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Pulmonary Nocardiosis: A Clinical Analysis of 30 Cases

Yasuo Takiguchi[1], Shunsuke Ishizaki[1], Takayuki Kobayashi[1], Shun Sato[1], Yaeko Hashimoto[1], Yosuke Suruga[2] and Yoko Akiba[2]

Abstract

Objective Pulmonary nocardiosis frequently develops as an opportunistic infection in patients with malignant tumor and is treated with steroids. This study was performed to clarify the clinical features of pulmonary nocardiosis in Japan.

Methods The patients definitively diagnosed with pulmonary nocardiosis at our hospital between January 1995 and December 2015 were retrospectively investigated.

Results Nineteen men and 11 women (30 in total) were diagnosed with pulmonary nocardiosis. Almost all patients were complicated by a non-pulmonary underlying disease, such as malignant tumor or collagen vascular disease, or pulmonary disease, such as chronic obstructive pulmonary disease or interstitial pneumonia, and 13 patients (43.3%) were treated with steroids or immunosuppressors. Gram staining was performed in 29 patients, and a characteristic Gram-positive rod was detected in 28 patients (96.6%). Thirty-one strains of *Nocardia* were isolated and identified. Seven strains of *Nocardia farcinica* were isolated as the most frequent species, followed by *Nocardia nova* isolated from 6 patients. Seventeen patients died, giving a crude morality rate of 56.7% and a 1-year survival rate of 55.4%. The 1-year survival rates in the groups with and without immunosuppressant agents were 41.7% and 59.7%, respectively, showing that the outcome of those receiving immunosuppressants tended to be poorer than those not receiving them.

Conclusion Pulmonary nocardiosis developed as an opportunistic infection in most cases. The outcome was relatively poor, with a 1-year survival rate of 55.4%, and it was particularly poor in patients treated with immunosuppressant agents. Pulmonary nocardiosis should always be considered in patients presenting with an opportunistic respiratory infection, and an early diagnosis requires sample collection and Gram staining.

Key words: Pulmonary nocardiosis, opportunistic infection, Gram-stain

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Introduction

Nocardia is an aerobic Gram-positive rod belonging to the *Actinomycetales* order and is mainly distributed in the soil. While *Nocardia* infection does occasionally occur in healthy individuals, it more frequently occurs in patients with impaired cellular immunity due to malignant tumor, diabetes mellitus, and acquired immune deficiency syndrome, and steroids and immunosuppressor treatments are known risk factors of this disease (1-14). Pulmonary nocardiosis most frequently develops among *Nocardia* infections, and the presence of chronic respiratory disease, such as chronic obstructive pulmonary disease and bronchiectasis, is a risk factor of pulmonary nocardiosis (1-14). However, only a few cases of pulmonary nocardiosis have been reported in Japan, and only a few studies involving many patients have been performed (15, 16). This study was performed to clarify the clinical features of pulmonary nocardiosis in Japan.

Materials and Methods

Study subjects

Patients diagnosed with pulmonary nocardiosis at our hospital between January 1995 and December 2015 were retro-

[1]Department of Respiratory Medicine, Chiba Aoba Municipal Hospital, Japan and [2]Department of Laboratory Medicine, Chiba Aoba Municipal Hospital, Japan
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Correspondence to Dr. Yasuo Takiguchi, takiguchiyasuo@yahoo.co.jp

Table 1. Clinical Characteristics of Pulmonary Nocardiosis.

	No. (%) of Cases	
Gender (male)	19	(63.3)
Mean Age, Yr. [range]	65.6 [25-88]	
Non-pulmonary underlying disease	25	(83.3)
Hematologic malignancy	10	(33.3)
Solid tumor	5	(16.7)
Connective tissue disease, vasculitis	3	(10.0)
Cushing syndrome	2	(6.7)
Diabetes mellitus	2	(6.7)
Human immunodeficiency virus infection	2	(6.7)
Auto-immune hepatitis	1	(3.3)
Pulmonary underlying disease	9	(30.0)
Chronic obstructive pulmonary disease	3	(10.0)
Interstitial pneumonia	2	(6.7)
Bronchiectasis	2	(6.7)
Bronchial asthma	1	(3.3)
Non-tuberculous mycobacteria	1	(3.3)
No underlying disease	1	(3.3)
Immunosuppressant agents	13	(43.3)
Corticosteroids	8	(26.7)
Corticosteroids+Cyclosporin	4	(13.3)
Corticosteroids+Tacrolimus	1	(3.3)
Prophylaxis with sulfamethoxazole-trimethoprim	3	(10.0)

spectively investigated using their medical records. Cases in which *Nocardia* was isolated by a culture of respiratory samples, such as sputum, bronchoalveolar lavage, pulmonary puncture sample, and pleural effusion, or blood culture with subjective and objective symptoms and laboratory test and imaging findings suggesting respiratory infection were defined as pulmonary nocardiosis. Immunosuppressors, such as steroids and cyclosporine, were simultaneously analyzed as innumosuppressant agents. Cases without symptoms suggesting respiratory infection despite *Nocardia* being isolated from sputum and those with no new appearance of an abnormal shadow on chest radiography were judged as colonization and excluded from ttanalysis. Eight patients overlapped with those in the previous report (15).

