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Clinical Analysis of Pulmonary Nocardiosis in Patients With Autoimmune Disease

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Abstract: Nocardiosis is an opportunistic infection that most commonly involves the lung; however, only a few case reports of autoimmune disease complicated by pulmonary nocardiosis exist in the literature.

We conducted a retrospective analysis of 24 cases of both autoimmune disease and pulmonary nocardiosis at the Peking Union Medical College Hospital between 1990 and 2012.

Fifty-two cases were hospitalized with nocardiosis, 24 of whom had at least 1 autoimmune disease before the diagnosis of pulmonary nocardiosis. The cohort patients consisted of 5 men and 19 women, with a mean age of 44.2 years. All were negative for human immunodeficiency virus. All but 1 patient had received immunosuppressants, including corticosteroids, cyclophosphamide, azathioprine, methotrexate, or hydroxychloroquine. Fever (87.5%), cough (83.3%), and sputum (79.2%) were the most common clinical manifestations. Ten cases were accompanied by subcutaneous nodules and/or cutaneous abscesses, and 4 had brain abscess. Half of them were lymphocytopenic. Thirteen of the 16 cases who underwent lymphocyte subtype analysis had decreased CD4⁺ T-cell counts. Nineteen cases had decreased serum albumin levels. Nocardia was isolated from sputum (13/24), bronchoalveolar lavage fluid (4/6), lung tissue (5/6), pleural effusions (3/5), skin or cutaneous pus (7/10), and brain tissue (1/1). The most common imaging findings were air-space opacities (83.3%), followed by nodules (62.5%), cavitations (45.8%), and masses (37.5%). Five were administered cotrimoxazole only, and the others were treated with 2 or more antibiotics. All 5 cases with skin abscesses and 2 of the 4 cases with brain abscesses were treated by surgical incision and drainage. None underwent thoracic surgery. Corticosteroid dosages were decreased in all cases, and

cytotoxic agents were discontinued in some cases. Twenty-two cases recovered, and 2 died.

Pulmonary nocardiosis associated with an underlying autoimmune disease showed a female predominance and presentation at younger age. Immunosuppressant therapy, lymphocytopenia, particularly low CD4⁺ T-lymphocyte counts, and low serum albumin levels may be disease susceptibility factors. Air-space opacities and nodules were the most common chest imaging features, and disseminated nocardiosis with lung and skin involvement was more common among them. Early diagnosis and anti-nocardial antibiotics with modulation of the basic immunosuppressive therapy were important for them.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, BALF = bronchoalveolar lavage fluid, CBC = complete blood count, CD4⁺ = cluster of differentiation 4⁺, CNS = central nervous system, CRP = c-reactive protein, CT = computed tomography, ESR = erythrocyte sedimentation rate, HIV = human immunodeficiency virus, Ig = immunoglobulin, ITP = idiopathic thrombocytopenic purpura, MPA = microscopic polyangiitis, SLE = systemic lupus erythematosus.

INTRODUCTION

Nocardiosis is usually considered to be a rare and opportunistic infection that most commonly involves the lungs. Patients with depressed cellular immunity are at high risk for Nocardia infection, such as patients with acquired immunodeficiency syndrome (AIDS) and those who receive prolonged treatments with corticosteroids and/or cytotoxic therapy, for example, patients who have received solid organ and hematopoietic stem cell transplantation, patients with hematologic and solid-organ malignancies, and those with autoimmune disease.^{1–8} Cases of nocardiosis occurring in patients with cancer⁹ and those who have undergone transplantation^{10–12} have been reviewed systematically. However, only a few case reports on autoimmune disease complicated by Nocardia infection exist in the literature.^{4,13–21} To facilitate the recognition, diagnosis, and prognosis of this uncommon infection, we investigated the clinical, radiological, and microbiological features of 24 patients with autoimmune disease complicated by pulmonary nocardiosis.

MATERIALS AND METHODS

Patients

We performed a computer-assisted search to identify 52 patients hospitalized with nocardiosis at the Peking Union Medical College Hospital between January 1, 1990, and December 31, 2012. A review of the medical records and the radiological images revealed 24 cases with both autoimmune disease and pulmonary nocardiosis. Pulmonary nocardiosis was

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defined as a new radiographic infiltrate and positive microbiologic results for *Nocardia* in 1 or more types of respiratory specimens. For those who had only positive microbiologic results for *Nocardia* from sputum, positive results should have been obtained from at least 2 different sputum samples. Disseminated nocardiosis was diagnosed when the infection was present in 2 non-contiguous organs or in the central nervous system (CNS).

