

Pulmonary Nocardiosis Mimicking Pulmonary Tuberculosis in an Immunocompetent Patient Diagnosed by Cytology of Bronchoscopic Lavage

Bronkoskopik Lavaj Sitolojisiyle Teşhis Edilen İmmünokompetan Bir Hastada Pulmoner Tüberkülozu Taklid Eden Pulmoner Nokardiozis

İ Hülya Abalı¹, İ Efsun Gonca Ugur Chousein¹, İ Derya Hırçın Cenger², İ Neslihan Fener³

Abstract

Nocardia infections are common in immunocompromised and organ transplant patients, although Nocardia species only rarely cause infections in immunocompetent patients. Pulmonary nocardiosis is the most common clinical manifestation of Nocardia species, and may imitate several pulmonary diseases, such as pulmonary tuberculosis (TB) in such high-risk settings for TB as Türkiye. We present here a rare case of an immunocompetent patient with pulmonary nocardiosis mimicking tuberculosis in terms of the history, clinical symptoms and radiological findings. Acid-fast staining and real-time polymerase chain reaction testing of the bronchoscopic lavage were negative for TB, and no Mycobacterium species proliferated in the culture. Two similar diseases were differentiated by lavage cytology. The patient improved dramatically following a short course of treatment over two months.

Keywords: Pulmonary nocardiosis, tuberculosis, immunocompetent, lavage cytology.

Öz

Nokardiya enfeksiyonları, bağışıklığı baskılanmış ve organ nakli olan hastalarda sık görülür, ayrıca, Nokardiya türleri immünokompetan hastalarda nadiren enfeksiyona neden olur. Pulmoner nokardiozis, Nokardiya türlerinin en sık görülen klinik manifestasyondur ve Türkiye gibi pulmoner tüberküloz (TB) için yüksek riskli bölgelerde sıklıkla pulmoner tüberküloz gibi birçok pulmoner hastalığı taklid edebilir. Anamnez, klinik semptomlar ve radyolojik bulgulara göre pulmoner tüberkülozu taklid eden pulmoner nokardiozis tanısı alan nadir bir immünokompetan olguyu sunuyoruz. Bronkoskopik lavajın aside dirençli boyanması ve real-time polimeraz zincir reaksiyonu TB için negatif ve kültürde hiçbir Mikobakteri türü üremedi. İki benzer hastalığın ayırıcı tanısı lavaj sitolojisi ile yapıldı. İki aylık kısa süreli bir tedavi ile dramatik bir iyileşme gözlemlendi.

Anahtar Kelimeler: Pulmoner nokardiozis, tüberküloz, immünokompetan, lavaj sitolojisi.

¹Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

²Department of Infectious Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

³Department of Pathology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

¹Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, İstanbul

²Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Anabilim Dalı, İstanbul

³Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Patoloji Anabilim Dalı, İstanbul

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Correspondence (İletişim): Hülya Abalı, Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

e-mail: hulayab@gmail.com



Nocardia is a Gram-positive, poor acid-fast, mandatory aerobic and immotile microorganism (1). The most common infection type caused by *Nocardia spp.* is pulmonary nocardiosis, which is transmitted via inhalation from the environment (2). *Nocardia spp.* is responsible for opportunistic pulmonary infections in immunocompromised patients (3), and so may be overlooked in the preliminary diagnosis of immunocompetent patients. In developing countries in which tuberculosis (TB) is endemic, pulmonary nocardiosis can be underdetermined, and attempts may be made to treat it with first-line antitubercular drugs empirically (4), as the clinical and radiological characteristics of pulmonary nocardiosis overlap with pulmonary TB, and there is a lack of specific clinical findings indicating pulmonary nocardiosis (5). Herein, we present a case of an immunocompetent patient mimicking pulmonary TB and diagnosed by cytology of bronchoscopic lavage.

CASE

A 57-year-old female patient was referred to the chest diseases outpatient clinic for an examination of bilateral pulmonary infiltrates detected on thoracic CT. The patient complained of non-productive cough, fatigue and 6 kg weight loss over a period of two-months. Her son had been diagnosed with pulmonary TB 15 years earlier. The patient, whose only known disease was postmenopausal osteoporosis, had undergone surgery for the correction of a cervical and lumbar disc hernia three years earlier, and had been diagnosed with coronavirus disease 2019 (COVID-19) infection based on real-time polymerase chain reaction (RT-PCR) positivity in a nasopharyngeal swab, and had received two inactivated vaccines and two messenger ribonucleic acid (mRNA) vaccines within the month preceding admission to our hospital. Lab results revealed an elevated CRP of 32.9 (range: 0-5 mg/L), an erythrocyte sedimentation rate of 100 (range: 0-30 mm/h), neutrophil 72.4% (range: 50-70%), and mildly reduced hematocrit at 34% (range: 37-54%). The presence of conditions that could cause immunosuppression was investigated. Serology was negative for anti-human immunodeficiency virus (anti-HIV), anti-hepatitis C virus (anti-HCV) and hepatitis B surface antigen (HBsAg). Mildly increased total immunoglobulin G (IgG), IgG1 and IgG3 were detected on an IgG panel. Thoracic CT revealed tree-in-bud opacities in the upper and middle lobes of the right lung (Figure 1a), a 7.5 mm cavitory nodule in the posterior segment of the right lung upper lobe (Figure 1b), and a consolidation and ground glass opacities in the posterior basal segment of the left lung lower lobe (Figure 1c). Acid-fast bacilli (AFB) staining of the sputum was negative, and an RT-PCR of the sputum was unreactive for *Mycobacterium species* (*Myc spp.*). The sputum culture was negative for *Myc spp.* Fiberoptic bronchoscopy (FOB) was subsequently performed to