Microbiological identification

In the bacteriological investigation, when a Gram-positive rod was suspected as *Nocardia* on Gram staining, Kinyoun's stain was additionally performed, followed by culture on blood agar medium. The bacterial species was identified by biochemical identification tests, a 16S-ribosomal RNA base sequence analysis, or mass spectrometry. Regarding drug susceptibility, the minimum growth inhibitory concentration was measured using the broth microdilution method and judged in accordance with CLSI M24-A. When infection with other microorganisms was confirmed within one week before or after the date of the diagnosis of pulmonary nocardiosis, it was judged as a mixed infection.

Statistical analyses

The survival time was defined as the period from the date of the diagnosis of pulmonary nocardiosis to the date of death, and the observation of survivors was discontinued on December 31, 2015. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). The survival rate was calculated using the Kaplan-Meier method, and the survival curve was compared using the log-rank test. A p value of <0.05 was regarded as significant.

Results

Characteristics and clinical features

Thirty patients were diagnosed with pulmonary nocardiosis. Nineteen and 11 patients were men and women, respectively, and the age ranged from 25-88 years old (mean: 65.6 years old). Twenty-nine patients (96.7%) had a non-pulmonary underlying disease, such as hematologic malignancy, solid tumor (colon 2, stomach 1, lung 1, prostate 1), collagen vascular disease, Cushing's syndrome, and diabetes mellitus, or an underlying pulmonary disease, such as chronic obstructive pulmonary disease and interstitial pneumonia. Thirteen patients (43.3%) were treated with immunosuppressant agents. Three patients (10.0%) were treated with sulfatomethoxazole-trimethoprim (ST) to prevent *Pneumocystis* pneumonia (Table 1). The condition was judged as colonization in three patients during the investigation period.

The initial symptoms were a fever (33.3%) and sputum (30.0%) in many cases, and coughing (13.3%), chest pain (10.0%), and anorexia (10.0%) were also frequently noted. Three patients (10.0%) were asymptomatic, and the detec-

Table 2. Chest CT Findings of Pulmonary Nocardiosis.

	No. (%) of Cases		
Consolidation	9	*	(31.0)
Multifocal consolidation	1		(3.4)
Multifocal consolidation, cavitation	1		(3.4)
Nodule	6	*	(20.7)
Nodule, cavitation	2		(6.9)
Multiple nodules	4		(13.8)
Multiple nodules, cavitation	3	*	(10.3)
Multifocal consolidation+multiple nodules	1		(3.4)
Multifocal consolidation+multiple nodules, cavitation	2		(6.9)

*: Pleural Effusion (+)

Table 3. Microbiological Characteristics of Pulmonary Nocardiosis.

	No. (%) of Cases	
Source of culture		
Sputum	24	(80.0)
Broncho-alveolar lavage	4	(13.3)
CT-guided needle aspiration	2	(6.7)
Purulent pus	2	(6.7)
Pleural effusion	1	(3.3)
Blood culture	1	(3.3)
Isolated organism		
N. farcinica	7	(23.3)
N. nova	6	(20.0)
N. asteroides	4	(13.3)
N. cryriacigeorgica	4	(13.3)
N. brasiliensis	3	(10.0)
N. exelbida	2	(6.7)
N. abscessus	1	(3.3)
N. arthritidis	1	(3.3)
N. asiatica	1	(3.3)
N. beijingensis	1	(3.3)
N. elegans	1	(3.3)
Co-Isolated organism		
Aspergillus fumigatus	2	(6.7)
Cytomegalovirus	2	(6.7)
Streptococcus pneumoniae	1	(3.3)
Mycobacterium avium	1	(3.3)
Pneumocystis jiroveci	1	(3.3)

tion of an abnormal shadow on chest radiography led to the diagnosis.

Radiographic findings

On chest radiography, solitary or multiple shadows of infiltration and nodules with a homogeneous density were observed in many patients. Chest CT was performed in 29 patients. Solitary infiltrative shadows were observed in 9 (31.0%) of them, making them the most frequent finding, followed by solitary mass shadows in 6 (20.7%). Multiple shadows of infiltration or mass were observed or were mixed in many patients, and a cavity was present in the infiltration or mass shadows in 8 patients (27.6%). Retention of pleural effusion was observed in 3 patients (10.0%) (Table 2).

