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【 CASE REPORT 】

Pulmonary Nocardiosis Caused by *Nocardia exalbida* in a Patient with Lung Cancer and Radiation Pneumonitis: A Case Report and Literature Review

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Abstract:
We report a case of *Nocardia exalbida* (*N. exalbida*)-induced pneumonia in a 70-year old Japanese man with lung cancer and radiation pneumonitis. He initially received doripenem (1.5 g/day) for pneumonia treatment, and *N. exalbida* was identified by a clone library analysis of bronchoalveolar lavage fluid obtained from the pneumonia lesion. The doripenem dosage was therefore increased to 3.0 g/day with adjunctive trimethoprim/sulfamethoxazole, and his pneumonia improved. *N. exalbida* is susceptible to antibiotics; thus, in nocardiosis, *N. exalbida* infection might be associated with a good response to treatment, although its clinical findings are non-specific and similar to those of other *Nocardia* infections.

Key words: nocardia, pulmonary nocardiosis, lung cancer, radiation pneumonitis

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Introduction

Nocardia is an aerobic gram-positive rod bacterium that belongs to the Actinomycetes genus and which is primarily distributed in the soil (1-3). Human infection is predominantly caused via direct inoculation of the skin or inhalation (1-3). Nocardiosis occurs in various organs, including the brain, lungs, skin, and eyes. The lung is the most commonly infected organ (1-9). Immunosuppressed hosts are particularly susceptible to nocardiosis, which can occasionally be severe (10), and the incidence of nocardiosis has been increasing according to an increase in the number of elderly and immunocompromised patients (1, 11, 12). In addition, the prognosis of pulmonary nocardiosis often depends on the underlying disease, and the 1-year survival rate of pulmonary nocardiosis patients treated with immunosuppressants is approximately 40% (8).

Ninety-two *Nocardia* species have been reported thus far, and fifty-four have been recognized as clinically significant bacteria (10, 11). Clinically, the identification of the *Nocardia* species in nocardiosis is highly important because the drug susceptibility differs among the species (1, 4, 8). *N. exalbida* was first reported in Japan in 2006 (9). To date, only a few cases of *N. exalbida* infection have been reported (4, 5, 13-17), and the clinical characteristics of *N. exalbida* infection have not been fully elucidated.

We herein report a case of pulmonary nocardiosis caused by *N. exalbida* in a patient with lung cancer and radiation pneumonitis, and review the reported cases of *N. exalbida* infection.

Case Report

A 70-year old Japanese man was diagnosed with right hilar squamous cell carcinoma (SCC) (cT3N3M0, stageIIIB) in February 2011. He was an ex-smoker (39 pack-years). A single administration of systemic chemotherapy with cisplatin and vinorelbine and concurrent radiotherapy (total radiation dose: 50 Gy) to the right hilum and mediastinum were performed, resulting in a decrease in the tumor size. Radiation pneumonitis occurred in April, and treatment with prednisolone [PSL (50 mg/day)] was initiated. The radiation pneumonitis gradually improved, and the dose of PSL was

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Table 1. The Results of the Peripheral Blood Analysis on Admission.

<Blood cell counts>		<Blood chemistry>			
WBC	16,900 /μL	TP	5.2 g/dL	CYFRA21-1	10.0 ng/mL
Neutrophils	93.7 %	Alb	2.3 g/dL	SCC	7.0 ng/mL
Lymphocytes	3.3 %	T-bil	0.5 mg/dL	QFT (QuantiFeron®)	indeterminant
Eosinophils	1.0 %	AST	68 IU/L	measurements A	<0.10 IU/mL
Monocytes	2.8 /μL	ALT	53 IU/L	measurements M	<0.50 IU/mL
Basophils	0.1 g/dL	LDH	260 IU/L	β-D glucan	<6.0 pq/mL
RBC	300×10^4 /μL	ALP	429 IU/L	Aspergillus antigen	2.9
Hb	10.4 g/dL	γ-GTP	230 IU/L	Cryptococcus neoformans	(-)
Ht	30.9 %	BUN	17 mg/dL		
Platelets	18.7×10^4 /μL	Cre	0.54 mg/dL	<Blood gas analysis (O_2 3 L/min)>	
				pH	7.538
		<Serology>		PaO_2	86.0 mmHg
		CRP	13.5 mg/dL	$PaCO_2$	41.5 mmHg
		KL-6	350 U/mL	HCO_3^-	34.5 mmol/L