identify the microorganism responsible for the pulmonary infiltrates. No endobronchial lesion was observed in the tracheobronchial tree except for anthracosis in the mouths of segments on FOB. Lavage taken from the right upper lobe and the left lower lobe demonstrated negative AFB staining and RT-PCR for *Myc spp.*, and the lavage culture was negative for *Myc spp.* Furthermore, no *Nocardia spp.* was isolated from the cultures of sputum and lavage. Cytology of the lavage revealed basophilic hyphae suggestive of *Nocardia spp.*, and the patient was duly hospitalized for the treatment of pulmonary nocardiosis and follow-up. An imipenem+cilastatin and amikacin treatment regimen was initiated by an infectious diseases consultant lasting one month during hospitalization. The Trimethoprim-sulfamethoxazole (TMP-SMX) treatment initiated after discharge was withdrawn due to the adverse effects in the patient, including fever and widespread maculopapular rash occurring on the 12th day, and was replaced with oral amoxicillin-clavulanate. The total duration of treatment with this regimen was planned for 6 months. Significant regressions of the infiltrates, cavitory nodule (4.3 mm), and ground glass opacities were detected on thoracic CT, and clinical and laboratory (CRP: 0.4 mg/L, sedimentation: 21 mm/h, neutrophil: 64.4%) improvements were observed upon admission to the outpatient clinic of chest diseases after 2 months of treatment (Figure 1d, Figure 1e, Figure 1f).

DISCUSSION

Pulmonary TB can hinder diagnosis of pulmonary nocardiosis in locations where there is a high risk of TB. The incidence of pulmonary nocardiosis ranges between 1.7% and 6.7% (6), while the incidence of the co-existence of pulmonary nocardiosis and TB in patients with suspected pulmonary TB is 4.8% (6). The low frequency of pulmonary nocardiosis detected in studies may be due to misdiagnosis and under-diagnosis, given its similarity to such diseases such as pneumonia, pulmonary TB, fungal infections, malignancy, Wegener's granulomatosis and pulmonary sarcoidosis (4,7-9).

Nocardia infections are usually chronic and progress with nonspecific symptoms and findings, occurring in immunocompetent patients at the rate of 10-50% (10). Nocardiosis worsens faster than TB, within several months (11). Opportunistic *Nocardia spp.*, which causes immunosuppression in the host, has the potential to disseminate through entry into the blood circulation, and may cause brain abscesses and skin infections. Nocardiosis is life-threatening in cases of central nervous system involvement unless diagnosed and treated early (12). The mortality rate of pulmonary nocardiosis is 41%, and increases to 64% in cases of disseminated infection and 100% in central nervous system infections (13), meaning early diagnosis and treatment are crucial, while TB and

fungal infections that may cause misdiagnosis should be ruled out in developing countries.

Our patient's symptoms of chronic non-productive cough, fatigue, and weight loss were primarily suggestive of TB, and this was reinforced by her previous exposure to TB. Consolidation, parenchymal nodules, and mediastinal lymphadenopathy, with or without cavitation, are seen in approximately 70% of patients, and these common thoracic CT signs in pulmonary nocardiosis (14), as well as cavitation and tree-in-bud infiltrates, which are associated mainly with TB (15), were observed in our patient.

The diagnosis of *Nocardia* spp. is based on microbiological examinations, among which Gram staining is more sensitive than acid-fast (Kinyoun) staining for the identification of branching Gram-positive filamentous rods. Antimicrobial-containing environments should be used to inhibit the proliferation of oropharyngeal flora in the culture of respiratory specimens. The incubation time for the specimens (i.e. sputum, blood culture) of suspected Nocardiosis patients should be two weeks (16).