Diagnosis and microbiological identification

Nocardia was isolated by culture from sputum in 24 patients (80.0%), bronchoscopic samples in 4 (13.3%), and CT-guided fine-needle aspiration samples in 2 (6.7%). It was also isolated by culture of purulent pus from the skin in 2 (6.7%) and pleural effusion and blood in 1 each (3.3%) (Table 3). The final diagnosis was pneumonia in 16 patients (53.3%) and lung abscess in 14 (46.7%), and one patient each was complicated by sepsis, brain abscess, iliopsoas abscess, and skin abscess.

Characteristic Gram-positive rods were confirmed by Gram and Kinyoun's stain in 28 (96.6%) of 29 patients excluding 1 patient in whom the bacterium was cultured only from blood. Thirty-one strains of *Nocardia* were isolated and identified. Seven strains (23.3%) of *Nocardia farcinica* were isolated, making this species the most frequent, followed by 6 strains (20.0%) of *Nocardia nova* and 4 strains (13.3%) each of *Nocardia asteroids* and *Nocardia cryriacigeorgica* (Table 3).

Twenty-six strains were subjected to drug susceptibility tests. All strains were susceptible to imipenem (or meropenem), amikacin, and minocycline, but susceptibility to other antibiotics varied. Two strains of *Nocardia farcinica* (7.7%) were resistant to ST.

Seven patients (23.3%) were diagnosed with mixed infection, and the causative microorganism was *Aspergillus fumigatus* and cytomegalovirus in 2 patients each (6.7%), and *Streptococcus pneumoniae*, *Mycobacterium avium*, and *Pneumocystis jiroveci* in one patient each (3.3%) (Table 3).

Treatment and outcome

Treatment was initiated with single or combination antibiotics therapy, such as ST, carbapenem, and minocycline in most cases. The duration of treatment ranged from 3 days to 55 months. ST was inevitably withdrawn due to adverse reactions, such as digestive symptoms, renal insufficiency, and drug eruptions, in 47% of ST-treated patients.

Regarding the outcome, 17 patients died, and the crude mortality rate was 56.7%. The duration of the observation

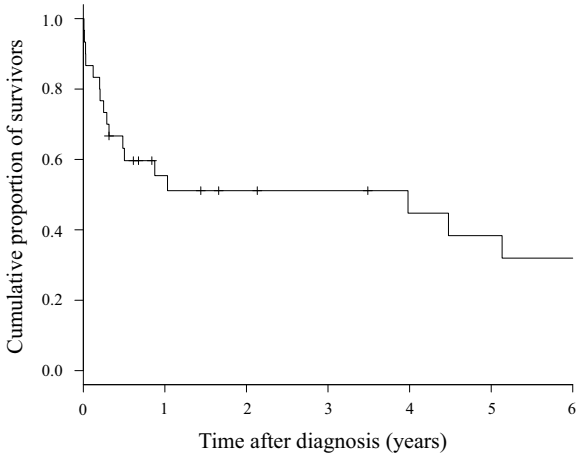

Figure 1. Kaplan-Meier survival curve of patients with pulmonary nocardiosis (n=30).

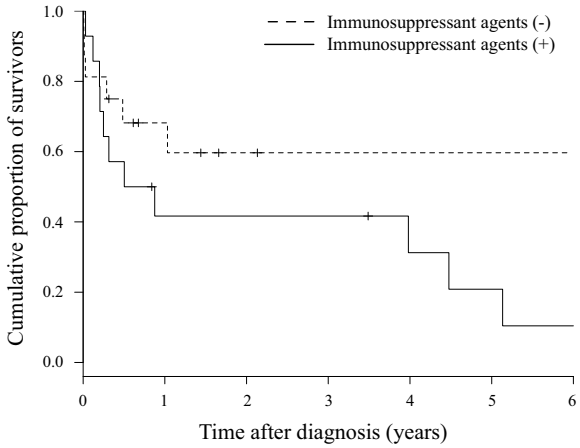

Figure 2. Kaplan-Meier survival curve of patients with pulmonary nocardiosis without immunosuppressant agents (n=17, the dotted line) and with immunosuppressant agents (n=13, solid line).

period ranged from 3 days to 190 months (median: 9.2 months), and the 1-year survival rate was 55.4% (Fig. 1). When the survival period was investigated based on the presence or absence of immunosuppressant agents, the 1-year survival rates in the group with (13 patients) and without (17 patients) these treatments were 41.7% and 59.7%, respectively, showing that the prognosis tended to be poorer in the treated group (p=0.098) albeit without a significant difference (Fig. 2). The cause of death was assumed to be the underlying disease, such as malignant disease, in 10 of the 17 patients that died and *Nocardia* infection in the other 7 patients, but no marked differences were noted in the survival period between these 2 groups.

