



## Nocardiosis mimicking lung cancer in a heart transplant patient with end-stage renal disease

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### ABSTRACT

Nocardiosis is a rare bacterial opportunistic infection that most commonly manifests as lung disease. However, disseminated infection and abscess formation can occur. Due to diverse radiographic findings and difficult cultivation it is not an easy diagnosis to make. Antibiotics such as Trimethoprim-sulfamethoxazole alone or in combination with imipenem or imipenem in combination with amikacin need to be administered over a period of at least six to twelve weeks.

We report a case of a 64-year old female heart transplant recipient requiring dialysis who suffered from dyspnea and a productive cough among other symptoms. Computed tomography revealed a tumor in the left upper lobe suggesting lung cancer. Both transbronchial and transthoracic biopsy could not confirm a malignant disease. Finally, *Nocardia nova* was isolated from a bronchoalveolar lavage and specific antibiotic treatment was initiated. As a result, the mass in the left upper lobe significantly regressed after a few weeks.

### 1. Introduction

*Nocardia* are ubiquitous bacteria that most commonly cause lung disease or extrapulmonary abscess formation in the immunocompromised host [1]. Radiographic findings are diverse and therefore rarely indicative of the disease [2]. Treatment options include trimethoprim-sulfamethoxazole (TMP-SMX) or a combination of imipenem with either TMP-SMX or amikacin over a period of at least six to twelve months [3]. Prognosis is poor especially following organ transplantation [4,5].

### 2. Case report

A 64-year-old woman with a history of heart transplantation and renal failure requiring dialysis was admitted to our hospital in September 2019 with a suspected diagnosis of lung cancer.

The patient had been complaining about progressive dyspnea, a productive cough, chest pain, and weight loss for about six weeks. In August 2019, an initial outpatient chest X-ray was performed that revealed an infiltrate in the superior left lung. Blood tests showed an elevated white blood cell count of 16,5 Gpt/l and an elevated C-reactive protein of 245 mg/l. Consequently, bacterial pneumonia was suspected and an oral course of amoxicillin was started. Due to a lack of improvement both clinically and radiologically antibiotic treatment was

changed to ciprofloxacin. Ten days later the patient was admitted to a hospital due to increased shortness of breath. On the day of admission, she presented with a leukocyte count of 18,2 Gpt/l and a C-reactive protein of 278 mg/l suggesting a lack of response to antibiotic treatment for the second time. Computed tomography of the lungs finally revealed an eight by eight-centimeter mass in the left upper lobe (Fig. 1). Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage was performed. The former showed no evidence of malignancy. However, lung cancer remained the most likely diagnosis. Therefore, the patient was transferred to our hospital for further evaluation. At this point, the microbiologic results of the bronchoalveolar lavage were still incomplete.

We performed an ultrasound-guided transthoracic needle biopsy of the tumor in the left upper lobe. Similar to the histological assessment of the transbronchial biopsy, the sample showed an inflammatory process with no evidence of malignancy. Meanwhile, we received the results of the bronchoalveolar lavage obtained in the previous hospital identifying *Nocardia nova* by culture. Antibiotic susceptibility testing showed sensitivity towards amoxicillin, cefotaxime, amikacin, tobramycin, imipenem and linezolid. We started the patient on a combination of amikacin and imipenem. Because the patient suffered from renal failure requiring dialysis, there was a need for dose adjustment. On days of dialysis our patient received 500 mg of amikacin administered after dialysis if the trough level was below 1 mg/l in combination with 1000 mg of imipenem. On dialysis-free days she received 500 mg of imipenem

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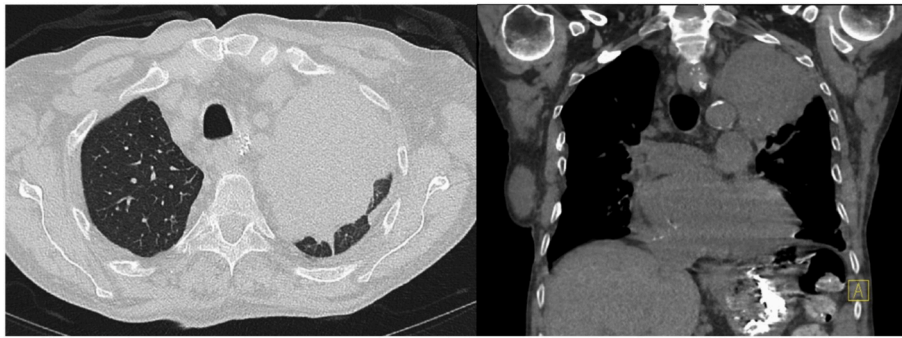


Fig. 1. Computed tomography shows the tumor mass in the left upper lobe.

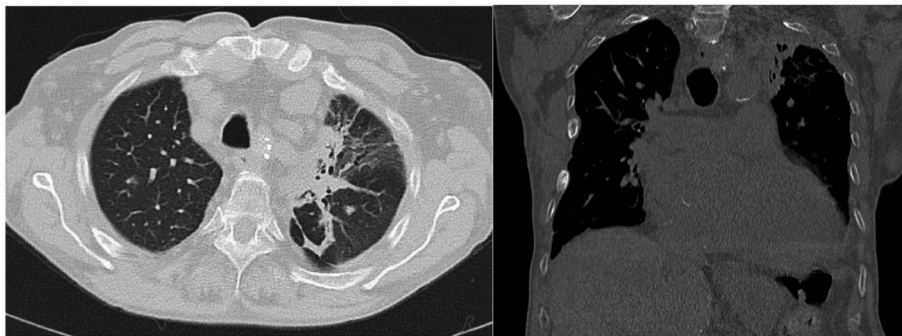


Fig. 2. Computed tomography shows a significant regress of the tumor mass in the left upper lobe.

twice daily. Immunosuppressive medication given to avoid rejection after heart transplantation was adapted meaning the tacrolimus trough level was reduced from 8 to 10  $\mu\text{g/l}$  to 4–6  $\mu\text{g/l}$ . The dose of Cellcept was initially reduced by fifty percent to 500 mg twice daily and eventually paused. Prednisolon 10 mg was continued.

