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【 CASE REPORT 】

Pulmonary Nocardiosis Due to *Nocardia exalbida* Infection Following Living-donor Liver Transplantation

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Abstract:

Nocardia exalbida, an uncommon *Nocardia*, was first identified in 2006. We herein report a 70-year-old man with pulmonary nocardiosis caused by *N. exalbida* after living-donor liver transplantation. We also review 11 previously reported cases of *N. exalbida* infections. To our knowledge, there are no case reports available on nocardiosis consequent to *N. exalbida* infection following transplantation, thus highlighting the importance of identifying bacterial species for the successful management of infection.

Key words: *Nocardia*, pulmonary nocardiosis, transplantation

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Introduction

Nocardia species are aerobic, gram-positive, weakly acid-fast soil bacteria that cause localized or disseminated infections in animals and humans (1). Immunocompromised hosts, including patients with cancer or human immunodeficiency virus infection, those undergoing corticosteroid therapy, and post-transplantation patients, are particularly susceptible to *Nocardia* infection (2). The prognosis of *Nocardia* infection in immunocompromised patients is poorer than that in immunocompetent patients; the mortality rate of *Nocardia* infection in solid organ transplant recipients, for example, is approximately 15-20% (2-4).

Currently, more than 100 species of *Nocardia* have been characterized, many of which have been implicated in human diseases (5). Antibiotic susceptibility guides treatment but differs considerably depending on the species and strain; therefore, accurate identification of the bacterium at the species level and susceptibility testing are paramount (3). However, these assays can only be performed in specialized reference laboratories (6).

Nocardia exalbida infection was first reported in 2006, and it has rarely been reported since then (7-16). We herein report the first known case of pulmonary nocardiosis caused by *N. exalbida* in a patient after liver transplantation. We also review previously published case reports in conjunction with the case included in the present study to summarize the susceptibilities and clinical manifestations of *N. exalbida*.

Case Report

A 70-year-old Japanese man was evaluated at our hospital during a regular follow-up visit following liver transplantation. He was found to have leukocytosis and multiple bilateral lung nodules on chest radiography and was subsequently admitted for a further evaluation. He had originally been diagnosed with hepatitis C 29 years earlier. He received interferon-based therapy and achieved sustained virologic control, but he subsequently developed decompensated liver cirrhosis and hepatocellular carcinoma. He underwent transcatheter arterial chemoembolization and radiofre-

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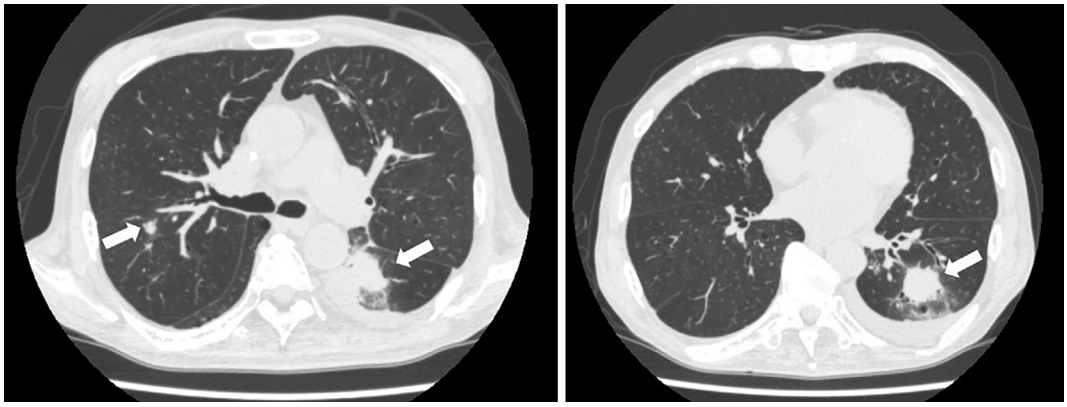

Figure. **Chest CT showing multiple bilateral lung nodules.**

quency ablation several times to treat the relapsed hepatocellular carcinoma. He had also undergone splenectomy for portal hypertension 12 years previously. He developed hepatic encephalopathy and portal vein thrombosis and had received a living-donor liver transplant four months earlier. The postoperative course had been uneventful, and the patient had been discharged from the hospital two months prior.

