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Original Article

Clinical characteristics of pulmonary nocardiosis in immunocompetent patients

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ABSTRACT

Pulmonary nocardiosis is a rare but potentially serious infection typically in immunosuppressed patients (ISPs). It is also known to occur in immunocompetent patients (ICPs). However, little is currently known regarding the clinical characteristics and radiographic findings of pulmonary nocardiosis specifically in ICPs. In this study, 30 patients with pulmonary nocardiosis were identified and 10 were considered to be colonized. Of all patients with pulmonary nocardiosis, 12 patients were ICPs and 18 were ISPs. Although half of ISPs were infected by *Nocardia nova*, ICPs were affected by various *Nocardia* species. Compared with ISPs, chest CT findings of ICPs showed a higher prevalence of bronchiectasis (67% vs 6%, $p < .01$) and centrilobular nodular opacities (67% vs 11%, $p < .01$), both of which are often seen in pulmonary nontuberculous mycobacterial disease. Additionally, nontuberculous mycobacterium was isolated from 6 of 21 ICPs with positive *Nocardia* species culture. Therefore, we recommend that physicians carefully differentiate pulmonary nocardiosis from pulmonary nontuberculous mycobacterial disease in ICPs.

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1. Introduction

Nocardia species are weakly acid-fast bacteria and they are found in soils, water, and other organic matter worldwide [1]. Pulmonary nocardiosis is a well-described infectious disease in immunosuppressed patients (ISPs), but it can also occur in immunocompetent patients (ICPs). ICPs with pulmonary nocardiosis mostly have underlying chronic lung diseases such as chronic obstructive pulmonary disease (COPD) [2] and bronchiectasis [3]. However, the clinical and radiographic features of ICPs with pulmonary nocardiosis are not yet well-documented.

Nontuberculous mycobacteria (NTM) are also acid-fast bacteria and common natural inhabitants of soil and water throughout the world. Nontuberculous mycobacterial disease usually presents as a pulmonary disease in ICPs but can present as a disseminated disease especially in human immunodeficiency virus (HIV)-infected patients. Moreover, NTM were reported to be isolated from respiratory specimens of ICPs with pulmonary nocardiosis [4,5], suggesting that NTM and *Nocardia* sp. may be related in pulmonary infections. In this study, we compared clinical characteristics, radiological findings, microbiological findings and treatment outcomes of pulmonary nocardiosis between ICPs and ISPs, and also investigated an association of *Nocardia* species with NTM in ICPs.

2. Patients and methods

2.1. Patients and definitions

This study was a retrospective analysis that was undertaken of patients diagnosed with pulmonary nocardiosis over an eleven-year period at the Chiba University Hospital, Japan. Cases of pulmonary nocardiosis were identified with the clinical microbiology laboratory database for specimens collected between 2004 and 2014. Pulmonary nocardiosis was defined by the presence of clinical and radiographic manifestations and radiological improvement following appropriate treatments for *Nocardia* species in addition to positive cultures from a respiratory sample. However, even with a positive culture from a specimen, patients with no symptoms of pulmonary infection, or no radiological improvement following appropriate treatments for *Nocardia* species, were defined as having airway colonization. Disseminated nocardiosis was defined as involvement of organs other than the

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lungs. Medical records for all patients with pulmonary nocardiosis were reviewed to obtain symptoms, comorbidities, host immunological state, radiographic presentation, laboratory data, bacteriological reports, treatment course and outcomes. They were divided into ICPs and ISPs. ISPs were defined as: patients regularly administered corticosteroids (prednisolone equivalent dose ≥10 mg/day) [6] and/or immunosuppressive agents, in addition to those with immunodeficiency disease including HIV infection, chronic granulomatous disease, active malignancies, poorly controlled diabetes mellitus (HbA1c ≥ 7.0%) or solid organ transplantation. Such ISPs are at risk of other opportunistic infections such as cytomegalovirus infection and pneumocystis pneumonia. All other patients were considered to be ICPs. The Computed tomography (CT) images were evaluated by two pulmonary disease experts, who were blinded with regard to the clinical findings. The criteria for radiological findings were basically defined in the Glossary of Terms by the Fleischner Society [7]. In this study, 1) A mass was defined as a solid opacity greater than 3 cm in diameter, and 2) a nodule was a rounded or irregular opacity greater than 1 cm, measuring up to 3 cm in diameter. 3) Centrilobular nodular opacity was ill-defined, ranging in size from a few millimeters to a centimeter. These opacities were separated from the pleural surfaces, fissures, and interlobular septa by several millimeters, and included tree-in-bud patterns which represent centrilobular branching structures that resemble a budding tree.