WBC: white blood cell, RBC: red blood cell, Hb: haemoglobin, Ht: haematocrit, TP: total protein, Alb: albumin, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transferase, BUN: blood urea nitrogen, CRP: c-reactive protein, KL-6: Krebs von den Lungen-6, CYFRA21-1: cytokeratin-19 fragments, SCC: squamous cell carcinoma, O_2: oxygen, PaO_2: partial pressure of arterial oxygen, $PaCO_2$: partial pressure of arterial carbon dioxide, HCO_3^-: bicarbonate ion

reduced to 35 mg/day in May and was continued without prophylactic treatment with trimethoprim/sulfamethoxazole (TMP-SMZ).

In June, he suddenly experienced a high-grade fever (38.0°C), and his chest radiograph revealed infiltration in the right middle lung field with elevated C-reactive protein (CRP) levels (15.3 mg/dL). Bacterial pneumonia was suspected, and the oral administration of levofloxacin [LVFX (500 mg/day)] was started, resulting in a worsening of the chest radiography findings. He was eventually admitted to our hospital in July, due to a persistent high-grade fever (38.0°C) and blood-stained sputum.

Upon admission, he exhibited a poor general condition and strong breathlessness. A physical examination revealed the following findings: height, 159.1 cm; body weight, 49.5 kg; body temperature, 38.2ºC; heart rate, 130 bpm; blood pressure, 104/60 mmHg; and oxygen saturation, 85% in room air. Chest auscultation demonstrated audible coarse crackles in the right upper lung field, and pitting edema was observed in both lower legs. The laboratory findings on admission (Table 1) demonstrated an elevated peripheral blood white blood cell count (16,900 U/μL) and CRP level (13.5 mg/dL), and an interferon-gamma releasing assay for *M. tuberculosis* (QuantiFeron®) was inconclusive. The patient's serum was positive for *Aspergillus* antigen, but his ß-D glucan titer was within the normal range, and his serum was negative for *Cryptococcus neoformans* antigen. Increased serum levels of CYFRA21-1 (10.0 ng/dL) and the SCC antigen (7.0 ng/mL) were observed. The serum Krebs von den Lungen (KL)-6 level was within the normal limit (350 U/mL). A chest radiograph on admission revealed novel infiltrative shadows in the right upper and middle lung fields, and chest computed tomography on admission showed infiltrative shadows with air bronchograms in the right middle lobe as well as opacities in the hilum of the right lung that were associated with lung cancer and which narrowed the airway (Fig. 1, 2).

Bronchoscopy was performed on admission to investigate the source of the airway bleeding, and the adhesion of blood to the trachea, right main bronchus, and right upper leaf branch was revealed, but no active bleeding was observed. The examination of a bronchoalveolar lavage fluid (BALF) specimen obtained from a pneumonia lesion in the right B^5 revealed the presence of numerous filamentous gram-positive bacteria (Fig. 3). In addition, similar bacteria were observed in sputum smears and cultures obtained on admission. A clone library analysis targeting the 16S rRNA gene was performed using the BALF in order to evaluate the bacterial flora according to the methods of our previous reports (18-21). Briefly, approximately 600 bp of part of the 16S rRNA gene extracted from DNA samples from the BALF specimen were amplified via a polymerase chain reaction (PCR) using a universal primer, the PCR products were cloned, and the clone library was constructed (18-21). The sequences of the 16S rRNA gene of 96 randomly selected clones from the clone library were determined, and a homology search comparing the sequences with the recorded reference strains was then performed using the basic local alignment search tool algorithm (21). As a result, approximately 65.3% (49/75 clones) of the bacterial clones in his BALF sample were identified as *N. exalbida* (accession number, NR 11,732.1) (Table 2). The patient was then suspected of having pneumonia caused by *N. exalbida*. Sputum and BALF cultures were positive for *Nocardia* species on day 9; however, the *Nocardia* species was not identifiable. The bacterial strain obtained by culturing was identified as *N. exalbida* by a PCR targeting the 16S rRNA gene (1,500 bp). According to these findings, the patient was diagnosed