Approximately 1.5 months earlier, he had been admitted to another hospital and treated with intravenous piperacillin-tazobactam for presumed pneumonia. After discharge, the patient had shown no fever, cough, sputum, anterior chest pain, or headache. His medical history included hypertension, diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease. The patient was receiving methylprednisolone (6 mg), tacrolimus (10 mg), and mycophenolate mofetil (1,000 mg) daily. Notably, he had not been on anti-pneumocystis prophylaxis according to the institutional protocol, which uses a preemptive treatment approach based on plasma β-D-glucan levels (17). He did not have a history of exposure to soil or aquatic environments, such as gardening or swimming.

Upon admission, the patient was afebrile, and his other vital signs were within normal limits. Pulmonary and neurological examinations revealed no abnormalities. Laboratory findings for the patient were notable for a white blood cell count of 13,800 /μL, blood urea nitrogen level of 23.5 mg/dL, creatinine level of 1.70 mg/dL, lactate dehydrogenase activity of 305 U/L (reference range, 124-222), C-reactive protein level of 7.94 mg/dL (reference range, 0-0.3), and tacrolimus trough level of 8.6 ng/mL (reference range, 5-20). His serum tested negative for both galactomannan and cryptococcal antigens, and his β-D-glucan levels were within the normal biological reference interval. Chest computed tomography (CT) at admission revealed multiple scattered bilateral lung nodules, along with a 32-mm nodule in the left lower lobe (Figure).

After his sputum was submitted for smear testing and bacterial culture, the patient was empirically treated with intravenous piperacillin-tazobactam. He developed a fever on day 4 of hospitalization, but sputum culture did not reveal the presence of bacteria. Bronchoscopy was performed on day 9, and there were no bacteria on the smear of the gram stain from the bronchoalveolar lavage fluid.

However, growth of a small colony on blood agar was observed on day 11. *Nocardia* spp. were identified using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) Biotyper (Library BDAL 5627 Version 4; Bruker Daltonics, Bremen, Germany). The patient underwent magnetic resonance imaging of the brain; however, no lesions were observed.

Empirical treatment was initiated on day 11 with intravenous administration of imipenem-cilastatin and oral administration of trimethoprim/sulfamethoxazole (TMP-SMX) with 360 mg of TMP (approximately 7.5 mg per kg of body weight). A further evaluation was performed by analyzing the 16S rDNA sequence of isolated strain from the lavage fluid based on similarities with reference sequences in GenBank using the BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi). The results revealed 99.57% (1,393/1,399 bp) similarity of the sequence with type strain of *N. exalbida* IFM 0803 (GenBank accession number NR_041237) and 99.86% (1,409/1,411 bp) similarity of the sequence with type strain of *Nocardia gamkensis* W9743 (GenBank accession number NR_117399).

To supplement the results of 16S rRNA gene sequencing, additional gyrase B-encoding gene (*gyrB*) sequences of this strain were obtained and compared with those of *N. exalbida* and *N. gamkensis* from the GenBank database. A sequence analysis of *gyrB* showed that the sequence of this strain was 100% (1,197/1,197 bp) identical to that of *N. exalbida* IFM 0803 (GenBank accession number AB447397) and 98.79% (1,228/1,243 bp) similar to that of *N. gamkensis* W9743 (GenBank accession number GQ496112). Therefore, this strain was identified as *N. exalbida*.

A susceptibility test revealed that the isolate was susceptible to various antibiotics (Table 1) according to the Clinical and Laboratory Standards Institute (18). TMP-SMX was switched to oral linezolid on day 19 because of intractable nausea, while imipenem-cilastatin was continued. However, the patient developed thrombocytopenia, and linezolid was switched back to a reduced dose of TMP-SMX (160 mg

Table 1. Clinical Characteristics of 12 Adult Patients with *Nocardia exalbida* Infection.

