

[CASE REPORT]

Pulmonary Reinfection by *Nocardia* in an Immunocompetent Patient with Bronchiectasis

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Abstract:

Pulmonary reinfection by *Nocardia* has been rarely reported. We describe a case of pulmonary reinfection by *Nocardia* in an immunocompetent patient. An 82-year-old immunocompetent woman with bronchiectasis presented with exacerbation of cough. She had a history of pulmonary nocardiosis three years earlier. At that time, *Nocardia* species were cultured from the sputum and identified as *N. cyriacigeorgica* with 16S ribosomal RNA gene sequencing. In the present episode, cultures of sputum and bronchial washing specimens grew *N. beijingensis*, which was identified with 16S ribosomal RNA gene sequencing. Pulmonary reinfection by different *Nocardia* species can occur in immunocompetent patients.

Key words: pulmonary nocardiosis, reinfection, immunocompetent, bronchiectasis, 16S ribosomal RNA gene sequencing

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Introduction

Nocardia is a Gram-positive, filamentous, branching and aerobic bacterium of the order *Actinomycetales* commonly found in soil and water. *Nocardia* causes various types of infections, ranging from localized lung or skin infections to disseminated diseases. Infection most commonly occurs through the respiratory tract, leading to pulmonary nocardiosis (1, 2), which accounts for about 70% of *Nocardia* infection (3). Pulmonary nocardiosis is considered an opportunistic infection, but previous studies have shown that pulmonary nocardiosis can occur in immunocompetent patients (4-6). Furthermore, pulmonary reinfection by *Nocardia* has been rarely reported in immunocompetent patients.

We herein report a case of pulmonary reinfection by different *Nocardia* species in an immunocompetent patient with bronchiectasis, which was distinguished from relapse of nocardiosis using 16S ribosomal RNA gene sequencing.

Case Report

An 82-year-old woman presented with a 1-month history

of productive cough in 2016. She had a history of pulmonary nocardiosis three years earlier. In 2013, she had suffered from a chronic productive cough. A Gram stain of the sputum showed branching Gram-positive filaments, and the culture grew *Nocardia* species (Fig. 1a). With the cooperation of the Medical Mycology Research Center of Chiba University, the isolates were identified as *N. cyriacigeorgica* using 16S ribosomal RNA gene sequencing. Minimal inhibitory concentrations for selected antimicrobial agents were determined by the broth microdilution method following the guidelines of the Clinical and Laboratory Standard Institute (7) (Table); the isolates were susceptible to trimethoprim and sulfamethoxazole (TMP/SMX). She therefore received TMP/SMX (80/400 mg thrice per day) for 1 year under a diagnosis of pulmonary nocardiosis with apparent improvement in her productive cough.

Compared with the findings of chest computed tomography (CT) in 2013 (Fig. 2a), the chest CT findings in 2014 showed the improvement of small centrilobular nodules and inflammatory changes around the ectatic bronchi in the left lower lobe of the lung (Fig. 2b). She had minor symptoms over the next three years. In 2016, she was referred again to our hospital due to deterioration of cough. Her medical his-

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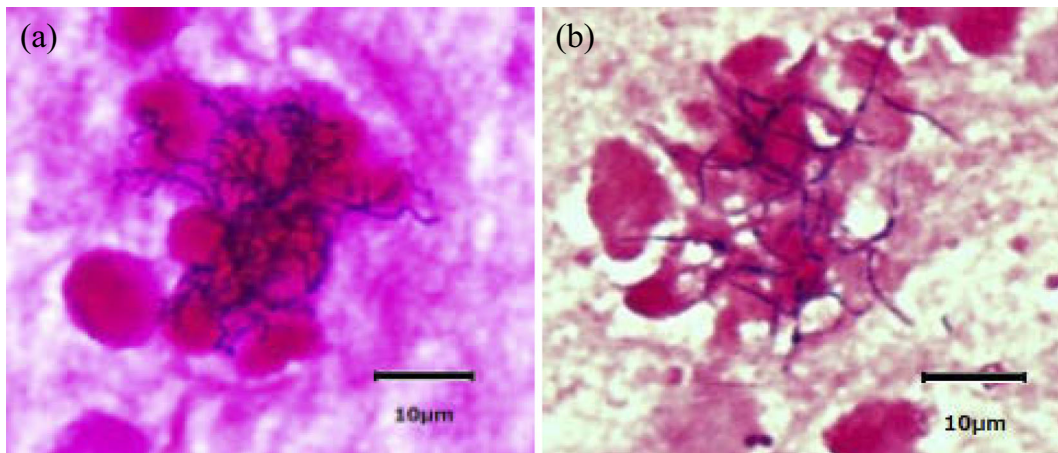