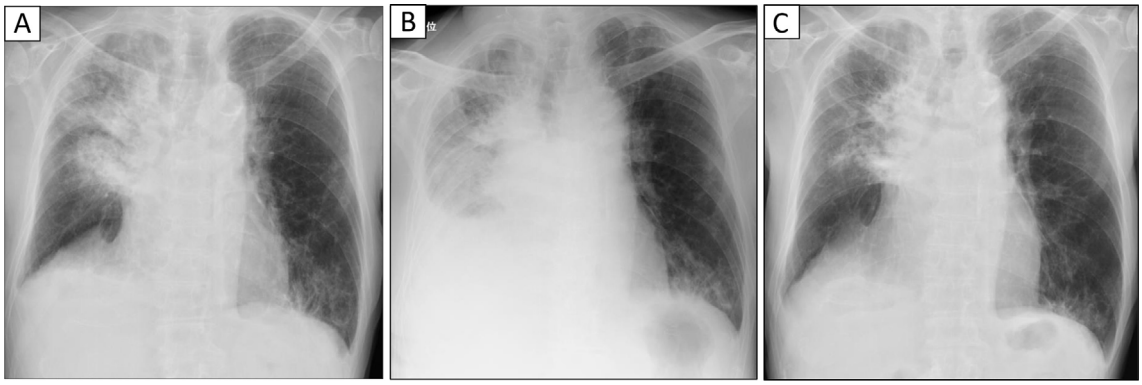

Figure 1. **A chest X-ray obtained on admission showed new infiltration in the right upper and middle lung fields (A). The chest X-ray obtained on day 4 showed worsening infiltration of the right lung field with right pleural effusion (B). After increasing the dose of DRPM from 1.5 g/day to 3.0 g/day with adjunctive TMP-SMZ treatment (day 14), the pulmonary infiltration and right pleural effusion on chest X-ray improved (C).**

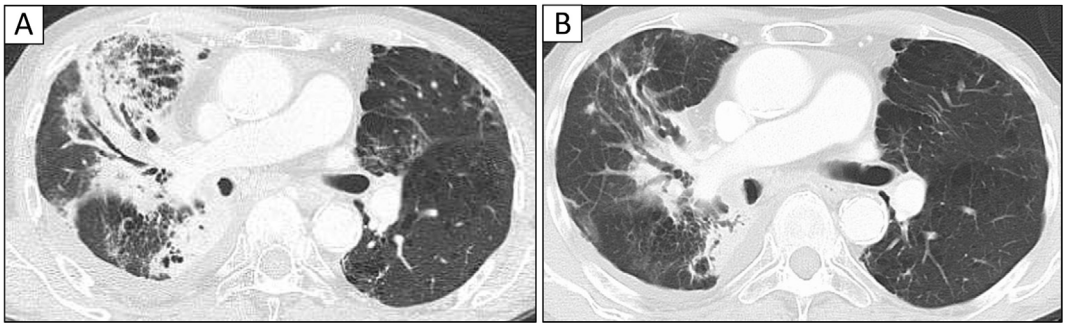

Figure 2. **Chest computed tomography (CT) on admission (A). Chest CT on admission demonstrated consolidation with air bronchogram in the right middle lobe (A). After antibiotic treatment (day 14), most sites of pulmonary infiltration improved (B).**

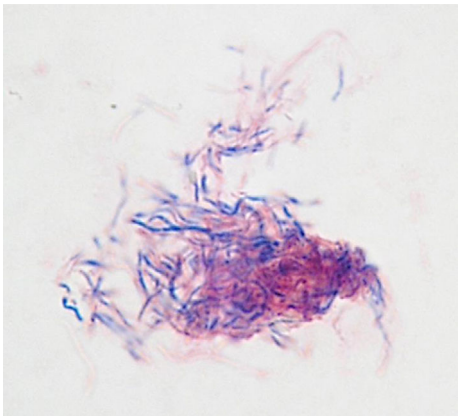

Figure 3. **The observation of Gram-stained bronchial lavage fluid by light microscopy (×1,000).**

with pulmonary nocardiosis caused by *N. exalbida*.

