A CLINICAL CASE OF PULMONARY NOCARDIOSIS IN AN IMMUNOCOMPROMISED PATIENT

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ABSTRACT

Nocardia microorganisms are saprophytes, either non-pathogenic or pathogenic, causing nocardiosis. The clinically significant disease occurs in immunocompromised people, most often as pneumonia with cough, dyspnea, and fever. Antibiotic therapy, which is longer in time, is necessary. The main treatment is with sulfonamides, but the sensitivity of these bacteria varies. Therefore, the antibiotic susceptibility of the respective strain is important to apply combined therapy if needed. The risk of death without treatment is high, especially if the infection disseminates and the brain is involved. Antibacterial prophylaxis is therefore recommended in patients at high risk of nocardiosis. Our clinical case concerns an immunocompromised patient with isolated *Nocardia* from bronchoalveolar lavage (BAL).

Keywords: Nocardia, Aspergillus, MALDI TOF

INTRODUCTION

The species Nocardia are widespread saprophytes that can cause infections inhuman. These infections can be localized or disseminated, and are more common in immunocompromised patients (transplant on solid organs, HIV) (1, 2). Different Nocardia species are of medical importance. The most often isolated and responsible for most human infections are representatives of the former *Nocardia asteroides* complex. It includes *N. abscessus, N. brevicatena, N. farcinica, N. nova complex (N. africana, N. nova, N. veterana* and others (3). Nocardiosis is difficult to diagnose – clinically, radiologically, and histologically. *Nocardia nova* was isolated and first described by Tsukamura in 1982. Nocardia- microorganisms are gram-positive filamentous rods with branches. In culture, they require aerobic conditions, but growth on blood agar may require more than 48 hours. Literature on the role of this microorganism in lung infections is scarce (14). Clinical manifestations can vary from a cutaneous form, a pulmonary form to disseminated nocardiosis with the development of brain lesions and a mortality rate of over 85% (4). Nocardial endocarditis is suspected when there is no lung or central nervous system (CNS) involvement (5). In brain abscesses, CSF is positive in up to 20% of these cases (6). Pulmonary nocardiosis can most often appear with pneumonia, sometimes associated with cavitation (7). These infections can lead to pleural effusion, empyema, pericarditis, mediastinitis and, less often, to the development of local abscesses on the neck and chest wall.

Most often, the samples that are examined are sputum, broncho-alveolar lavage (BAL), exudate, or cerebrospinal fluid. In addition to cultural examination, the microscopic assessment is important. By Gram staining, branched delicate threads are visible. Histological examination by hematoxylin and eosin staining or Gomori staining is also very useful (8). These species are often acid-tolerant, unlike actinomycetes, which are generally not acid-tolerant.

Chest radiography in pulmonary nocardiosis usually shows consolidation, nodular lesions, cavitation, or abscesses. Computed tomography (CT) of the lungs can show the presence of an abscess earlier than plain radiography (12).

Regarding the therapy of nocardiosis, representatives of the following antimicrobial classes can be used: sulfonamides, aminoglycosides, beta-lactams, quinolones, macrolides and tetracyclines (18). The main drug of choice is trimethoprim-sulfamethoxazole (TMP-SMX), especially preferred in pulmonary nocardiosis. When TMP-SMX is not tolerated, the patient can be treated with the macrolide clarithromycin, although macrolides are less commonly used, possibly due to insufficient

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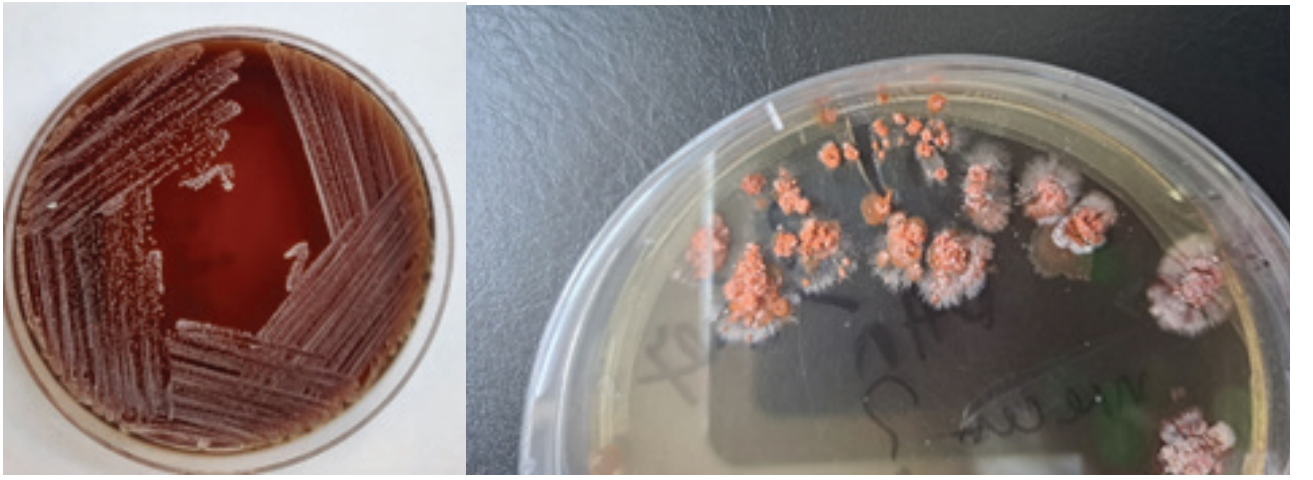

