Pulmonary Nocardiosis Caused by *Nocardia concava* with a Literature Review

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Abstract

A 68-year-old man was admitted to our hospital with anorexia and leg pain. He was diagnosed with ANCA-associated vasculitis through a renal biopsy. Immunosuppression with two courses of steroid pulse therapies and intravenous cyclophosphamide followed by oral prednisolone at 40 mg/day were administered. About one month after starting the immunosuppression therapy, he complained of hemoptysis. Chest computed tomography showed a cavitary lesion in the lung. Cultures from his sputum showed *Nocardia* species, and we were able to identify the species as *N. concava* using a 16S rRNA gene sequence analysis. Only three detailed reports of *N. concava* infection have so far been published worldwide.

Key words: *Nocardia concava*, review, pulmonary nocardiosis

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Introduction

Nocardia concava is a new *Nocardia* species identified in 2005 (1). There have been only 3 case reports of *N. concava* infection and its clinical characteristics have not been clearly described (2-4).

Nocardia spp. are aerobic, Gram-positive bacteria of the order *Actinomycetales*. They often enter through the respiratory tract, and the infection develops and spreads throughout the body. *N. brasiliensis*, *N. otitidiscaviarum*, *N. abscessus*, *N. nova*, *N. farcinica* and *N. cyriacigeorgica* are frequently associated with clinical infections (5). The antimicrobial sensitivity of *Nocardia* spp. varies by species (6). Therefore, identifying *Nocardia* species is important to select adequate antimicrobial agents. Here, we report the case of an immunocompromised patient who developed pulmonary nocardiosis caused by *N. concava* and review the previous case

reports.

Case Report

A 68-year-old man was admitted to our hospital with the chief complaints of anorexia and leg pain that had continued for a month. His medical and family history was unremarkable. He had retired from the construction industry eight years previously, and his hobby was gardening. His body weight was 56.8 kg and his height was 167.4 cm. Laboratory data revealed an elevated white cell count of 16,100/μL with neutrophil predominance (81%), an increased C-reactive protein level (22.86 mg/dL), renal dysfunction (creatinine 2.04 mg/dL, BUN 32 mg/dL) and increased myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA) (87.5 U/mL). His urinary sample showed high red cell counts (50-99/HPF). Chest computed tomography (CT) revealed no abnormal findings including nodules or masses.

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Figure 1. Chest radiograph and CT findings at onset and one month post-treatment. a, b: Chest radiograph and chest CT findings at the onset. A radiograph showed a cavity lesion in the left middle lung field. Chest CT showed a 22-mm cavitory lesion with wall thickness in the left upper lobe. c, d: A chest radiograph and CT scan at one month after the TMP/SMX. The wall thickness of the cavity was reduced.

He was diagnosed with ANCA-associated vasculitis via a renal biopsy. From hospital day 3, steroid pulse therapy for three days at a dosage of 1,000 mg/day was started and repeated twice daily for six days after the first steroid therapy, followed by the administration of oral prednisolone at 40 mg/day. In addition, cyclophosphamide (500 mg/day) was administered intravenously on the 20th day.

About one month after the induction of immunosuppression therapy, the patient complained of hemoptysis. Prophylaxis with trimethoprim and sulfamethoxazole (TMP/SMX) was not administered at this time. On physical examination, body temperature was 36.6°C, blood pressure was 116/84 mmHg, pulse rate was 67 bpm and the oxygen saturation level was at 98% while breathing in ambient air. Neither crackles nor heart murmurs were heard. Abdominal, dermal and neurological examinations did not reveal any particularly remarkable features.

A chest radiograph showed a cavity lesion in the left middle lung field. Chest CT showed a 22-mm cavitory lesion

with wall thickness in the left upper lobe of the lung (Fig. 1). A Gram stain of the sputum showed branching Gram-positive filaments suggesting nocardial infection (Fig. 2). Other lesions including in brain, liver and skin were not observed on brain or abdominal CT. The patient was diagnosed with pulmonary nocardiosis. A laboratory examination showed the following: a hemoglobin level of 11.1 g/dL, red cell count of $3.57 \times 10^6/\mu\text{L}$, platelet count of $18.8 \times 10^4/\mu\text{L}$, white blood cell count of $6,000/\mu\text{L}$, C-reactive protein level of 1.85 mg/dL, creatinine of 1.83 mg/dL and BUN of 35 mg/dL. Liver enzymes were within normal ranges. The β -D glucan test result was elevated (56.1 pg/mL), and the serum galactomannan antigen was positive (0.6 cut-off index). However, the serum *Aspergillus* precipitating antibody test was negative, and no fungi grew in the sputum cultures. An HIV antibody test was negative.