Doripenem (DRPM) (1.5 g/day) was initiated after admission, with the continuation of PSL (35 mg/day) for radiation pneumonitis. However, recurrent blood-stained sputum and an elevated serum CRP level were observed on day 3, and

Table 2. **The Results of Clone Library Analysis Targeting the 16S Ribosomal RNA Gene Using Bronchoalveolar Lavage Fluid.**

Species	%
Nocardia exalbida	65.3
Propionibacterium acnes	1.3
Prevotella veroralis	2.7
Gemella haemolysans	1.3
Gemella sanguinis	2.7
Staphylococcus epidermidis	1.3
Granulicatella adiacens	2.7
Veillonella dispar	1.3
Fusobacterium canifelinum	1.3
Leptotrichia shahii	1.3
Brevundimonas vesicularis	2.7
Curvibacter delicatus	4.0
Campylobacter mucosalis	4.0
Shigella flexneri	5.3
Actinetobacter junii	1.3
unclassified	1.3

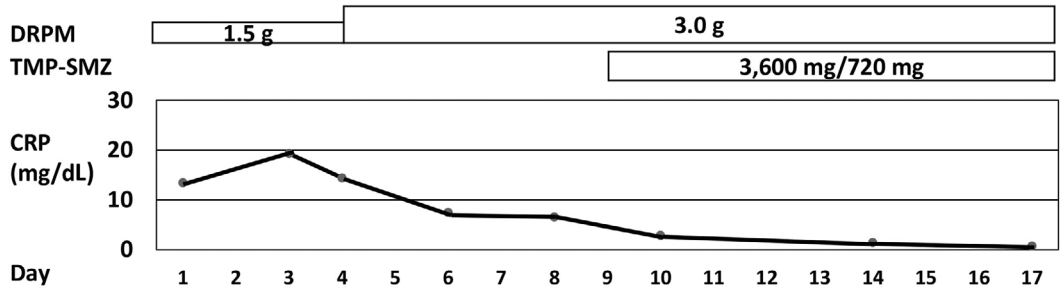

Figure 4. **The clinical course of the present patient. DRPM: doripenem, SMX/TMP: sulfamethoxazole/trimethoprim, PSL: prednisolone**

Table 3. **The Reported Cases of *Nocardia exalbida*.**

Reference	Age(y) / Sex	Presentation	Comorbidity	Antibiotics used for outcome	Outcome
4	47 / M	Pneumonia	HIV, Hepatitis B, Type-II diabetes	IPM+AMK for 17days → GRNX for 6 months	improved
13	43 / unknown	Pulmonary abscess	Immunocompromised patient (details unknown)	unknown	unknown
14	68 / M	Pneumonia	HIV	TMP/SMX for 12 months	improved
5	63 / M	Brain abscess	Follicular lymphoma	MEPM+TMP-SMZ for 2 months → TMP	improved
15	38 / F	Keratitis	none	TMP-SMZ for 10 days Topical therapy: TOB+CP+SZ+ colistin sodium methanesulfonate	improved
16	56 / M	Endophthalmitis	none	TMP-SMZ for 6 months	improved
17	57 / M	Blebitis	Open-angle glaucoma	TMP-SMZ+Topical therapy: sulfonamide+AMK for 6 months	improved
13	60 / unknown	Pemphigus vulgaris	Immunocompromised patient (details unknown)	unknown	unknown
Present case	70 / M	Pneumonia	Lung cancer, Radiation pneumonia (oral steroids)	DRPM+TMP-SMZ	improved

HIV: human immunodeficiency virus, IPM: imipenem, AMK: amikacin, GRNX: garenoxacin, MINO: minocycline, TMP-SMZ: trimethoprim/sulfamethoxazole, MEPM: meropenem, TOB: tobramycin, CP: chloramphenicol, SZ: sulfisoxazole., DRPM: doripenem

his hypoxemia worsened and a chest radiograph showed worsening infiltrative shadows of the right lung field and increased right pleural effusion on day 4, Thus, the dose of DRPM was increased from 1.5 g/day to 3.0 g/day on day 4. The blood-stained sputum, hypoxemia, serum levels of CRP, and radiological findings subsequently improved. Adjunctive treatment with TMP-SMZ (3,600 mg/720 mg) was administered in addition to DRPM (3.0 g/day) after the identification of *N. exalbida*. This led to a gradual improvement in his laboratory and chest radiography findings (Fig. 1, 2, 4).