A follow up computed tomography after two weeks of antibiotic treatment showed an improvement of the alterations in the left upper lobe. However, a new infiltrate in the right upper lobe was found. To exclude an additional malignant disease with maximum certainty a CT-guided needle biopsy of the infiltrate in the right upper lobe was performed. Histopathology showed an inflammatory process as well as a mycotic superinfection through a positive periodic acid schiff reaction, but still no malignancy. In a second bronchoalveolar lavage *Pseudomonas aeruginosa* was detected. Neither fungi nor *Nocardia* species were found. Consequently, no further specification of the mycotic superinfection was possible. Therefore, the established antibiotic treatment against *Nocardia nova* based on imipenem and amikacin was supplemented with piperacillin/tazobactam and voriconazole for a period of three weeks. After eight weeks of antibiotic treatment respiratory symptoms such as productive cough, dyspnea and chest pain improved significantly. At this point the chest X-ray showed a reduction of the inflammatory tumor of the left upper lobe to half of the original extent. Furthermore, inflammatory values normalized to a white blood cell count of 4,9 Gpt/l and a C-reactive protein of 2,13 mg/l.

Consequently, the patient was discharged from our hospital. She continued antibiotic treatment with amikacin given after outpatient dialysis when the trough level was below 1 mg/l.

Computed tomography of the chest one month after the patient was discharged showed further reduction of all infiltrates indicating a successful treatment (Fig. 2). Due to difficulties in monitoring the amikacin trough level in an outpatient setting and signs of hearing loss antibiotic therapy was stopped after twelve weeks.

A reevaluation after another twelve weeks and possibly a restart and completion of the antibiotic therapy is planned.

### 3. Nocardiosis

Nocardiosis is a rare opportunistic bacterial infection. More than 50 *Nocardia* species associated with human disease have been identified [6]. *Nocardia* is a genus within the order of Actinomycetales that are gram-positive and partially acid-fast. As ubiquitous bacteria they can be found in soil, both fresh and salt water, and decomposing vegetation [1].

Most patients suffering from Nocardiosis are immunocompromised. Incidences of Nocardiosis up to 3,5% have been described following heart or lung transplantation [7]. Almost 70% of the study population in a series of 55 cases of Nocardiosis had received a long-term corticosteroid therapy making chronic steroid exposure an important risk factor [4]. Other relevant risk factors include pulmonary comorbidities such as chronic obstructive pulmonary disease or tuberculosis [8].

Airborne droplet infection is the most common route of transmission. Consequently, pulmonary disease is the predominant clinical presentation of Nocardiosis [9]. Symptoms can include non-productive or productive cough, shortness of breath, chest pain and weight loss [10]. Radiographic findings may suggest a wide range of differential diagnoses. A recently published study of 55 cases described a variety of consolidation, nodules, cavitation, bronchiectasis and infiltrates as possible imaging manifestations [11]. In the case demonstrated an unusually large solid lesion in the patient's left upper lobe suggested lung cancer as the most likely diagnosis.

Secondary extrapulmonary disease occurs in about fifty percent of all cases and usually manifests as abscess formation [3].

To confirm the diagnosis of Nocardiosis a positive culture is necessary. Usually sputum or a bronchoalveolar lavage is obtained. Cultures of *Nocardia* may take a long time to grow and can easily be missed in mixed cultures. Molecular methods can be helpful with the identification of *Nocardia* species [3,12].

Prognosis of Nocardiosis is poor. A retrospective study described a mortality rate of 34,5% with cardiopulmonary arrest due to septicemia or respiratory failure being the most common causes of death [4]. Organ transplant recipients with Nocardiosis have a significantly lower one

year survival rate than other patients [5]. Therefore, early diagnosis and effective treatment are crucial.

Due to a lack of prospective controlled trials there are no standard treatment guidelines. Initial antibiotic therapy should be selected depending on the severity and location of the infection as well as the patient's comorbidities and the species of *Nocardia*. Susceptibility testing should always be performed. trimethoprim-sulfamethoxazole (TMP-SMX) has successfully been used in stable patients with pulmonary disease [3]. However, drug resistance is not uncommon. In a retrospective study of over 700 *Nocardia* isolates 42% were resistant to TMP-SMX [13]. Patients with severe pulmonary or disseminated disease and immunocompromised individuals should receive a combination of two antibiotics. Imipenem in combination with amikacin or TMP-SMX proved to be successful in many cases. In life-threatening situations, all three substances can be administered simultaneously [3].

In addition to antibiotic treatment surgery can become necessary in the presence of abscess formation [14]. Duration of treatment should be at least six months. In case of severe disease or an immunocompromised host treatment should be continued for at least twelve months [1]. Therefore, we strive to restart antibiotic therapy in our patient after the current interruption despite the difficulties due to dialysis.

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