitations are there in some of these lesions. Multiple focal points of "tree in bud" and bronchiectasis, with prevalent cystic type, in both lung apices are also present. No significant mediastinal lymphadenopathy. These findings are consistent with chronic TB" (Fig. 2).

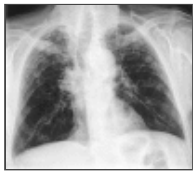

Fig. 1
Chest X-ray showing sclerosis and multiple nodules with cavitations in upper and medium lung zones bilaterally.

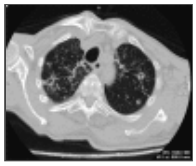

Fig. 2
Chest HRCT scan showing multiple nodular lesions with cavitations in upper lung zone bilaterally.

Three sputum samples on three different days were collected and submitted for the search of *Mycobacteria* spp. Specimen were digested and decontaminated according to Kubica procedure; sputum smears for acid-fast bacilli examination using Kinyoun staining and culture on solid (Löwenstein–Jensen) and liquid medium (Mycobacteria Growth Indicator Tube) were then prepared. The microscopic examination showed filamentous, slim, branched (mycelium and hyphae), blue-to-fuchsia colored (acid-alcohol variable) elements (Fig. 3). *Nocardia* spp. was suspected and confirmed by Gram staining (not shown) and blood agar culture (Fig. 4). Culture on Löwenstein–Jensen medium is showed in Fig. 5. All the previous exams were negative for *M. tuberculosis*.

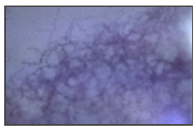

Fig. 3
Kinyoun-stained sputum sample showing filamentous, slim, branched (mycelium and hyphae), blue-to-fuchsia colored (acid-alcohol variable) elements.

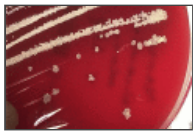

Fig. 4
Sputum culture on blood agar showing wrinkled chalky white or cream-to-pink colored colonies.

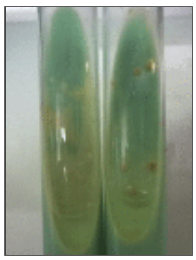

Fig. 5
Sputum culture on Lowenstein-Jensen showing wet salmon-to-yellow colored colonies.

Genotypic identification was performed by amplification and sequencing of a DNA fragment coding a rRNA 16S (Applied Biosystem, USA). Sequences were compared with the reference ones present in the GenBank database through BLAST and *Nocardia cyriacigeorgica* with 100% identity was identified.

Minimal inhibitory concentrations were determined on Mueller Hinton Agar following a 24 h incubation at 37 °C (Etest, BioMérieux). Results were revised and interpreted according to CLSI criteria: amikacin 0.25 μg/mL; amoxicillin plus clavulanic acid (8 μg/mL); ceftriaxone (1 μg/mL); cefepime (2 μg/mL); ciprofloxacin (4 μg/mL); clarythromycin (4 μg/mL); imipenem (0.38 μg/mL); linezolid (0.50 μg/mL); tobramycin (0.047 μg/mL); trimethoprim plus sulfonamide (0.006 μg/mL).

Patient was then started on trimethoprim-sulfamethoxazole (160/800 one tablet twice per day) for 6 months. Following this, a rapid improvement of symptoms, regression of the purulent sputum and of the neutrophilic leukocytosis had been achieved. A second chest radiograph was performed 2 months later, showing an improvement of radiological findings too. A spirometry test was then repeated, confirming the suspect of COPD; specific therapy was started.

The patient gave an informed consent for the case report.

3. Discussion

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Although nocardiosis is a rare disease, the clinical suspicion even in immunocompetent patients and the microbiological warning can lead to an early diagnosis and a life-saving treatment. Our case represents a typical presentation of PN with clinical and radiological findings mimicking TB.

3.1. Which patients should be suspected of PN?

Characteristics of PN may be summarized as follows. The disease is more common among males (73%) [20], [41]. The mean age is 66 years, even if it can be higher in COPD cases or lower among organ transplant recipients and patients with HIV or pulmonary alveolar proteinosis [4], [44]. As already mentioned in Section 1, symptoms of PN are far from being specific. Among the laboratory tests, neutrophilic leukocytosis and elevated C-reactive protein levels are commonly seen in patients without HIV infection, leukopenia in patients with HIV infection [5], [20], [42], [45].

3.2. Which is the radiological presentation of PN?

As already mentioned in Section 1, radiographic findings are also non pathognomonic. Very scanty information is available in the literature about PN on HRCT. The predominant presentation is a bilateral involvement with areas of consolidations, sometimes associated with cavitations; nodules with or without cavitation are most common in HIV-infected patients [46], [47], [48], [49], [50]. According to two recent reviews, other findings may include masses, bronchial wall and septal line thickening, bronchiectasis, ground glass opacity and a crazy paving appearance around the previous lesions which are in general more common in middle rather than peripheral areas; intrathoracic lymphadenopathy, pleural effusion and pericardial effusion have also been described [22], [51].