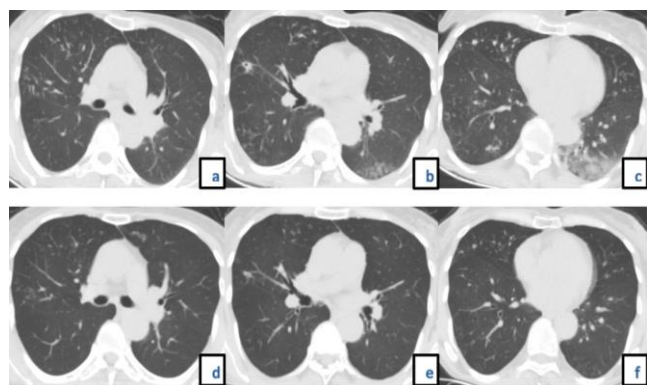


Figure 1: Thoracic CT revealed tree-in-bud opacities in the upper lobe of the right lung (a), a 7.5 mm cavitory nodule in the posterior segment of the right lung upper lobe and ground glass opacities in the posterior basal segment of the left lung lower lobe (b), as well as multiple nodules in the middle lobe of the right lung and consolidation and ground glass opacities in the posterior basal segment of the left lung lower lobe (c). Thoracic CT performed after two months of treatment revealed improvements of the tree-in-bud opacities (d), a 7.5 mm cavitory nodule to a 4.3 mm and ground glass opacities (e), and multiple nodules, consolidations and ground glass opacities (f)

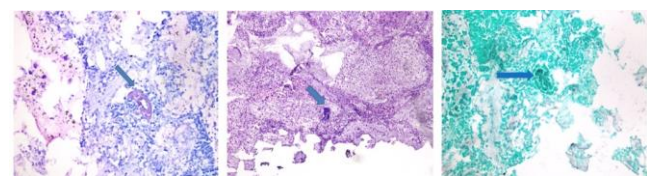


Figure 2: Basophilic hyphae organisms stained positively with Ehrlich-Ziehl-Neelsen (20x10) (a), Basophilic hyphae-like organisms stained positively with Papanicolaou (20x10) (b), Basophilic hyphae organisms stained positively with Grocott's methenamine silver (20x10) (c)

Molecular analyses such as amplifications and the sequencing of genes (*rrs*, *hsp65*, *secA1* and *sodA*) and PCR-based assays are more sensitive in patients using antibiotics and produce faster results than culture-based analyses (17,18), although molecular biology methods are limited as they are applied in only a few reference laboratories. The sputum AFB staining, RT-PCR and culture for *Myc* spp. results were analyzed based on the assumption that the patient had pulmonary TB, and after the AFB staining and RT-PCR came back negative for *Myc* spp., FOB was performed for diagnostic lavage without waiting for the culture result. The cultures of sputum, and lavage were negative for *Myc* spp. at the 45th day of the incubation period, and so pulmonary TB was ruled out.

A cytological diagnosis is a confirmation of a definitive microbiological diagnosis. Positive stainings of basophilic long thin filamentous branching organisms on lavage with separate Ehrlich-Ziehl-Neelsen (EZN) (Figure 2a), Papanicolaou (PAP) (Figure 2b), and Grocott's methenamine silver (Figure 2c) highlight the diagnosis of pulmonary nocardiosis. The cytological diagnosis resulted in 7 days; the patient was referred to an infectious diseases consultant for the timely initiation of treatment.

The first-line anti-biotherapy for pulmonary nocardiosis is TMP-SMX, and in the event of any adverse effects, alternative medications may be substituted, including imipenem, meropenem, amoxicillin/clavulanate, amikacin, ceftriaxone, cefotaxime, levofloxacin, linezolid or tobramycin (19). Immunocompetent patients should undergo at least 6 months of treatment (20).

Several limitations were encountered in the present case. As Nocardiosis is diagnosed by microbiological and molecular analyses. *Nocardia* spp. requires a special media given its idiosyncratic proliferation characteristics, however *Nocardia* spp. could not be identified within the sputum and lavage cultures of our case. Since the prediagnosis of our case was primarily pulmonary tuberculosis, a prediagnosis of pulmonary nocardiosis was not reported to the microbiology laboratory, and so the samples could not be cultivated in an appropriate media for *Nocardia* spp. Additionally, there was no molecular biology laboratory in the hospital.

CONCLUSION

In countries, where pulmonary TB is endemic, pulmonary nocardiosis may easily be overlooked. After pulmonary TB is ruled out, pulmonary nocardiosis should be considered. When molecular methods, as the fastest diagnostic tools for the identification of nocardiosis, cannot be applied, a rapid cytological diagnosis of nocardiosis can lead to early treatment and prevent the progression of the infection to its fatal disseminated form. Amoxicillin-clavulanate is a favorable treatment option for patients

who are withdrawn from TMP-SMX treatment due to its adverse effects.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - H.A., E.G.U.C., D.H.C., N.F.; Planning and Design - H.A., E.G.U.C., D.H.C., N.F.; Supervision - H.A., E.G.U.C., D.H.C., N.F.; Funding -; Materials - H.A., N.F.; Data Collection and/or Processing - H.A., D.H.C., N.F.; Analysis and/or Interpretation - H.A., E.G.U.C., D.H.C., N.F.; Literature Review - H.A.; Writing - H.A., D.H.C.; Critical Review - H.A., E.G.U.C., D.H.C., N.F.

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