Figure 1. Macroscopic characterization of *Nocardia nova*

studies (9). The isolates of *Nocardia nova* are always sensitive to erythromycin (10).

Pathogenic Nocardia produces beta-lactamases and only 44% of *N.nova* isolates are sensitive to ampicillin (11). Most strains are resistant to cefuroxime, cefotaxime and ceftriaxone, although all isolates of *N.nova* are resistant to cefixime (12). Most *N.nova* isolates are resistant to ciprofloxacin and other quinolones (13). Combination therapies are also available to treat nocardiosis.

Here, we describe a clinical case with lung disease in which *Nocardia nova* was isolated from broncho-alveolar lavage (BAL).

MATERIAL AND METHODS

The patient was a 34-year-old woman diagnosed with bronchial asthma, bronchiectasis, and Churg-Strauss syndrome. She was on regular corticosteroid therapy. According to the epicrisis, she reported episodic epistaxis associated with atrophy of the nasal mucosa and a previous operation to remove the middle conch on the left. She was allergic to pollen and house dust. In addition, the patient had established iron-deficiency anemia, thyroid hypofunction, otitis media with hearing loss affecting both ears, as well as chronic glomerulonephritis.

Churg-Strauss syndrome is an inflammation of the blood vessels leading to restricted blood flow to tissues and organs, and possible permanent damage. It is also called "eosinophilic granulomatosis with polyangiitis (EGPA)". The most common symptom in adulthood is asthma. In our patient, the disease debuted with proteinuria, otitis, and granulomas in the lung.

The woman was hospitalized in a satisfactory general condition, adequate and oriented, with the aim of diagnostic and therapeutic clarification. Chest – normosthenic, with bilateral vesicular breathing, no wheezing, sinus rhythm on electrocardiogram (ECG). The paraclinical examinations demonstrated an erythrocyte sedimentation rate (ESR) of 51.0 mm/h, and C- reactive protein (CRP) of 46.0 mg/l, proteinuria was also detected.

A chest radiograph visualized inhomogeneous shadowing in the left lung base, consistent with an inflammatory infiltrate. Dilated bronchial lumens with thickened walls were seen in the parenchyma of the right lung.

Computed tomography (CT) showed bilateral maxillary sinusitis, frontal sinusitis, as well as bilateral mastoiditis. Chest CT was without evidence of pleural effusions. The lungs showed multiple nodular areas of varying density, most of them with scars of excavation. Peripherally dilated bronchial lumens with thickened walls and bronchiectasis were also seen.

The histologic lung examination visualised pulmonary parenchyma with fibrotic interstitium, perivasal fibrosis around thin-walled vessels, and reactive pneumocytes. Histology confirmed granulomatous vasculitis. The morphological picture was defined as non-specific for Churg-Strauss syndrome, possibly with pronounced post-therapeutic changes.

RESULTS AND DISCUSSION

During a fibro-bronchoscopy (FBS), broncho-alveolar lavage (BAL) was taken and sent for microbiological examination to the National Reference Laboratory