The patients' characteristics were recorded from their medical files, and their chest computed tomography (CT) images were downloaded from our hospital's image bank. Two radiologists conducted a consensus reading of the CT images. The patients' age, gender, symptoms at presentation, physical examination, laboratory and radiological findings, treatment, and outcomes were analyzed.

All patients in the cohort initially underwent a complete blood count (CBC) analysis, urinalysis, biochemical tests (including liver, renal function, serum albumin, and electrolyte levels), and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) determinations. Sputa for smear and Gram staining were obtained from all of the enrolled patients when they presented to the clinics. When *Nocardia* infection was suspected by the clinicians, modified Kinyoun acid-fast staining and sputum microbiologic cultures, including *Nocardia* and routine bacterial and fungal cultures, were performed. The lymphocyte subset analysis using flow cytometry was performed in cases of lymphocytopenia and/or when *Nocardia* infection was suspected or diagnosed in the patients. Most of the lymphocyte subset analysis results were available within 1 to 3 weeks of the diagnosis of acquired nocardiosis. The immunoglobulin analysis was performed for most of the enrolled cases when *Nocardia* infection was suspected or diagnosed.

Other definitions in this study included the following: (1) anemia was defined as a hemoglobin level < 110 g/l for women and < 120 g/l for men, (2) neutropenia was defined as a neutrophil count $< 1.5 \times 10^9$ /l, (3) lymphocytopenia was defined as a lymphocyte count $< 1 \times 10^9$ /l, and (4) hypoalbuminemia was defined as a serum albumin level < 35 g/l.

All patients were followed until December 2014. The data were collected by telephone and through letters and case records. All patients and/or their families provided written informed consent to publish their clinical details. The study was approved by the ethics committee of the Peking Union Medical College Hospital.

Statistical Analysis

Data were analyzed using the Statistical Analysis System (SAS) version 8.0 software package (SAS Institute Inc, Cary, NC). Quantitative data are presented as means \pm SD and categorical data are presented as frequencies and percentages in the text and tables.

RESULTS

Demographics and Clinical Manifestations

The clinical characteristics of the 24 cases included in this study cohort are summarized in Table 1.

The study group consisted of 5 male and 19 female patients with a mean age of 44.2 years (range, 15–72 years). All of the patients had at least 1 autoimmune disease before being diagnosed with nocardiosis, including systemic lupus erythematosus (SLE) (5 cases, 20.8%), dermatomyositis (4 cases, 16.7%), microscopic polyangiitis (3 cases, 12.5%), idiopathic

thrombocytopenic purpura (ITP) (3 cases, 12.5%), Henoch–Schonlein purpura nephritis (2 cases, 8.3%), inflammatory myositis (1 case, 4.2%), rheumatoid arthritis (1 case, 4.2%), rheumatoid arthritis and secondary Sjogren's syndrome (1 case, 4.2%), nodular panniculitis (1 case, 4.2%), Evans syndrome (1 case, 4.2%), SLE and Evans syndrome (1 case, 4.2%), and SLE and rheumatoid arthritis (1 case, 4.2%). There were 3 cases with microscopic polyangiitis who had pulmonary fibrosis. The other 21 cases had no underlying lung disease. Pulmonary nocardiosis appeared to be an "emerging infectious disease" found in our hospital's patients with autoimmune disease. Specifically, 3 cases (12.5%) were diagnosed before 2005; 6 cases (25%) were diagnosed from 2005 to 2009; and the remaining 15 cases (62.5%) were diagnosed from 2010 to 2012.

All of the patients were negative for antibodies to the human immunodeficiency virus (HIV). Only 1 patient who had rheumatoid arthritis was not taking steroids or cytotoxic medications; the other 23 cases were receiving immunosuppressants, including steroids, cyclophosphamide, azathioprine, methotrexate, or hydroxychloroquine. Regarding corticosteroids, most of the patients were administered prednisone at doses ranging from 10 to 60 mg d^{-1} , and some of them were administered an equivalent dosage of methylprednisolone or dexamethasone. Three of these patients were initially given high-dose methylprednisolone, which ranged from 500 to 1000 mg d^{-1} for 3 days. The mean duration of steroid treatment was 11.8 months (range, 1–60 months). Seven patients were not receiving cytotoxic medications.