The sudden progression of hypoxemia was observed on day 18, and chest radiography revealed right middle lobe atelectasis, due to airway narrowing in association with progressive lung cancer. With the deterioration of his respiratory function and general condition, intravenous continuous administration of morphine hydrochloride was started from day 20 to provide relief from pain and dyspnea. He died on day 22.

Discussion

N. exalbida was first isolated from two Japanese immunocompromised patients with a cutaneous lesion and lung abscess in 2006 (13). To date, nine cases of nocardiosis caused by *N. exalbida* have been reported, including our patient (Table 3). The lung is generally the most common site of infection in nocardiosis, with lung infections accounting for approximately 40-70% of nocardiosis cases (2, 22-25). Four of the nine reported cases of *N. exalbida* infection involved the lung (44.4%) (4-13), and ocular lesions were also reported in three of the cases (33.3%) (15-17). Nocardiosis tends to develop in patients with underlying diseases such as diabetes, malignancy, or chronic obstructive pulmonary disease, and immunosuppressed patients. Comorbid diseases are reported in approximately 60-90% in nocardiosis patients (2, 22, 23, 25). Seven (77.7%) of the nine cases of *N. exalbida* infections had comorbid diseases. There are no characteristic clinical symptoms or radiological findings that can be used to distinguish *N. exalbida* infection from other

Table 4. **Antimicrobial Susceptibility to *Nocardia exalbida*.**

Reference	Presentation	CTX	CTRX	MEPM	IPM/CS	MINO	GRNX	AMK	SMZ/TMP	LZD
4	Pneumonia		4	1	0.5	1	2	≤1	≤4.75/0.25	0.5
			(S)	(-)	(S)	(S)	(S)	(S)	(S)	(S)
13	Pulmonary abscess							16	2/4	
								(-)	(-)	
14	Pneumonia				<0.5				4.75/0.25	
					(-)				(-)	
5	Brain abscess	0.12		0.5	<0/13	0.25			0.12	
		(S)		(-)	(S)	(S)			(S)	
13	Pemphigus vulgaris							>16	2/4	
								(-)	(-)	
Present case	Pneumonia	1	1	0.5		<0.12	2			
		(-)	(-)	(-)		(-)	(-)			

The upper row presents the minimal inhibitory concentration (MIC), μg/mL.

The lower row shows drug susceptibility. S: sensitive, I: intermediate, R: resistant, (-): not described

CTX: cefotaxime, CTRX: ceftriaxone, MEPM: meropenem, IPM/CS: imipenem/cilastatin sodium, MINO: minocycline, GRNX: garenoxacin, AMK: amikacin, TMP-SMZ: trimethoprim/sulfamethoxazole, LZD: linezolid

nocardiosis infections, although the symptoms and radiological findings are generally nonspecific in nocardiosis (1-3, 8, 26, 27). It is therefore difficult to differentiate *N. exalbida* infection and other nocardiosis infections based on the clinical background, symptoms, and radiographic findings.

The early diagnosis and treatment of pulmonary nocardiosis are highly important because the mortality rate of such patients is approximately 40%, and a higher mortality rate of approximately 60% has been reported in cases with dissemination (27). However, the diagnosis of pulmonary nocardiosis is often delayed due to its nonspecific clinical symptoms and radiological findings, and the absence of specific methods for the serological diagnosis of nocardiosis. A definitive diagnosis of nocardiosis is only made by the separation and identification of *Nocardia* species using the culture method (3, 26). However, culturing of *Nocardia* species is difficult and requires several days to several weeks (1, 3, 6), and the rate of successful sputum culture ranges from 10 to 70% (28). Gram staining of *Nocardia* species reveals a characteristic structure of delicate, beaded, branching filaments; thus, gram staining is useful when nocardiosis is suspected (1, 3).