2.2. Microbiological methods

Nocardia isolates were presumptively identified based on colonial and microscopic morphology as well as the demonstration of positive Gram staining and partial acid-fast staining (modified acid-fast staining) at the Microbiology Department in Chiba University Hospital. The cultures were incubated for 2–7 days at 35–37 °C on blood agar and chocolate agar. Growth characteristics, standard biochemical tests, antimicrobial susceptibility tests and 16S rRNA gene sequence analysis were used to identify the *Nocardia* isolates to species levels. *Nocardia asteroides* was initially believed to be a single species and considered the most common species associated with human disease. However, it was later found to belong to a group of related bacteria with a heterozygous pattern of antimicrobial susceptibility, named *N. asteroides* complex. This complex was classified with 16S rRNA gene sequence analysis into *Nocardia abscessus*, *Nocardia brevicatena-paucivorans complex*, *Nocardia nova complex*, *Nocardia transvalensis complex*, *Nocardia farcinica* and *Nocardia asteroids* sensu strico [8].

2.3. Statistical analysis

Differences between groups were identified using the Mann–Whitney test or Fisher's exact test. Survival analysis was performed with the Kaplan–Meier method. A p-value of <0.05 was considered to be statistically significant.

3. Results

3.1. Characteristics of the individuals (Table 1)

Thirty patients with pulmonary nocardiosis were identified. Among them 12 (40%) were ICPs (8 males and 4 females) while 18 (60%) were ISPs (10 males and 8 females), 4 of whom had disseminated nocardiosis. Mean age of ICPs (69.0 years) was higher than that of ISPs (54.6 years). Additionally, 10 were considered colonized, nine (90%) of whom were immunocompetent and one was immunosuppressed. In ICPs with pulmonary nocardial infections, underlying lung structural abnormalities were common (bronchiectasis, 8; pulmonary emphysema, 1; prior pulmonary tuberculosis, 1; interstitial pneumonia, 1). The most common bronchiectasis etiologies were idiopathic (n = 3) followed by connective tissue disease (CTD) (n = 2; rheumatoid arthritis and Sjögren's syndrome). Other etiologies were sinobronchial syndrome (SBS) (n = 1), pulmonary nontuberculous mycobacterial disease (pNTM) (n = 1) and post-tuberculosis infection (n = 1). There were no instances of bronchiectasis due to cystic fibrosis (CF). Idiopathic bronchiectasis was defined as not having well-known secondary causes such as CTD, SBS and post-lung infections although it might include *Nocardia*-induced bronchiectasis. pNTM was diagnosed according to the American Thoracic Society criteria [9]. Furthermore, cases diagnosed as pNTM for the first time after *Nocardia* sp. had been detected were excluded. Non-CF bronchiectasis was also seen in 7 out of 9 ICPs with airway colonization (Online Resource 1). The underlying diseases of the ISPs were as follows: connective tissue disease (n = 9), hematologic disease (n = 5), human immunodeficiency viral infection (n = 2), chronic granulomatous disease (n = 2), alcoholic liver cirrhosis (n = 1), autoimmune hepatitis with primary biliary cirrhosis (n = 1), drug-induced hepatitis (n = 1), diabetes mellitus (n = 5). Sixteen ISPs were treated with chronic corticosteroid therapy, 7 of whom also received other immunosuppressive drugs. The average corticosteroid dose was 27 mg day^{-1} of prednisolone equivalent. Preexisting pulmonary diseases were uncommon in ISPs.

Table 1
Patients' characteristics and presenting symptoms.

	ICPs (n = 12)	ISPs (n = 18)	P value
Age, years, mean ± SD	69.0 ± 13.5	54.6 ± 19.9	0.03
Male/Female	8/4	10/8	0.71
Symptom, n (%)			
Cough	8 (67)	7 (39)	0.26
Sputum	7 (58)	4 (22)	0.06
Hemoptysis	3 (25)	2 (22)	0.36
Fever	3 (25)	9 (50)	0.26
Chest pain	1 (8)	4 (22)	0.62
Fatigue		2 (11)	0.50
Dyspnea		1 (6)	1.00
Disturbance of Consciousness		1 (6)	1.00
Appetite loss		1 (6)	1.00
Disseminated infection, n (%)		4 (22)	0.13
Cerebral abscess		2 (11)	0.50
Muscle abscess		2 (11)	0.50
Bacteremia		1 (6)	1.00
Preexisting lung disease, n (%)	9 (75)	5 (28)	0.02
Bronchiectasis	8 (67)	1 (6)	<0.01
Pulmonary emphysema	1 (8)	1 (6)	1.00
Interstitial pneumonia	1 (8)	1 (6)	1.00
Obsolete pulmonary tuberculosis	1 (8)	1 (6)	1.00
Post lung cancer operation		1 (6)	1.00
Sleep apnea	1 (8)		0.40
Bronchial asthma		1 (6)	1.00
None	3 (25)	13 (72)	0.02

ICPs; Immunocompetent patients, ISPs; immunosuppressed patients.

3.2. Symptoms (Table 1)

ICPs exhibited nonspecific symptoms such as cough (67%), sputum (58%), fever (25%), hemoptysis (25%), and chest pain (8%), which were no different from ISPs in a statistically significant manner. The onset of symptoms in ICPs was subacute or chronic while those of ISPs were mostly acute.

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