Twenty-one patients (87.5%) had a moderate to high fever. Respiratory symptoms included cough (20 cases, 83.3%), sputum production (19 cases, 79.2%), dyspnea (8 cases, 33.3%), chest pain (7 cases, 29.2%), and hemoptysis (5 cases, 20.8%). Some patients, mostly those whose CNS was involved, had headache (6 cases, 25%), vomiting (4 cases, 16.7%), and disturbances of consciousness (4 cases, 16.7%). Ten cases (41.7%) were accompanied by subcutaneous nodules and/or cutaneous abscesses. Four patients (16.7%) had brain abscesses, which were diagnosed by head magnetic resonance imaging and clinical symptomatology. Only 1 of these 4 cases underwent a brain biopsy because brain malignancy was suspected initially. The involved lesions of these 24 cases were listed in Table 2.

Laboratory Tests

Peripheral white blood cell counts ranged from 1.54×10^9 /l to 22.88×10^9 /l (mean, 9.67×10^9 /l), with neutrophils comprising the largest portion (mean, 78.2%; range, 61.4–94.7%). Peripheral lymphocyte counts ranged from 0.29×10^9 /l to 3.41×10^9 /l (mean, 1.13×10^9 /l). Only 1 case exhibited neutropenia (1.24×10^9 /l), and in 12 cases (50%), the lymphocyte counts were $< 1 \times 10^9$ /l. Eleven cases (45.8%) had variable anemia, with hemoglobin ranging from 62 to 106 g/l (mean, 79.5 g/l). Most patients had an elevated ESR and CRP level (91.6% and 76.5%, respectively), and the ESR ranged from 27 to 140 mm/h (mean, 75.1 mm/h). As T-lymphocyte subtype analysis came into wider use after 2008 in our hospital, only 16 cases (66.7%) in this cohort had undergone this test. Among them, the cluster of differentiation 4⁺ (CD4⁺) T cell count was $> 400/\mu\text{l}$ in 5 cases (31.25%); however, the CD4⁺ T-cell counts were normal ($[561-1137]/\mu\text{l}$) in only 3 cases (18.75%). Moreover, the CD4⁺ T-cell counts were $< 200/\mu\text{l}$ in 6 cases (37.5%). Serum immunoglobulin (Ig) G levels were evaluated in 19 cases. Although only 1 case had normal B-cell counts, only 3 cases (15.8%) had decreased IgG levels in our cohort. Serum albumin was evaluated in all cases, and it was normal in only 5

TABLE 1. Demographics and Clinical Features of Patients in the Study

No	Age (yr)/Sex	Autoimmune Disease	Duration of Steroids	Cytotoxic Drug	Affected Organ (s)	Positive Specimen (s)	Treatment	Outcomes
1	26/F	Nodular panniculitis	8 m	No	Lung+pleura	BALF	TMPco	Recovered
2	30/F	SLE	11 m	CTX	Lung+pleura+ brain+skin	Lung+plueral effusion	TMPco	Recovered
3	37/F	SLE	12 m	No	Lung+skin	Lung	Ceftriaxone +TMPco	Recovered
4	53/F	SLE	6 m	CTX	Lung+brain+pleura	Plueral effusion	Cefoperazone+ Ciprofloxacin	Died
5	15/F	HSPN	60 m	CTX+HCQ	Lung+skin	Sputum+skin	TMPco	Recovered
6	31/F	SLE	24 m	No	Lung	Sputum	TMPco	Recovered
7	28/M	ITP	3 m	VCR	Lung+pleura +skin	Skin+pleural effusion	TMPco+Co-amoxiclav+ Amikacin	Recovered
8	20/F	HSPN	5 m	CTX	Lung+brain+ pleura	Sputum	Ceftriaxone +TMPco+ Moxifloxacin	Recovered
9	54/M	RA	No	No	Lung+skin	Lung	TMPco, Levofloxacin	Recovered
10	45/F	Myotitis	2 m	No	Lung	Lung	Imipenem+ Minocycline	Recovered
11	58/F	DM	4 m	AZA	Lung	BALF	Imipenem+ TMPco	Recovered
12	62/F	ITP	2 m	No	Lung	Sputum	Imipenem+ TMPco	Recovered
13	61/F	RA, SS	1 m	CTX+LEF	Lung	BALF	TMPco+Co-amoxiclav	Recovered
14	31/F	ITP	46 m	No	Lung+skin	Sputum+pus*	TMPco+ Amikacin	Recovered
15	24/M	DM	3 m	THA	Lung	Sputum	TMPco+Co-amoxiclav	Recovered
16	47/F	Evans	23 m	CTX	Lung+brain+skin	Sputum+pus*	TMPco+Co-amoxiclav	Recovered
17	72/M	MPA	4 m	T _{II}	Lung	Sputum	TMPco,Co-amoxiclav+ Minocycline	Recovered
18	65/F	DM	12 m	CTX+MTX	Lung+skin	Sputum+pus*	TMPco,Co-amoxiclav	Recovered
19	41/F	SLE	24 m	HCQ	Lung+skin	Sputum+pus*	TMPco + Minocycline	Recovered
20	44/F	DM	2 m	CTX+MTX	Lung	Lung	Ceftriaxone +TMPco	Recovered
21	40/F	SLE, Evans	1 m	CTX	Lung	Sputum	TMPco	Recovered
22	56/F	MPA	2 m	CTX	Lung	BALF	Imipenem+ TMPco	Died
23	57/M	SLE, RA	1 m	MTX+LEF	Lung	Sputum	TMPco+ Moxifloxacin	Recovered
24	64/F	MPA	24 m	AZA	Lung+skin	Sputum+skin	TMPco,Co-amoxiclav	Recovered

