

Prikaz bolesnika | Case report

A Case of Pulmonary Co-Infection by *Mycobacterium Tuberculosis* and *Nocardia* spp. in a Lung Transplant Recipient

Koinfekcija pluća s *Mycobacterium tuberculosis* i *Nocardia* spp. kod bolesnika s transplantiranim plućima

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Summary

Lung transplantation is a therapeutic option for the treatment of advanced lung disease. The risk of pulmonary infections is increased in lung transplant recipients. We report a case of a pulmonary coinfection with *Mycobacterium tuberculosis* and *Nocardia* species in a lung transplant recipient.

Sažetak

Transplantacija pluća jedna je od terapijskih opcija kod liječenja uznapredovale plućne bolesti. Primatelji presađenih pluća imaju povećani rizik za nastanak plućnih infekcija. U radu prikazujemo slučaj koinfekcije pluća kod bolesnika s transplantiranim plućima, čiji su uzročnici *Mycobacterium tuberculosis* i *Nocardia* species.

Introduction

Lung transplantation is a final therapeutic option for advanced-stage lung and pulmonary circulation diseases for patients in which all conservative and surgical modes of therapy have been exhausted^[1].

The main limitations of lung transplantation were technical complications until the 1980s when they were substantially reduced by the development of surgical technique, postoperative care, immunosuppressive drugs, and more careful candidate selection processes^[2,3]. The most important complications at present are infection and allograft rejection. Pneumonia, pleuritis, wound infection, urinary tract and central nervous system infections all cause significant morbidity and mortality among lung transplant recipients^[4-6]. Lung

infections are important risk factors for both acute transplant rejection and chronic allograft dysfunction through immunologic mechanisms^[6]. Lung transplant recipients develop pneumonia more often compared to other solid organ transplant recipients due to direct allograft exposure to the environment, a defective cough reflex, and impaired mucociliary clearance^[3].

In the first-month post-transplant infections are the result of surgical procedures and hospital stay, and are typically caused by nosocomial bacteria. The most common pathogens are *Pseudomonas aeruginosa*, Enterobacterales, and methicillin-resistant *Staphylococcus aureus*^[2]. During the next six months, the risk for opportunistic infection, such as *Pneumocystis jirovecii*

is the highest, while common pathogens such as *Streptococcus pneumoniae* and gram-negative bacteria are responsible for infection in the later stages after lung transplantation^[5,6].

Defining the aetiology of pneumonia in lung transplant recipients can be challenging.

Clinical presentation is usually non-specific due to immunosuppressive therapy and can resemble acute transplant rejection^[6]. Furthermore, some patients may be asymptomatic.

Laboratory findings are also nonspecific. Leukocytosis is often a consequence of immunosuppressive therapy, and the only procalcitonin can be useful as a sign of infection^[6,7]. Other diagnostic methods include computerized tomography (CT) and bronchoscopy with bronchoalveolar lavage and lung biopsy^[6].

Here we report a rare case of lung coinfection by *Nocardia* spp. and *Mycobacterium tuberculosis* in a lung transplant recipient.

Case report

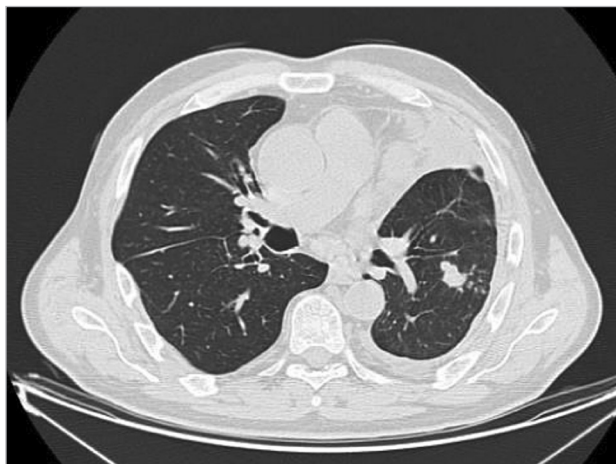
A 58-year-old man with a history of arterial hypertension and diabetes mellitus received a bilateral lung transplant due to idiopathic pulmonary fibrosis. The early post-transplant period was unremarkable.

Nine months post-transplant a chest CT was performed due to a decline in lung function during routine follow-up. The CT scan revealed bilateral bronchial deformities with newly formed peribronchial infiltrates, nodules and subpleural consolidates and a „tree in bud“ pattern in the left lung. The patient was hospitalized and microbiological sputum analysis revealed *Acinetobacter baumannii*, pneumococcus, and *Aspergillus niger*. Targeted antibiotic therapy was started after antimicrobial susceptibility testing (colistin, piperacillin-tazobactam, voriconazole). Clinical, radiological, and lung function test improvement followed after therapy completion.

During the next month, the patient was hospitalized again due to a low-grade fever. Chest x-ray revealed an upper left lobe infiltrate with elevated inflammatory marker (C reactive protein 60.9 mg/L) and empirical antibiotic therapy (meropenem, ciprofloxacin) was started with only mild improvement. Follow up chest CT scan showed a newly formed lobulated consolidate (21x13 mm) in the superior segment of the lower left lobe (Figure 1). Radial probe endobronchial ultrasound with biopsy was performed but the aetiology of the disease was not immediately clarified. The sputum and bronchial wash were microscopically negative for acid resistant bacilli.

Positron emission tomography/CT was also performed revealing metabolic active areas in the left lung

FIGURE 1. A LOBULATED CONSOLIDATE IN THE SUPERIOR SEGMENT OF THE LOWER LEFT LOBE, PRIOR TO THE INTRODUCTION OF THERAPY
SLIKA 1. LOBULIRANI KONSOLIDAT APIKALNOG SEGMENTA DONJEG REŽNJA, PRIJE UVOĐENJA TERAPIJE



(perihilar SUVmax 6.03, lower lobe SUVmax 7.61) and mediastinal lymph nodes.