The identification of the *Nocardia* species is important in nocardiosis because they show susceptibility to different antibiotics (1, 4, 7, 13, 29). For example, *N. farcinica*, a common species in nocardiosis, is resistant to most of the antibiotics that are normally used for the treatment of nocardial infections (13, 30, 31). The identification of the *Nocardia* species can be performed according to a combination of biochemical tests, growth characteristics, and the antimicrobial susceptibility patterns of cultured bacteria (2, 3, 26). However, the relatively low rate of successful sputum culture of *Nocardia* species (28), the relatively long time required to identify the cultured bacteria, and the number of *Nocardia* species may make it more difficult to a achieve completely accurate identification of the *Nocardia* species. Thus, a bacterial 16S rRNA sequence analysis has recently become the gold standard for the identification of *Nocardia* species (4-7, 26, 32), and all nine cases of *N. exalbida* infection, including our patient, were identified by 16S rRNA sequencing. In addition, we evaluated the bacterial flora of the BALF sample by a clone library analysis targeting the 16S rRNA gene according to previous reports (18-21); 65.3% of the bacterial clones were found to be *N. exalbida*, and the patient was determined to have pulmonary infection with *N. exalbida* (Table 2). 16S rRNA sequencing to identify the bacterial species is generally performed after obtaining a cultured bacterial strain, and is therefore time-consuming. However, the clone library analysis we used takes only a few days after specimen collection without estimating the bacterial species, and we believe that an earlier definitive diagnosis of nocardiosis can help to facilitate appropriate treatment.

TMP-SMZ is widely used as the mainstay in the treatment of nocardiosis (4, 5, 27). Carbapenems such as imipenem/cilastatin sodium (IPM/CS) and meropenem (MEPM), amikacin, minocycline, and linezolid are also used (4, 5, 11). In the present patient, the combination of TMP-SMZ and DRPM was administered after the diagnosis of *N. exalbida* infection. Although our patient ultimately died due to the progression of lung cancer, the clinical response to antibiotic therapy was good (Fig. 4). Susceptibility to antibiotics greatly affects the prognosis for nocardiosis (12, 32), and as summarized in Table 4, among the *Nocardia* species, *N. exalbida* is susceptible to antibiotics. All seven reported cases of *N. exalbida* infection noted that the prognosis improved after treatment, and that the identification of *N. exalbida* might be associated with a good response to treatment in nocardiosis. DRPM is effective for the treatment of pulmonary nocardiosis as well as IPM/CS and MEPM. In our patient, DRPM (1.5 g/day) was ineffective, but the increased dose of 3.0 g/day was effective. Carbapenem antibiotics require ≥50% time above minimum inhibitory concentration (% TAM) to achieve the maximum bactericidal effect, and the plasma concentration of MEPM clearly increased after increasing the dose of MEPM from

1.5 g/day to 3.0 g/day (33). Thus, an increase in the antibiotic dose can be effective when the clinical response to a medium dose of carbapenem is poor.

Combination treatment with TMP-SMZ and DRPM was effective in our case. The synergistic effect of combination therapy with IPM/CS and TMP-SMZ on *N. asteroides* infection was reported *in vitro* (34), and the synergistic effect of a combination of DRPM and TMP-SMZ might have been obtained in our case. In addition, it is reported that TMP-SMZ monotherapy resulted in a high mortality rate in nocardiosis. Thus, physicians should consider combination therapy with amikacin, imipenem, or a third-generation cephalosporin, in addition to TMP-SMZ in severe cases (5, 28, 35).

In conclusion, we reported a case of pulmonary nocardiosis caused by *N. exalbida* in a patient with lung cancer and radiation pneumonitis treated with corticosteroids. *N. exalbida* is extremely rare among the *Nocardia* species, but the response to proper treatment seems to be favorable. The further accumulation of the clinical characteristics in each *Nocardia* species is expected to facilitate their early diagnosis and appropriate treatment.

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

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