AZA = azathioprine, BALF = bronchoalveolar lavage fluid, CTX = cyclophosphamide, DM = dermatomyositis, Evans = Evans syndrome, F = female, HCQ = hydroxychloroquine, HSPN = Henoch-Scho?nlein purpura nephritis, ITP = idiopathic thrombocytopenic purpura, LEF = leflunimide, M = male, MPA = microscopic polyangiitis, MTX = methotrexate, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, SS = Sjogren syndrome, THA = thalidomide, T_{II} = tripterygium wilfordii, TMPco = co-trimoxazole, VCR = vincristine.

* Pus in this table was from cutaneous abscesses.

cases (20.8%). Serum albumin ranged from 2 to 4.5 g/dl (mean, 3.03 g/dl).

In all cases, the microbiological results for *Nocardia* were positive in at least 1 clinical specimen (Table 3). Sputum smears and cultures were obtained at least 3 times in all cases, with sputum samples (54.2%) responsible for the diagnosis of *Nocardia* infection in 13 cases. Bronchoscopy and

bronchoalveolar lavage were performed in 6 patients (25%). Bronchoalveolar lavage fluid (BALF) cultures were obtained in these 6 cases (25%), and in 4 of these cases (66.7%, n=6), the diagnosis of pulmonary nocardiosis was confirmed. Six patients (25%) underwent CT-guided percutaneous fine needle lung biopsy, with lung tissue sent for microbial culture and pathological examination, and *Nocardia* was isolated in 5 cases (83.3%, n = 6). Ten patients (41.7%) had pleural effusions, and 5 cases required thoracentesis, with *Nocardia*-positive effusions detected in 3 patients (60%, n = 5). All 10 of the cases (41.7%) exhibiting subcutaneous nodules and/or cutaneous abscesses underwent culture of skin tissue and/or pus for *Nocardia*, with 7 cases (70%, n = 10) showing positive microbiological results for *Nocardia*. Eleven of these patients underwent peripheral blood culture; however, none of the cultures were positive for *Nocardia*.

CT Images

All patients underwent chest CT and X-ray imaging, and their CT features at the time of diagnosis of nocardiosis were analyzed. Only 8 cases (33.3%) had 1 type of shadow on

TABLE 2. The Involved Lesions of These 24 Cases

Involved Lesions (n = 24)	No. (%)
Lung	11 (45.8%)
Lung + skin	7 (29.2%)
Lung + pleura + brain	2 (8.3%)
Lung + pleura	1 (4.2%)
Lung + skin + brain	1 (4.2%)
Lung + pleura + skin	1 (4.2%)
Lung + pleura + brain +skin	1 (4.2%)

TABLE 3. The Diagnostic Microbiological Results of the 24 Cases

Type of Specimen	Number of Case With Specimen No. (%)	Positive Test Results No. (%)
Sputum	24 (100%)	13 (54%)
BALF	6 (25%)	4 (67%)
Lung tissue	6 (25%)	5 (84%)
Pleural effusion	5 (21%)	3 (60%)
Subcutaneous nodules/pus	10 (42%)	7 (70%)
Brain	1 (4%)	1 (100%)

BALF = bronchoalveolar lavage fluid.

chest CT images, whereas the others had at least 2 types of shadows.