Discussion

Nocardiosis develops as an opportunistic infection in patients with impaired cellular immunity due to steroids and immunosuppressor treatments, malignant tumor, and acquired immune deficiency syndrome. In addition, the presence of chronic respiratory disease, such as chronic obstructive pulmonary disease, is a risk factor of pulmonary nocardiosis (1-14). Underlying disease was present in 96.7% of the patients, and 13 patients (43.3%) received immunosuppressant agents, but the initial symptom and laboratory test findings were nonspecific in all cases. Shadows of multiple masses and infiltration and cavity formation, which are typical conventional findings, were observed on CT, but no characteristic findings of this disease were clarified (17-19).

An important finding of this study was the detection of the characteristic Gram-positive rods of *Nocardia* in 28 (96.6%) of the 29 patients examined by Gram staining, and it led to the rapid initiation of treatment. At present, Gram staining is the only method for the rapid diagnosis of *Nocardia* infection. Culture of this pathogen requires several days to several weeks, and continuation of culture is difficult due to overgrowth of other bacteria unless their growth is kept in check. It was reconfirmed that Gram staining is the most important method for achieving not only an early diagnosis and treatment but also improving the success rate of culture and administering optimum treatments based on drug susceptibility.

Drug susceptibility of *Nocardia* varies among the bacterial species, and *Nocardia farcinica* and *Nocardia nova* are resistant to various antibiotics. Resistance to ST, the first-choice agent, has recently been attracting attention, and the resistance rate was reported to be 0-58%. In our study, 2 strains (7.7%) were resistant. Drug susceptibility test results may vary markedly depending on differences in the epidemic bacterial species, regional differences in drug resistance, and susceptibility measurement methods (3, 20-27), but a susceptibility surveillance of *Nocardia* in Japan is desired. In addition, 3 patients treated with oral ST to prevent *Pneumocystis* pneumonia developed pulmonary nocardiosis. ST is a first-line drug against *Nocardia* infection. Normally, the dose of ST administered to prevent *Pneumocystis* pneumonia is 1 g daily or 2 g two to three times a week, which is lower than the dose against nocardiosis. A poor pulmonary nocardiosis-preventive effect of low-dose ST has been reported (5, 6, 10, 28, 29), and our study also suggested that the preventive effect is insufficient.

The optimum antibiotics and dose and duration for the treatment of pulmonary nocardiosis are unclear because no prospective study has been performed. ST is recommended as the first choice, and the combination of imipenem and amikacin is recommended for severe cases and central nervous system infections. Regarding the duration of treatment, 6-12 months is recommended for many cases corresponding to the underlying disease and infection lesions (2-7, 25). We also initiated treatment with one or several of the drugs recommended above until the results of drug susceptibility tests were obtained. Naturally, the potential presence of a resistant strain must be considered in patients who develop nocardiosis while being treated with antibiotics. Furthermore, pulmonary nocardiosis induces mixed infection at a high

frequency, being a cause of aggravation to a severe state (12-14, 28). Mixed infection was noted in 7 patients (23.3%), showing that the presence of a mixed infection should be considered when diagnosing this disease and selecting antibiotics.

The 1-year survival rate in all patients was 55.4% (Fig. 1). A simple comparison of the outcome is difficult because the outcome is strongly affected by factors such as the patient background and timing of the investigation, but the outcome was poor compared with previously reported survival rates (40-100%) (6, 8-13, 28-30). Furthermore, the 1-year survival rate in the group treated with immunosuppressant agents was 41.7%, which was poorer than that (59.7%) in the untreated group (Fig. 2).

Several limitations associated with the present study warrant mention. First, this was a long-term 20-year retrospective study. Since there are various differences in the medical care environment between 20 years ago and now, it may be problematic to investigate the overall treatment effect and outcome. The short-term prospective accumulation of cases should therefore be performed to achieve a more accurate view. Second, pulmonary nocardiosis was unlikely to be definitively diagnosed unless it was strongly suspected based on the results of Gram staining; as such, it is very possible that patient selection was biased, with our population potentially including only subjects in whom the characteristic Gram-positive rod had been detected. Pulmonary nocardiosis might be included in an opportunistic respiratory infection treated as those of unclear causative pathogens. Third, *Nocardia* species were identified by various methods, such as biochemical identification tests, a 16S-ribosomal RNA nucleotide sequence analysis, and mass spectrometry. Since an increasing number of *Nocardia* species have recently been identified, those previously identified by biochemical tests may be differently named today.

Although pulmonary nocardiosis is relatively rare, it is a major opportunistic infection. The prognosis of pulmonary nocardiosis is not favorable, and the outcome was particularly poor in patients treated with immunosuppressant agents. Pulmonary nocardiosis should be considered when a respiratory infection develops in these patients. We want to emphasize that confirmation of the characteristic Gram-positive rod by active high-quality sample collection and Gram staining is most important for the early diagnosis and appropriate treatment.

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

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