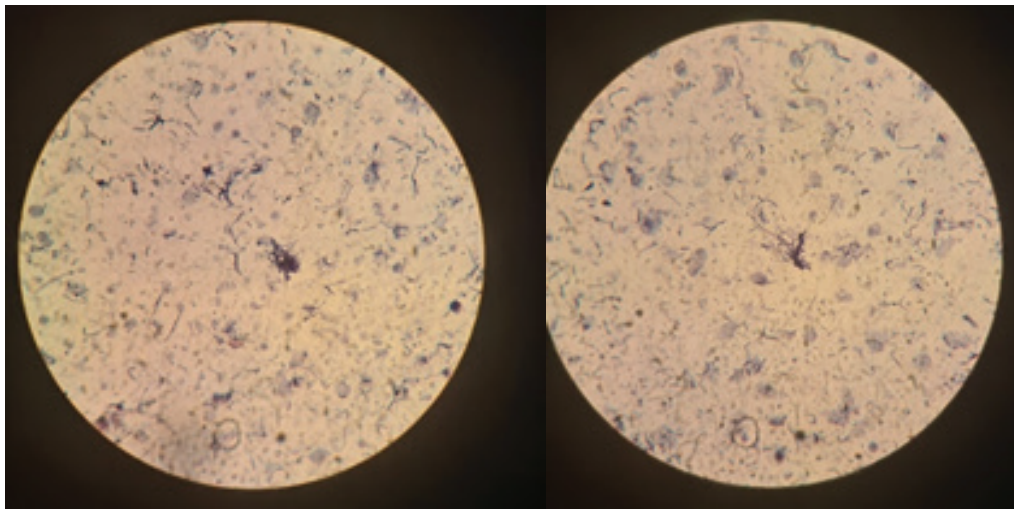

Figure 2. Microscopic characterization of *Nocardia nova*

"Mycoses" at the National Center of Infectious and Parasitic Diseases, Sofia.

ON microscopic examination by Gram staining, numerous leukocytes, lymphocytes, lymphoplasmic cells and epithelia were visualized. The cultural study on Blood Agar and on Sabouraud medium agar isolated no fungi. Instead, a microorganism with a whitish aerial and substrate mycelium, slightly buried in the agar (Fig. 1) was isolated. The microorganism was further identified by MALDI-TOF technology (Biotyper Bruker) as *Nocardia nova*.

The microscopic evaluation of the pure *N. nova* culture after Gram staining showed delicate gram-positive branched threads (Fig.2). Pathogenic *N. nova* act as facultative intracellular microorganisms in macrophages, where they inhibit the fusion of lysosomes with phagosomes (15).

The antimicrobial activity was evaluated by means of an antibiogram. The results are presented in Table 1.

The isolated *N. nova strain* was resistant to quinolones and aminoglycosides, to tetracyclines, and clindamycin. The bacteria also showed resistance to ampicillin and susceptibility to Amoxicillin/Clavulanic acid, probably because this was a beta-lactamase producing strain. Macrolide sensitivity for *N. nova* was expected.

According he European Committee on Antimicrobial Susceptibility (EUCAST 2022), there are data for interpretation only for gram-positive anaerobes, including Actinomyces, without specifying for representatives of Nocardia. Such criteria for interpretation are available at the Institute for Clinical and Laboratory Standards (CLSI) (12).

Given the demonstrated sensitivity of *Nocardia nova* to biseptol, (TMP/SMX), *p.o* was assigned as therapy in the next 6 months, as well as inhaled corticosteroid therapy.

After a control examination, FBS was performed and

Table 1. Results of the antibiotic susceptibility of *Nocardia nova*

Nocadia nova			
Ampicillin	R	Erythromycin	S
Amoxacillin/ Clav.acid	S	Clindamycin	R
Rifampicin	R	Tetracycline	R
Imipenem	S	**TMP/SMX ***	S
Ceftriaxone	S	Linezolid	S
Cefixime	R	Ciprofloxacin	R
Cefepime	S	Levofloxacin	R
Cefotaxime	S	Gentamycin	R

* *TMP/SMX – Trimethoprime-Sulfametoxazole*

S-susceptible R- resistent

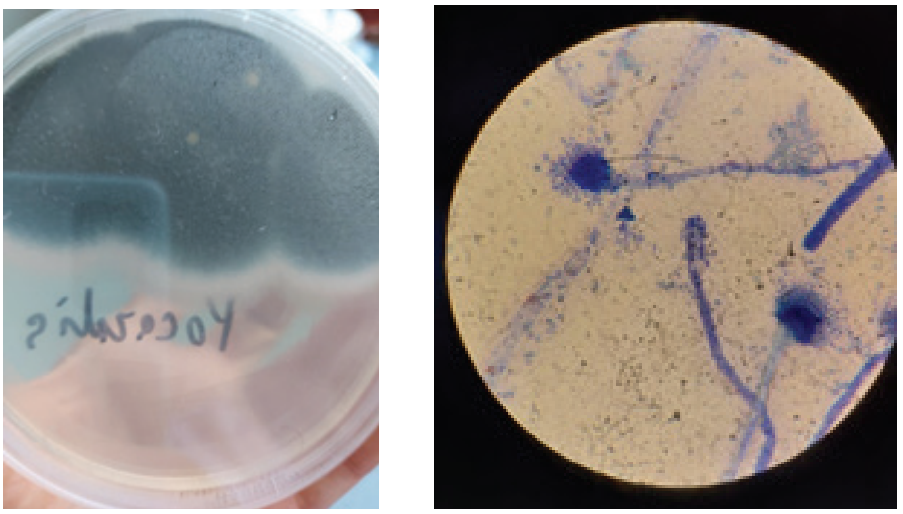

Figure 3. Macroscopic and microscopic characterization of *Aspergillus fumigatus*

BAL was again sent for microbiological examination in our laboratory. Microscopic evaluation after Gram staining visualized a pavement of leukocytes, lymphocytes, lymphoplasmacytic cells and epithelia. The cultural examination on blood agar at 37 °C, detected no bacterial growth while on Sabouraud agar for fungi, incubated at 30 °C, a significant amount of pure fungus-mold culture was isolated. The mold was identified by MALDI-TOF (Biotyper Bruker), as well as by microscopic and macroscopic analysis as *Aspergillus fumigatus*.