The most common parenchymal findings were air-space opacities (83.3%) (Figures 1–3), followed by nodules (62.5%) (Figure 2). Some of them showed cavitary lesions (45.8%) (Figure 2) and masses (37.5%). Pleural effusions were not rare phenomena in the study group (Figure 1); 10 cases (41.7%) had effusions, and 5 of them required effusion drainage. Localized pleural thickening, present below the lung shadows, was observed in half of the cases (12/50%). Some patients had pericardial effusions (3/12.5%) or a localized pneumothorax (3/12.5%). Some patients (12/50%) had concomitant mediastinal and/or hilar lymphadenopathy.

Diagnosis, Treatment, and Prognosis

In all cases, positive cultures for *Nocardia* were obtained from at least 1 clinical specimen, including sputum, BALF, pleural effusions, abscesses, wound drainage fluids, and tissues. Extrapulmonary infections were detected in 13 cases (54.2%). Ten cases (41.7%) were complicated by skin infection, 5 and 5 of which manifested as subcutaneous abscesses and subcutaneous nodules, respectively. None of these infections were ulcerative lesions. Twelve cases (50%) of disseminated nocardiosis were observed. Four cases (16.7%) had involvement of the lung and brain, and 2 of them also had a concurrent skin infection. Patients with nocardiosis may be co-infected with other pathogens. Five (20.8%) and 2 (8.3%) cases were co-infected with *Aspergillus* species and cytomegalovirus, for

which anti-fungals and ganciclovir, respectively, were prescribed. The antimicrobial susceptibilities of all the isolated *Nocardia* species were assessed in the study.

All patients were treated with antibiotics. Co-trimoxazole was prescribed to all patients whose *Nocardia* isolates were sensitive to the antibiotic (in 2 patients, *Nocardia* isolates were resistant). Five cases were administered only 1 medication, that is, co-trimoxazole, and the others were treated with 2 or more antibiotics. The daily therapeutic dose of co-trimoxazole ranged from 1600 to 4800 mg of trimethoprim and 3200 to 9600 mg of sulfamethoxazole, and the mean duration of treatment was 10 months. The patients with only pulmonary nocardiosis were treated for at least 8 months, and patients who had brain involvement were treated with antibiotics for at least 12 months, 1 of whom received a 24-month course of co-trimoxazole. Three patients had hepatic damage during the treatment. After they were diagnosed with nocardiosis, the dosage of steroids was reduced in all patients, and the cytotoxic drugs were discontinued temporarily in some patients.

The median follow-up period was 18.9 months (range, 8–57 months). All 5 cases with skin abscesses underwent incision and drainage of the lesions. Two of the 4 cases with brain abscesses underwent drainage. No patient underwent thoracic surgery. Twenty-two cases recovered, and 2 cases (8.3%) died. Of the deceased patients, 1 had disseminated nocardiosis with lung, pleura, and brain involvement, and the other patient was elderly with microscopic polyangiitis (MPA) and was co-infected with *Aspergillus*.

DISCUSSION

Nocardia is a Gram-positive, aerobic, environmental bacterium that can be found in soil, decomposing vegetation, and other organic matter, as well as in fresh and salt water. Although up to one-third of patients with nocardiosis are immunocompetent, *Nocardia* is usually an “opportunistic pathogen”. Inhalation is the primary route of *Nocardia* exposure, which accounts for 50 to 70% of cases presenting with pulmonary involvement.^{5–6} Most of the autoimmune disease patients were prescribed long-term corticosteroids and/or cytotoxic agents, which placed them at risk for acquiring various opportunistic infections, such as mycosis, *Pneumocystis jirovecii* pneumonia, mycobacteriosis, and nocardiosis. Our study is the largest single-center study of autoimmune disease cases complicated by pulmonary nocardiosis.