On the basis of his renal function, TMP/SMX (64mg-320 mg/day) were administered. Cultures from the sputum showed *Nocardia* species, and we were able to identify the

Figure 2. A Gram stain ($\times 1,000$) of sputum showed branching Gram-positive filaments suggesting a nocardial infection.

species as *N. concava* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS). We confirmed the identification result using a sequence analysis of the 16S rRNA gene. After the initiation of antimicrobial therapy, his symptoms improved, the wall thickness of the cavity decreased and the patient recovered from the infection.

Initially, the elevated β -D glucan test result made us suspect a mixed infection with *Aspergillus* spp. However, as the cavity lesion decreased in size without antifungal agents, we believe this was a false-positive result, and the β -D glucan test result decreased into the normal range (12.3 pg/mL) two months after the initiation of TMP/SMX.

Discussion

Nocardiosis is an uncommon Gram-positive bacterial infection caused by aerobic actinomycetes in the genus *Nocardia*. Nocardiosis is commonly regarded as an opportunistic infection, but approximately one-third of infected patients are immunocompetent (7). The genus *Nocardia* includes more than 80 species; over 30 *Nocardia* species have been shown to cause disease in humans (8). They are found worldwide in the soil and in aquatic environments (9). In the present case, considering that the patient's hobby was gardening, the route of infection might have been the inhalation of the organism from the soil.

Nocardia concava is a new *Nocardia* species identified by Kageyama et al. in 2005 (1). Advanced molecular diagnosis methods such as a 16S rRNA gene sequence analysis enable us to distinguish *N. concava* from other species (2). *N. concava* is reported to be most similar to *N. otitidiscaviarum* and *N. uniformis* given their biochemical characteristics. In addition, phylogenetic analysis demonstrated that it forms a monophyletic clade associated with *N. seriolae*. We guess that *N. concava* might have been misidentified as these species before recent methods such as a 16S rRNA gene sequence analysis and MALDI-TOF MS began to be applied in clinical settings. To date, only three case reports of *N. concava* infection have been published; these reports were

from Japan, China and Korea (2-4). The present case is from Japan; all remaining case reports have been from East Asian countries. Additional reports of *N. concava* infection may clarify its epidemiologic and clinical characteristics.

Table 1 lists the clinical manifestations of the three previously reported cases (2-4) in comparison with our case. All of them developed in immunocompromised hosts who had underlying diseases and were administered glucocorticoid therapy. All cases except ours developed disseminated nocardiosis. In all cases, antibiotic therapies were administered including sulfonamides, and combined antimicrobial therapies were initially administered in two severe cases. In the fatal case, the patient's condition had initially improved with antimicrobial therapies and he had discharged himself once, but his condition led to multiple organ failure after leaving the hospital. In the other cases, the patients' conditions improved. Kobayashi et al. reported that linezolid was associated with an improvement in their case, as the response to β -lactam antibiotics was poor.

Table 2 shows the antimicrobial susceptibility patterns of *Nocardia* spp. in our case. The minimum inhibitory concentrations (MIC) were determined using a microdilution method excluding trimethoprim-sulfamethoxazole. According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, our case was susceptible to ceftriaxone, cefepime, gentamicin, clarithromycin, minocycline and levofloxacin; however, it was resistant to cefotaxime and imipenem (10). The MIC for trimethoprim-sulfamethoxazole was determined using Etest[®] (bioMérieux, Lyon, France). The level of TMP/SMX that our case was susceptible to was 0.19 μ g/mL, for reference. McTaggart et al. recently reported that some *Nocardia* spp. such as *N. nova*, *N. farcinica* and *N. cyriacigeorgica* are generally susceptible to imipenem, while other strains such as *N. brasiliensis*, *N. otitidiscaviarum* and *N. abscessus* are not (11). *N. concava* tends to be resistant to imipenem and cephalosporin from the previous reported cases and our case, so these antibiotics should not be used as a first-line treatment.