Figure 1. A Gram stain of the sputum in 2013 showed branching Gram-positive filaments, suggestive of *Nocardia* species, surrounded by white blood cells (a). A Gram stain of the sputum in 2016 showed branching Gram-positive filaments, suggestive of *Nocardia* species, surrounded by white blood cells (b).

Table. Antibiotic Susceptibility Test Results for *N. cyriacigeorgica* and *N. beijingensis*.

Antibiotics*	MIC (µg/mL)		Susceptibility breakpoints based on CLSI M24-A2 (7)		
	<i>N. cyriacigeorgica</i>	<i>N. beijingensis</i>	Susceptible	Intermediate	Resistant
AMK	<0.5	<0.5	≤8	-	≥16
ACV	8/4	<1/0.5	≤8/4	16/8	≥32/16
CTRX	<2	4	≤8	16-32	≥64
CPFX	2	>4	≤1	2	≥4
IPM	2	8	≤4	8	≥16
LZD	4	8	≤8	-	-
MINO	2	1	≤1	2-4	≥8
TMP/SMX	19/1	19/1	≤38/2	-	≥76/4
TOB	<0.5	1	≤4	8	≥16
CTX	<2	16	≤8	16-32	≥64
CFPM	2	4	≤8	16	≥32
DOXY	2	2	≤1	2-4	≥8
GM	<0.5	<0.5	≤4	8	≥16
ABPC	>8	8			
CAM	>8	2	≤2	4	≥8
EM	>2	>2			

*AMK: amikacin, ACV: amoxicillin/clavulanate, CTRX: ceftriaxone, CPFX: ciprofloxacin, IPM: imipenem, LZD: linezolid, MINO: minocycline, TMP/SMX: trimethoprim-sulfamethoxazole, TOB: tobramycin, CTX: cefotaxime, CFPM: cefepime, DOXY: doxycycline, GM: gentamicin, ABPC: ampicillin, CAM: clarithromycin, EM: erythromycin

tory was significant for bronchiectasis, which had been noted 20 years earlier, in the absence of sinusitis. She had no history of solid organ transplantation, hematopoietic stem cell transplantation, human immunodeficiency virus (HIV) or diabetes mellitus. She had not received inhaled or systemic corticosteroids or any immunosuppressant agents. She was a rose grower by occupation. On an examination, her body weight and height were 43 kg and 152 cm, respectively. Chest auscultation revealed coarse crackles over the posterior area of the left hemithorax. A laboratory test showed the following results: white blood cell count, 6,600/µL; C-reactive protein, 2.32 mg/dL; β-D glucan, 7.0 pg/mL (≤20). Chest CT revealed an increased number of small centrilobular nodules and the exacerbation of inflammatory

changes around the ectatic bronchi in the left lower lobe of the lung (Fig. 2c). A Gram stain of the sputum again showed branching Gram-positive filaments suggestive of *Nocardia* species (Fig. 1b). No other findings to suggest disseminated nocardiosis, such as skin or central nervous system lesions, were detected.