It had been reported that nocardiosis was 2 to 3 times more common in 55 to 66 years old men;^{3–5,9,22–24} however, our

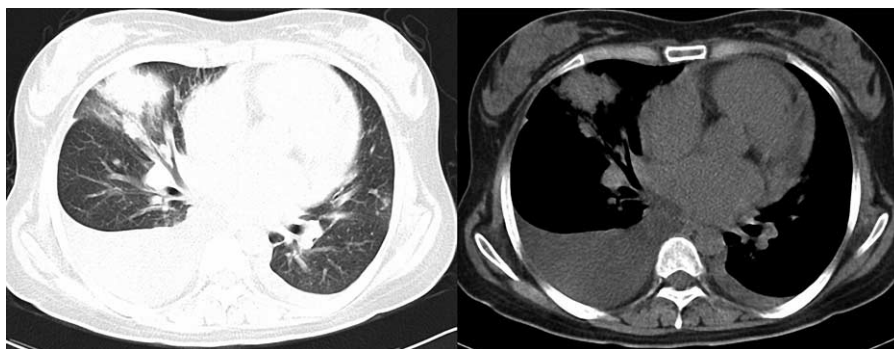


FIGURE 1. The chest CT showed consolidation in the right middle lung with bilateral pleural effusion in a case of pulmonary nocardiosis. CT = computed tomography.

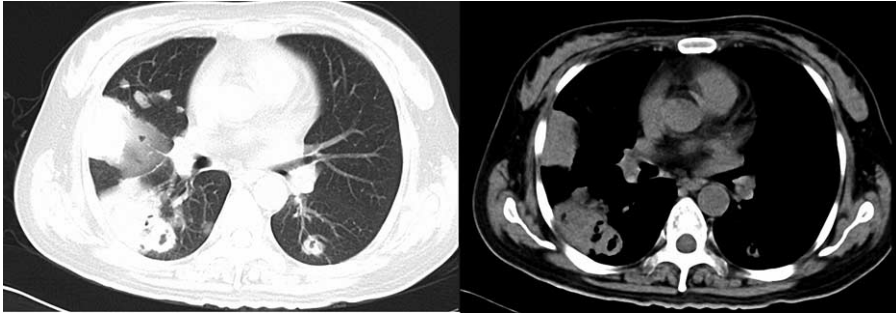


FIGURE 2. Chest CT images in a case of pulmonary nocardiosis showed multiple nodules and cavitations in the right middle lung and both lower lungs, as well as consolidations in the right middle and lower lung. CT = computed tomography.

cohort demonstrated a female predominance (male:female = 5:19) and younger, with an average age of 44 years. This difference may be related to the unique study population, that is, all cases enrolled in our study had at least 1 type of autoimmune disease, most of which showed a female predominance.^{25–27} Yamagata et al reported a cohort of nocardiosis patients with rheumatic diseases, 50% of whom were women.²¹

Ambrosioni et al⁹ and Wang et al⁹ reported that nocardiosis cases had increased over time. Better recognition of *Nocardia*, greater use of 16S gene sequencing for reliable identification, increased culture volumes, improved cancer care leading to longer survival, and increased numbers of immunocompromised patients were the likely reasons for this phenomenon. In our hospital, we reported a clinical analysis of nocardiosis cases in 2010 in a Chinese medical journal.²⁸ This study improved the recognition of nocardiosis by both clinicians and microbiology technicians. Alternatively, our hospital is the only medical center that treats rare and difficult cases in China, with an increasing number of patients with complex medical conditions presenting to our hospital. This may be another reason for the emergence of pulmonary nocardiosis in our hospital over the past 3 years.

Some recent analyses of pulmonary nocardiosis cases were systematically reviewed, and the results are shown in Table 4. Similar to the reported cases analyzed in the present study, fever and cough were the most common clinical manifestations of pulmonary nocardiosis.^{2,22–24} In most of the case reports of autoimmune disease complicated by *Nocardia* infection, SLE was the most common disease. In our study, we also observed that SLE patients were more common than other patients, with 7 cases (29.2%) of SLE, including 5 cases with SLE, 1 case with