In the meantime, *Mycobacterium tuberculosis* was detected in sputum culture and antituberculosis (ATL) therapy was started- isoniazid, ethambutol, pyrazinamide, and rifampin which was later replaced with rifabutin due to drug-drug interactions with tacrolimus. After polymerase chain reaction (PCR) testing *Nocardia* spp. was also detected in the lung biopsy material and sulfamethoxazole-trimethoprim was added to the therapeutic regimen.

After four months of ATL and sulfamethoxazole-trimethoprim therapy follow-up chest CT scan showed regression of the left lower lobe consolidation and mediastinal lymphadenopathy (Figure 2). Isonia-

FIGURE 2. REGRESSION DYNAMIC OF LUNG CONSOLIDATE AFTER THE INTRODUCTION OF THERAPY

SLIKA 2. REGRESIVNA DINAMIKA PLUČNOG KONSOLIDATA NAKON UVOĐENJA TERAPIJE



zid and rifabutin were continued and the sulfamethoxazole-trimethoprim dose was reduced to the usual *Pneumocystis jirovecii* prophylactic dose.

The ATL therapy was continued for 15 months with a follow-up chest x-ray showing regression of the lung consolidation. The patient had no symptoms during the diagnostic and therapeutic period except for the intermittent low-grade fever, which eventually subsided completely after four months of therapy.

Discussion

Tuberculosis is one of the most significant public health problems in the world with more than ten million cases in 2019 worldwide^[8]. The incidence of tuberculosis among lung transplant recipients is 6.4 to 10%, making it the highest among solid organ transplant patients^[6,9]. In this group of patients, tuberculosis is caused either by latent tuberculosis reactivation due to immunosuppressive therapy or direct mycobacterium transmission from an infected person^[6,9]. The main diagnostic issue is the long waiting period for culture analysis results.

ATL therapy is the same in lung transplant recipients as in other tuberculosis patients with an induction phase where four or five drugs are used (most commonly isoniazid, rifampin, ethambutol, and pyrazinamide) which is followed by the continuation phase with dual therapy (isoniazid, rifampin)^[6,9].

The major issue with ATL therapy in transplant recipients is rifampin, a powerful cytochrome 3A4, and P-glycoprotein inductor, which interferes with calcineurin inhibitors^[6,9]. Some authors suggest that rifampin should be replaced with levofloxacin or rifabutin^[9]. Rifabutin was used successfully in our case after rifampin discontinuation due to interactions with tacrolimus.

The recommended therapy duration is 5 to 24 months with clinical, radiological, and microbiological monitoring^[6,9]. The most common treatment side effect is hepatotoxicity. Therapy should be discontinued in the case of a triple increase in liver enzymes in symptomatic patients, and a fivefold increase in asymptomatic patients^[6]. In our case, the therapy duration was 15 months, without any side effects.

Nocardia spp. is a weakly acid resistant actinomycete, an opportunistic pathogen that causes infection in transplant recipients mostly within a year of transplantation, and can affect any organ^[6]. Compared to other solid-organ transplant recipients, nocardiosis is the most common in lung transplant recipients, with an incidence of 3.5%^[6]. Radiological findings and clinical presentation are nonspecific and pulmonary infection can be similar to tuberculosis. Microbiological diagnostic methods involve microscopy (weakly acid-resistant, grainy filaments), culture sample analysis, and PCR^[6,10].

In our case, *Nocardia* was not detected in the culture of respiratory samples and was only confirmed using the PCR method.

For patients with mild illness the treatment of choice is sulfamethoxazole-trimethoprim monotherapy and for more severe forms (disseminated disease, central nervous system disease) an antibiotic combination regimen (imipenem, meropenem, amikacin, minocycline, ceftriaxone, cefotaxime) is used^[6]. The recommended therapy duration is 6 to 12 months^[6]. Sulfamethoxazole-trimethoprim is used as *Pneumocystis jirovecii* prophylaxis in lung transplant recipients but this does not protect our patients against nocardiosis. Fortunately, this prophylactic dose does not induce *Nocardia* resistance to the drug^[6].

To our knowledge, this is the first case of *Mycobacterium tuberculosis* and *Nocardia* coinfection in a lung transplant recipient. The majority of available cases of this coinfection are in cancer patients, patients with human immunodeficiency virus infection, or those with acquired immunodeficiency due to immunosuppressive therapy (Chron's disease, rheumatoid arthritis, corticosteroid therapy). Diagnosis of a pulmonary coinfection in lung transplant recipients can be challenging due to a nonspecific clinical presentation and microbiological diagnostic method limitations.

Pulmonary nocardiosis is rarely suspected and clinical presentation and radiological findings can be similar to those in tuberculosis. Our opinion is that it is important, especially among immunocompromised patients, to consider both infections in the diagnostic process. Nowadays PCR is an important method, but medical professionals have to be aware of its limitations, especially in the diagnosis of nocardiosis, since it can be challenging to differentiate colonization and active infection^[10]. Nocardiosis should be suspected in patients with proven tuberculosis in which there is no improvement with ATL therapy.

Conclusion

Lung transplantation is specific due to constant allograft exposure to the environment. Immunosuppressive therapy is a risk for opportunistic infections, primarily lung infections. Further development in microbiological diagnostic methods is mandatory to achieve a correct and timely diagnosis of infection in lung transplant recipients. Clinicians managing transplant patients should always be aware of the possibility of coinfection with rare and opportunistic pathogens.

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