3.3. How can the clinical and radiological suspect of PN be confirmed?

The diagnosis of PN requires isolation and identification of the organism from a clinical samples: sputum, tracheal aspiration or bronchoalveolar lavage. Sputum samples can be diagnostic in 77–90% patients. The physician should inform the laboratory about the suspect in order to increase the overall accuracy of the exam. Specimen should first be processed and stained for microscopy, then cultured for at least 48–72 hours; typical stains include modified acid-fast and Gram stains. When isolated, biochemical reactions and enzymatic tests based on a panel of a nine conventional phenotypes can be used for the rapid identification of the most common *Nocardia* spp. [52]. Molecular techniques (polymerase chain reaction, restriction enzyme, 16S rRNA gene sequencing) are also available, even if restricted to referral laboratories. In patients intolerant to sulfonamides, in severe cases and in refractory cases, an antimicrobial susceptibility testing should be performed [4], [28], [53].

3.4. Differential diagnosis

TB, Pneumonia, carcinoma or abscessus are the most common diseases with a similar presentation.

Based on clinical and imaging findings, fungal infections (aspergillosis, zigomycosis, hystoplasmosis, blastomycosis, cryptococcosis), bacterial infections (mycobacterial infections, actinomycosis and *Rhodococcus equi* infections) and malignancies (primary and secondary lung cancer) should all be considered in differential diagnosis of PN. Based on HRCT, pulmonary abscess, septic emboli, sarcoidosis, Wegener granulomatosis should also be taken into consideration when multiple nodules with cavitation are present [14].

The most important differential diagnosis is Mycobacterial infection, including *Mycobacterium tuberculosis* and non-tuberculosis species. As already stated in Section 1, PN can mimic TB because of both similar clinical presentation and radiological findings; this can easily lead to an initial unconfirmed diagnosis of TB. Cases of concurrent PN and TB especially in HIV-infected patients are also reported in literature. According to some case series, more than two thirds of PN cases were initially misdiagnosed with TB and about 5% of the patients with proven pulmonary TB were shown to be co-infected by *Nocardia* spp [11], [12], [35], [45], [54], [55], [56], [57], [58], [59], [60]. Concurrent infection of PN and *Mycobacterium avium-intracellulare complex* and PN and aspergillosis have also been reported [29], [61], [62].

3.5. Is truly COPD an isolated risk factor for PN?

The main characteristics of PN case series and PN single case in COPD reported in literature are listed in Table 1 and Table 2, respectively. A significant association between PN and COPD is evident, but the analysis of case series and case reports shows that many patients have a severe COPD with respiratory failure and/or other comorbidies and coinfections.

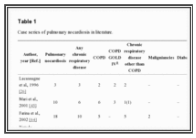

Table 1

Case series of pulmonary nocardiosis in literature.

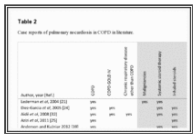

Table 2

Case reports of pulmonary nocardiosis in COPD in literature.

In particular, it has been argued that COPD patients generally receive chronic systemic and/or inhaled steroid [35], which could be confounding when considering lung disease as the only risk factor; this is considered to be true at least in two COPD phenotypes: COPD with frequent exacerbations and COPD with presence of bronchiectasis.

Four patients - one per each of the following case series: Valerio Minero et al. [9], Chedid et al. [13], Hui et al. [29], Mari et al. [45] - had no comorbidities and did not undergone systemic steroid treatment; but no additional information on spirometry and chronic inhaled steroid therapy was reported on those patients and no emphasis was given to the COPD as only risk factor. The only clinical case with features similar to our patient is the one described by Rivière et al. [23]: given that the patient had never undergone a chronic oral and/or inhaled steroid therapy, the Authors questioned themselves whether COPD could represent a single risk factor for PN. However, their patient had suffered from bronchiectasis after pulmonary tuberculosis many years before.

However, as noted by some Authors, this confounding factors is usually brief and doesn't cause a significant impairment of cellular immune responses: the review of Stuck et al. shows that patients administered with <10 mg/day or a cumulative dose of <700 mg of prednisone have similar infectious rates of the general population [34]. Apart from the possible use of steroids, patients with COPD may have an increased susceptibility to bacterial and fungal infections for several reasons, such as a change in bronchial architecture, mucociliary dysfunction, epithelial damage, frequent hospitalization or antibiotic treatments, and comorbidities [4], [23], [63]. Moreover, in some case in immunocompetent patients genetic factors could play a role in determining susceptibility to infection [23].

4. Conclusions

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PN is an infrequent but challenging disease which should always be considered both in immunocompromised and immunocompetent patients. Symptoms, signs and imaging features (chest X-ray, HRCT) can mimic other diseases, in particular TB, therefore a high order of suspicion is crucial for a prompt microbiological evaluation and a life-saving treatment.

COPD is commonly considered a risk factor for PN. The reported case - COPD patient with no respiratory failure, never treated with systemic and inhaled steroid therapy and without comorbidies–is an exemplary case for having COPD as the only risk factor for PN. Whether COPD on its own is able to promote PN is still unclear and requires further assessment.

Conflict of interest

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Dr. Giorgio Castellana has nothing to disclose. Dr. Anna Grimaldi has nothing to disclose. Dr. Marco Castellana has nothing to disclose. Dr. Claudio Farina has nothing to disclose. Dr. Giuseppe Castellana has nothing to disclose.

Funding sources

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