SLE and Evans syndrome, and 1 case with SLE and rheumatoid arthritis. However, pulmonary nocardiosis may occur in patients with many other types of autoimmune disease, for example, dermatomyositis (4 cases, 16.7%), microscopic polyangiitis (3 cases, 12.5%), and ITP (3 cases, 12.5%). All but 1 patient had been prescribed long-term systemic corticosteroids and cytotoxic agents. It was reported that prolonged therapy with systemic corticosteroids and cytotoxic agents, for example, azathioprine, cyclosporine, and mycophenolate mofetil, causes potent selective suppression of T-cell activation and proliferation. These agents inhibit the inflammatory response to microbial invasion and thereby facilitate opportunistic infections by a variety of organisms, for example, herpes group viruses, fungal and mycobacterial species, and a variety of intracellular pathogens.²⁹ Because T cells are the key components of the immune response to *Nocardia* upon the activation of macrophages,³⁰ long-term systemic corticosteroids and cytotoxic agents appear to be major predisposing factors for pulmonary and disseminated nocardiosis.^{2,4–5} In our cohort, there was only 1 case of neutropenia ($1.24 \times 10^9/l$); however, in 12 cases (50%), the lymphocyte counts were $< 1 \times 10^9/l$. As this study was a retrospective analysis and lymphocyte subset analysis was not generally performed in our hospital before 2008, this test was only performed in 16 cases (66.7%). However, this may be the first study with detailed lymphocyte data for most patients with pulmonary nocardiosis. In 11 cases (68.8%, $n = 16$), the primary peripheral CD4⁺ T-cell counts were $< 0.4 \times 10^9/l$. Although only 3 patients had low IgG levels, all but 1 had decreased B-cell counts. The possible relationship between *Nocardia* infection and lymphocytopenia had been observed in previous studies.^{2,4–5,31–32} In AIDS patients, it

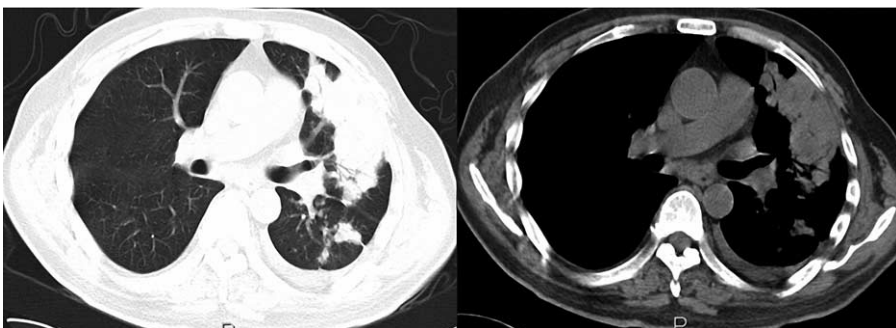


FIGURE 3. The chest CT images of a case of pulmonary nocardiosis showed multiple consolidations in the left lung. CT = computed tomography.

TABLE 4. Comparison of Different Recent Analysis of Pulmonary Nocardiosis Cases

Ref Characters	Martinez ²	Chen's ²³	Kurahara's ²²	Chen's ²⁴	Ours
Published year	2007	2012	2014	2014	2015
Location	Spain	Taiwan	Japan	China (Zhejiang)	China (Beijing)
Total cases	31	20	59	17	24
Systemic steroids/cytotoxic therapy cases (n/%)	19/61.3%	5/25%	1/1.7%	15/88.2%	23/95.8%
Autoimmune disease case (n/%)	4/12.9%	2/10%	2/3.4%	3/17.6%	24/100%
Mean age	54 ± 16	64.8 ± 15.5	66 ± 13	51.1 ± 9.5	44.2 ± 15.7
Male%	23/74.2%	12/60%	43/72.9%	13/76.5%	5/20.8%
Main symptoms	Cough (77%) Fever (74%)	Cough (80%) Fever (50%)	Cough (76%) Dyspnea (76%)	Cough (94%) Fever (71%)	Fever (87.5%) Cough (83.3%)
Pleural effusion	11/36%	8/40%	1/1.7%	11/64.7%	10/41.7%
Main chest CT showings	Alveolar pattern+ nodules	Consolidation+ pleural effusion	Consolidation+ nodules	Nodules+ cavitation	Air-space opacities+ nodules
Positive sputum results	20/77%	2/10%	NA	12/70.6%	13/54.2%
Disseminated cases (n/%)	11/35.5%	NA	1/1.7%	4/23.5%	13/54.2%
Died cases (n/%)	12/39%	13/65%	NA	3/18.8%	2/8.3%

CT = computed tomography, NA = not applicable.

was reported that the incidence of nocardiosis was ~140-fold higher than that in the general population, and those whose peripheral CD4⁺ T-cell counts were $< 0.1 \times 10^9/l$ were at the highest risk.^{2,4-5} Because more than half of our cases had lower CD4⁺ T-cell counts, it appeared that lymphocytopenia, particularly low peripheral CD4⁺ T-cell counts, may be a risk factor in patients with autoimmune disease complicated by pulmonary nocardiosis.