Reference	Age (y) / Sex	Clinical signs	Presentation	Comorbidities	Geographical location	Treatment	Outcome
(7)	43/ Unknown	Unknown	Lung abscess	Immuno-compromised	Japan	Unknown	Unknown
(7)	60/ Unknown	Unknown	Unknown	Pemphigus vulgaris	Japan	Unknown	Unknown
(8)	38/F	Corneal ulcer	Keratitis	None	Japan	TMP-SMX for 10 days+topical agent	Resolved
(9)	63/M	Fever, headache, nausea, vomiting	Brain abscess	Follicular lymphoma	Japan	TMP-SMX+MEPM for 2 months → TMP-SMX for 6 months[a]	Resolved
(10)	47/M	Fever, dry cough	Pneumonia	HIV infection, hepatitis B, Type-2 diabetes	Japan	IPM+AMK for 17 days → GRNX for 6 months	Resolved
(11)	56/M	Scotoma, pain in eye	Endophthalmitis	Chronic angle closure glaucoma	United States	TMP-SMX for 6 months	Resolved
(12)	68/M	Fever, altered mental status	Pneumonia	HIV infection	Japan	TMP-SMX for 12 months	Resolved
(13)	57/M	Redness, tearing, decreased vision in his left eye	Blebitis	Open-angle glaucoma	United States	TMP-SMX+topical agent for 6 months[b]	Resolved
(14)	70/M	Fever, blood-stained sputum	Pneumonia	Lung cancer, radiation pneumonia	Japan	DRPM for 9 days → DRPM+TMP-SMX for 8 days	Died due to lung cancer
(15)	76/M	Cough, sputum, chest discomfort	Pneumonia	Overactive bladder, hemorrhoids	Japan	MEPM+TMP-SMX → TMP-SMX+LVFX for 3 months	Resolved
(16)	77/M	Fever, sputum, cough	Pneumonia	None	Japan	TMP-SMX for 4 months → MINO for 1 month	Resolved
Present case	70/M	None	Pneumonia	LDLT, diabetes	Japan	IPM/CS+TMP-SMX for 8 days → IPM/CS+LZD for 16 days → IPM/CS+TMP-SMX for 7 days → IPM/CS+MINO for 8 days → MINO for 12 months	Resolved

F: female, HIV: human immunodeficiency virus, LDLT: living donor liver transplantation, M: male, TMP-SMX: trimethoprim/sulfamethoxazole, MEPM: meropenem, IPM: imipenem, AMK: amikacin, GRNX: garenoxacin, DRPM: doripenem, LVFX: levofloxacin, MINO: minocycline, IMP/CS: imipenem-cilastatin, LZD: linezolid

[a]The case was published during treatment, and the author planned to continue TMP-SMX for 12 months.

[b]Patient received a longer course of treatment, but it was not described.

TMP component daily) on day 35 because of kidney impairment and intractable nausea. Owing to the gradual worsening of the renal function, TMP-SMX was replaced with oral minocycline (100 mg twice daily) on day 42. Chest CT on day 43 demonstrated a decrease in the size of pulmonary nodules.

The patient was discharged on day 50, with minocycline alone. He completed minocycline therapy for 1 year in accordance with the guidelines of the American Society of Transplantation, which recommend 6-12 months of treatment (19), and remained free of recurrence at the 18-month follow-up.

Discussion

N. exalbida was first isolated in 2006 from 2 immunocompromised patients (7), and 12 cases of its infection, including the present one, have been reported to date based on a search using the term of "Nocardia exalbida" in PubMed/MEDLINE (7-16). Nocardiosis caused by *N. exalbida* presents with various manifestations, including pulmonary lesions in 6 (50%) and ocular lesions in 3 (25%) (Table 1). Most cases were reported in Japan, except for two cases reported in the United States. In most reported cases, identification was performed by sequencing the 16S rRNA

Table 2. **Antimicrobial Susceptibility of *Nocardia exalbida*.**

	References, MIC (drug susceptibility)							
Antibiotic (s)	**(7) (Lung abscess)**	**(7) (Pemphigus vulgaris)**	**(9)**	**(10)**	**(12)**	**(14)**	**(16)**	**Present case**
TMP-SMX	0.12/2.4 (S)	0.12/2.4 (S)	0.12/2.4 (S)	≤0.25/4.75 (S)	0.25/4.75 (S)	-	0.2/4.75 (S)	≤0.5/9.5 (S)
IPM	-	-	<0.13 (S)	0.5 (S)	<0.5 (S)	-	1 (S)	≤2 (S)
AMK	-	-	-	≤1 (S)	-	-	<4 (S)	≤4 (S)
MINO	-	-	0.25 (S)	1 (S)	-	<0.12 (S)	2 (I)	≤1 (S)
CTRX	-	-	0.12 (S)	-	-	1 (S)	4 (S)	≤0.25 (S)
CPFX	-	-	-	2 (I)	2 (I)	-	4 (R)	2 (I)
AMPC/CVA	-	-	16 (R)	-	-	-	-	>8 (NS)
LZD	-	-	-	0.5 (S)	-	-	-	≤0.5 (S)
MFLX	-	-	-	-	-	-	-	-
CAM/AZM	1 (S)/-	2 (S)/-	<0.5 (S)/-	2 (S)/-	-	-	4 (I)/-	≤0.25 (S)/-
TGC	-	-	-	-	-	-	-	-