For a definitive diagnosis, she underwent flexible bronchoscopy, which showed inflammatory swelling of the bronchial submucosa and pooling of purulent sputum in the left inferior lobar bronchus. *Nocardia* species were predominantly cultured from the sputum and the bronchial washing specimen in the left lower lobe. Although small quantities of *Pseudomonas fluorescens* were also cultured from the bronchial washing specimen, mycobacterium was not isolated

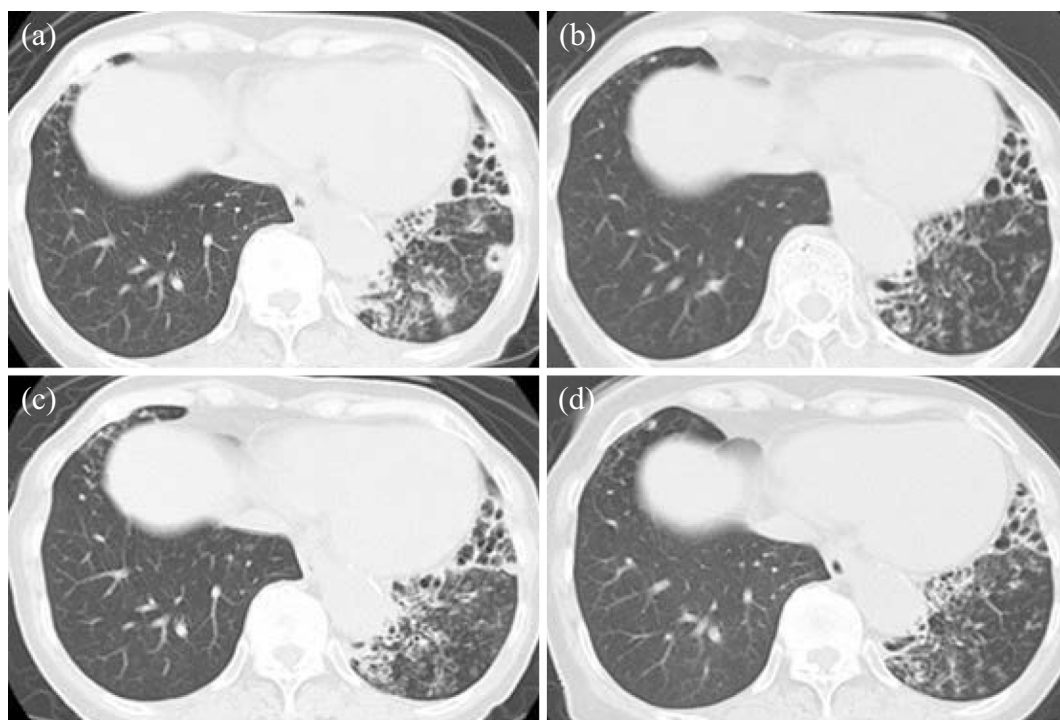


Figure 2. Chest CT in 2013 revealed small centrilobular nodules and inflammatory changes around the ectatic bronchi in the left lower lobe of the lung (a). Chest CT in 2014 showed improvement of the aforementioned lesions (b). Chest CT in 2016 revealed an increased number of small centrilobular nodules and the exacerbation of inflammatory changes in the left lower lobe of the lung (c). Chest CT in 2017 demonstrated improvement of the aforementioned lesions (d).

from either the sputum or bronchial washing specimen. Given her history of pulmonary nocardiosis and concern about resistance to TMP/SMX, we empirically started oral combination therapy of TMP/SMX (80/400 mg thrice per day) and minocycline (MINO) (100 mg once per day). The isolates were later identified as *N. beijingensis* using 16S ribosomal RNA gene sequencing and found to be susceptible to TMP/SMX (Table).

Because of nausea associated with MINO, MINO was stopped after one week of the treatment. TMP/SMX was continued with improvement of her respiratory symptoms. Chest CT performed nine months after the initiation of TMP/SMX therapy revealed improvement in the small centrilobular nodules and inflammatory changes around the ectatic bronchi in the left lower lobe of the lung (Fig. 2d).