Aspergillus fumigatus is a fungus that has an aerial and substrate mycelium, conidiophores with a vesicle, and numerous spores (Fig. 3).

Antifungal susceptibility of *Aspergillus fumigatus* (antimycogram) was tested against the following antimycotics Itraconazole, Voriconazole, Nystatin, Isavuconazole, Anidulafungin, Amphotericin B and Posaconazole. Fluconazole resistance was congenital. The results are presented in Table 2.

The E-test method was used to determine the minimum inhibitory concentration (MIC) (EUCAST 2022). (Fig. 4)

After prescribed Itraconazole therapy, *Aspergillus fumigatus* was cleared in a post-therapy follow-up study.

The recommendation was the inclusion of antifungal agents in long-term antibiotic therapy, as well as in the case of inhaled corticosteroids as a proven risk factor for the occurrence of medically significant fungi.

CONCLUSION

No specific measures to prevent nocardiosis exist. However, it was shown that the concomitant administration of TMP/SMX prophylactically while receiving high-dose immunosuppressants after heart transplantation could reduce the risk of nocardial infections (16).

Recent studies, clinical observations, and taxonomic developments suggest that therapeutic decisions in nocardiosis regarding the most appropriate drug and duration of therapy are not straightforward. An individual approach may be required depending on the infection and the specific Nocardia species. Therefore, antimicrobial susceptibility tests are necessary (17;18).

Table 2. *Aspergillus fumigatus* antimycogram results

Aspergillus fumigatus			
Fluconazole	R – congenital	Isavuconazole	S
Itraconazole	S	Anidulafungin	S
Voriconazole	S	AmphotericinB	S
Nystatin	S	Posaconazole	S

S-susceptible R- resistent

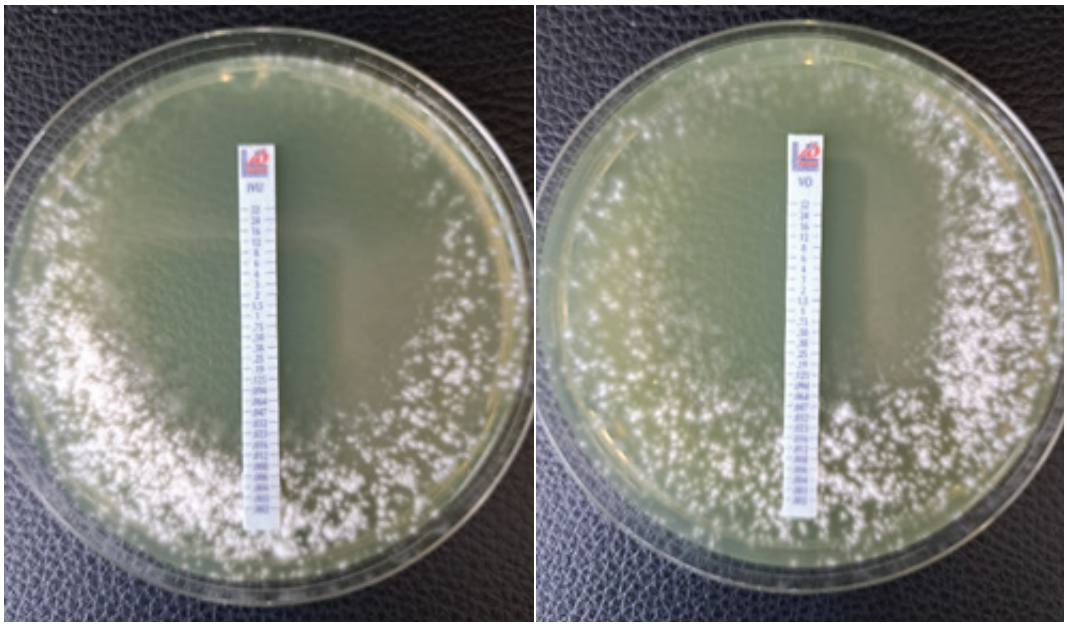

Figure 4. Antimycotic susceptibility of *Aspergillus fumigatus*

The application of appropriate identification methods, including the development of molecular-biological methods for diagnosis, increases the probability, respectively the number of Nocardia isolates (14).

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