MIC (minimal inhibitory concentration) values at μg/mL. Drug susceptibility: S: sensitive, I: intermediate, R: resistant, NS: non-susceptible.
TMP-SMX: trimethoprim/sulfamethoxazole, IPM: imipenem, AMK: amikacin, MINO: minocycline, CTRX: ceftriaxone, CPFX: ciprofloxacin, AMPC/CVA: amoxicillin-clavulanic acid, LZD: linezolid, MFLX: moxifloxacin, CAM: clarithromycin, AZM: azithromycin, TGC: tigecycline

gene (7-16). Nearly half of the patients (5/12, 42%) were immunocompetent, and the prognosis was favorable.

To our knowledge, this is the first reported case of *N. exalbida* infection following solid organ transplantation. Solid organ transplant recipients are at high risk of opportunistic infections, including *Nocardia* infection. Risk factors for *Nocardia* infection of solid organ transplant recipients include high-level immunosuppression, cytomegalovirus disease, supratherapeutic calcineurin inhibitor levels, and an elevated patient age (3, 4). Among the transplanted organs, *Nocardia* infection is the most common post-kidney transplant, followed by the heart, lung, pancreas, and liver (3). Although our patient was a liver transplant recipient, the use of multiple immunosuppressants and an older patient age were risk factors for *Nocardia* infection.

One potential reason for the lack of reports of *N. exalbida* infections among transplant recipients is the geographically heterogeneous distribution of *Nocardia* species. In the United States, *N. farcinica*, *N. cyriacigeorgica,* and *N. nova* are common pathogens causing *Nocardia* infection in patients with or without solid organ transplants; *N. exalbida* infection has rarely been reported (4, 20). In contrast, *N. exalbida* is more common in Japan. A study analyzing 317 clinical samples submitted to a Japanese reference laboratory identified *N. exalbida* in 10 cases, constituting 3% of cases (21). Another potential reason for the lack of reports on *N. exalbida* infections is the difficulty in identification. Recently, MALDI-TOF has been shown to enable accurate identification of common *Nocardia* species. However, the identification of uncommon species remains challenging (6). In our case, the identification of *N. exalbida* required a nucleotide sequence analysis of the 16S rRNA and *gyrB* genes in a specialized laboratory. This difficulty in identification might lead to an underestimation of the actual number of *N. exalbida* infections, owing to the lack of access to testing. The identification of *Nocardia* species is important because each species has different drug susceptibilities and organ affinities.

Susceptibility testing is crucial for determining the therapeutic course, especially because susceptibility varies significantly between *Nocardia* species (3). Treatment protocols may extend over long periods, and multiple changes are sometimes required to respond to adverse drug reactions. Although central nervous system infections, including brain abscesses, were reported in only one case in our literature review, an observational study on nocardiosis reported that about one-third of patients had central nervous system infections (1). Therefore, it is desirable to use antimicrobial agents that penetrate the blood-brain barrier as an empirical treatment. Our patient was started on empirical treatment with imipenem-cilastatin and TMP-SMX but required changes in the regimen due to adverse reactions. Antimicrobial resistance has been recognized in certain species of *Nocardia* (19), and previous case reports indicate that *N. exalbida* is susceptible to many antimicrobial agents (7, 9, 10, 12, 14, 16), as summarized here (Table 2). Susceptibility to many antimicrobial agents may lead to a good prognosis, as multiple effective treatment options are available.

In conclusion, we reported a case of pulmonary nocardiosis caused by *N. exalbida* in a patient who underwent liver transplantation. Accurate species identification is essential for the successful management and understanding of the epidemiology of *Nocardia* infections.

Informed consent was obtained from the patient for publication of the report and associated images.

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

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