Discussion

We herein reported a case of pulmonary reinfection by different *Nocardia* species in an immunocompetent patient with bronchiectasis, wherein 16S ribosomal RNA gene sequencing was useful for distinguishing between relapse and reinfection by *Nocardia*.

Pulmonary nocardiosis often occurs in immunocompromised patients. Solid organ transplantation, hematopoietic stem cell transplantation, chronic granulomatous disease, chronic alcoholism, diabetes mellitus and HIV infection are reported as risk factors for pulmonary nocardiosis (1). Fur-

thermore, previous studies have shown that pulmonary nocardiosis can occur in immunocompetent patients (4-6). Immunocompetent patients with pulmonary nocardiosis frequently show pulmonary structural abnormalities, such as chronic obstructive pulmonary disease and bronchiectasis. Kurahara et al. reported 59 cases of pulmonary nocardiosis in Japan (8). All but 1 patient appeared to be immunocompetent, and 88% of them had at least 1 underlying pulmonary disease. Fujita et al. also reported 30 cases of pulmonary nocardiosis in Japan. Among them, 12 patients were immunocompetent, and 8 of the 12 (67%) had bronchiectasis (9). They also reported that 7 out of 9 immunocompetent patients with *Nocardia* colonization had bronchiectasis. A US study also found an increased incidence of pulmonary nocardiosis associated with bronchiectasis in a retrospective study of 183 patients with *Nocardia* infections, although they did not attempt to distinguish infection from colonization (10). Despite the fact that the proportion of immunocompromised patients with *Nocardia* infection remained almost unchanged over the study period in their study, the proportion of patients with bronchiectasis who had *Nocardia* infection increased significantly. However, the reasons for the increased incidence of *Nocardia* infection among patients with bronchiectasis in the present study were not clear. In our case, the patient had long-standing bronchiectasis, which might have predisposed her to pulmonary reinfection by *Nocardia*. Furthermore, her occupation as a rose grower and the associated frequent contact with soil might

have induced pulmonary reinfection by *Nocardia*.

Reinfection by *Nocardia* is rarely reported. To our knowledge, this is the first case report of pulmonary reinfection by *Nocardia* in an immunocompetent patient. One report described pulmonary reinfection by *Nocardia* in a patient with chronic granulomatous disease (11). A polymerase chain reaction-restriction fragment length polymorphism analysis revealed this to be a case of reinfection by different *Nocardia* species. There have been several reports of recurrent nocardiosis after a clinical cure was achieved with adequate antimicrobial therapy (12-15). However, given that a molecular analysis, such as 16S ribosomal RNA gene sequencing, was not performed in those cases, reinfection by *Nocardia* might be underdiagnosed. While a molecular analysis by 16S ribosomal RNA gene sequencing has become the gold standard for the identification of *Nocardia* species recently, it lacks widespread use in general microbiological laboratories because of the technical difficulty and expense. This may be part of the reason so few reports have been published regarding reinfection by *Nocardia*.

In our case, 16S ribosomal RNA gene sequencing was useful for distinguishing between relapse and reinfection by *Nocardia*. When *Nocardia* is isolated from clinical specimens, the species should be identified. Different *Nocardia* species may have different susceptibility profiles, and this information is crucial for providing adequate antimicrobial therapy (16) as well as investigating the epidemiology of *Nocardia* infections.

In conclusion, pulmonary reinfection by *Nocardia* can occur even in immunocompetent patients and 16S ribosomal RNA gene sequencing is useful for distinguishing between relapse and reinfection by *Nocardia*. When *Nocardia* species are detected in patients with a history of pulmonary nocardiosis, reinfection by *Nocardia* should be considered not only in immunocompromised patients but also in immunocompetent patients, especially those with pulmonary structural abnormalities.

The authors state that they have no Conflict of Interest (COI).

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