Beaman et al. analyzed 1,050 nocardiosis cases and reported that the sites of nocardial infection were as follows: 32% of patients had systemic nocardiosis, 39% had pulmonary only, 9% had central nervous system (CNS) only, 8% had cutaneous or lymphocutaneous, and 12% had single-site extrapulmonary (e.g., eyes, bone) (7). We found two articles that reviewed nocardiosis caused by recently identified species. In cases of *N. veterana*, Ansari et al. reported that only one of nine cases developed disseminated nocardiosis, and the mortality rate was 11% (12). In *N. cyriacigeorgica*, Akcaglar et al. reported that 14% of patients developed disseminated nocardiosis, and the mortality rate was 14% (13). Although the number of cases was limited and the disease severity depends on the immunity of the host, *N. concava* has the potential to cause severe infections in comparison with other *Nocardia* species.

Recently, RNA sequencing based on 16S rRNA has become the gold standard for the identification of *Nocardia*

Table 1. Clinical Characteristic of Reported Cases of Nocardiosis Caused by *N. Concava*.

Reference	Age /Sex	Underlying diseases	Immunosuppressive agents	Symptoms	Infected organs	Antibiotics	Outcome
(2)	42 / M	polychondritis	prednisolone , azathioprine, mycophenolate mofetil	fever	lungs, liver	SDZ+VCM+IPM →SDZ+CPFX+AMK	died
(3)	64 / M	membranous glomerulopathy, liver cirrhosis	prednisolone	tender mass in the right upper arm	deltoid muscle, lungs	TMP/SMX	cured
(4)	73 / M	multiple myeloma	dexamethasone	erythemas with pain, fever	lungs, muscles, subcutaneous tissue, kidneys, CNS	TMP/SMX+CTRX+AMK →TMP/SMX+AMK+CPFX+MINO →TMP/SMX+MINO+LZD	cured
The present case	68 / M	ANCA-associated vasculitides	prednisolone, cyclophosphamide	bloody sputum	lung	TMP/SMX	cured

SDZ: sulphadiazine sodium, VCM: vancomycin, IPM: imipenem, CPFX: ciprofloxacin, AMK: amikacin, TMP/SMX: trimethoprim-sulfamethoxazole, CTRX: ceftriaxone, MINO: minocycline, LZD: linezolid

Table 2. Antibiotic Susceptibility Test.

Antimicrobial agents	MIC (μg / mL)
Cefotaxime	≥32
Ceftriaxone	4
Cefepime	8
Imipenem	≥32
Gentamicin	≤1
Clarithromycin	≤0.5
Minocycline	≤0.5
Levofloxacin	0.5
Trimethoprim-sulfamethoxazole	0.19

The antimicrobial breakpoints are as follows.

Cefotaxime: 8μg/mL, Ceftriaxone: 8μg/mL, Cefepime: 8μg/mL, Imipenem: 4μg/mL, Gentamicin: 4μg/mL, Clarithromycin: 2μg/mL, Minocycline: 1μg/mL, Levofloxacin: 1μg/mL.

species (14). The identification of *Nocardia* species is important in order to select appropriate antimicrobial agents because the antimicrobial sensitivity of *Nocardia* spp. varies by species. Because a gene sequence analysis is expensive, requires advanced techniques and is time-consuming, it is not routinely performed in most facilities at the current time. However, in the future, it is expected to be used in clinical settings more commonly with the advancement of technology.

We here reported the successful treatment of a pulmonary nocardiosis case caused by *N. concava*. Our case did not indicate disseminated infection, and it was successfully cured within six months of antimicrobial treatment, as we fortunately diagnosed it in the early phase of infection. It is important to identify causative species in order to select appropriate antibiotics in cases of nocardiosis. Thus, more cases need to be studied to clarify the characteristics of *N. concava* infection.

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

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