In contrast, corticosteroids can inhibit the activation of immature B cells, although established B-cell responses are relatively resistant to steroids. Whereas 15 patients had decreased B cell counts (n = 16), hypogammaglobulinemia was not very prevalent in our cohort, similar to the findings in Yamagata's study.²¹ However, most of the patients in the present study had hypoalbuminemia, in contrast to the results of Yamagata's study.²¹ Hypoalbuminemia was not analyzed in many other large studies on nocardiosis.^{4-5,9,22}

Lung consolidation and nodules were the most common CT findings in Kanne's cohort,³³ and these were also the main CT findings in our study and most recent analyses of pulmonary nocardiosis.^{2,22-23} However, in Chen's study (Zhejiang), nodules and cavitations were the most common chest CT findings,²⁴ which were similarly reported by Smilack.³⁴ Although many of our cases had lymphocytopenia and low CD4⁺ T-cell counts, cavitations were not as common in our cohort. Nevertheless, these findings were more common in HIV-positive pulmonary nocardiosis patients.³⁵ Pleural effusion was not rare among the cohorts in the most recent studies of pulmonary nocardiosis^{2,23-24} (Table 4; range, 36-64.7%), except for Kurahara's cohort.²² Moreover, 10 cases (41.7%) in our cohort were complicated by pleural effusion as well. Only 1 case in Kurahara's cohort was administered corticosteroids, and none received immunosuppressive agents. Most of their cases had at least 1 underlying pulmonary disease, and pre-existing lung structural abnormalities were common.²² However, immunosuppressive treatment was common in the other pulmonary nocardiosis studies and in our study. The different risk factors may cause this difference of the chest imaging.

Thus, pulmonary nocardiosis should be considered in the differential diagnosis of autoimmune diseases when new air-space patchiness and nodules are observed on chest CT, particularly when the cases are complicated by pleural effusion.

For pulmonary nocardiosis patients, *Nocardia* species could be isolated from the respiratory tract specimens, for example, sputum, endotracheal aspirates, pleural effusions, and lung tissues. In our study, the culture of lung tissue, which was harvested by CT-guided percutaneous lung biopsy, was the most sensitive method of isolating *Nocardia* species (83.3%), following by BALF culture (66.7%), pleural effusion culture (60%), and sputum culture (54.2%). As in Chen's (Taiwan)²³ cohort, more than half of the enrolled cases underwent endotracheal aspiration, and *Nocardia* species could only be isolated from expectorated sputum in 2 cases. In our study, more than half of the cases (13/54.2%) were sputum-positive for *Nocardia* species. In studies by Martinez² and Chen (Zhejiang),²⁴ *Nocardia* was isolated from sputum samples in 70.6 to 77% of cases. In suspicious cases, repeat sputum culture may be an economical and efficient noninvasive method for diagnosing pulmonary nocardiosis. As *Nocardia* species were isolated from 70% of samples from skin abscesses and/or subcutaneous nodules, this mini-invasive procedure was suggested for suspected cases with skin *Nocardia* infection. For patients who cannot expectorate, patients with negative sputum results, and patients in whom pulmonary nocardiosis is still suspected in cases of autoimmune disease, bronchoscopy, thoracentesis, and percutaneous lung biopsy can be considered. As shown in Table 4, disseminated nocardiosis was more common in our study than Kurahara's,²² and skin was the most common extrapulmonary site involved. This result may be related to the underlying risk factors, as only 1 case (1.7%) in Kurahara's cohort²² was diagnosed with dissemination. However, in the studies of Martinez² and Chen (Zhejiang),²⁴ the rates of disseminated nocardiosis were 35.5% and 23.5%, respectively.

Co-trimoxazole was the standard treatment of choice for localized and disseminated *Nocardia* infections until the end of the 1960s. Since then, tetracyclines (minocycline and

doxycycline), rifampicin, aminoglycosides, carbapenems, new fluoroquinolones, β -lactams, macrolides (clarithromycin), linezolid, and oxazolidinones have been used to treat nocardiosis. It was suggested that antinocardial treatment should be modulated according to the involved organs or sites, the severity of infection, and the presence of comorbidities.⁷ Because nearly all of our enrolled cases had been prescribed immunosuppressive agents and most of them had abnormal lymphocyte counts, most of our patients were treated with combination therapy consisting of at least 2 antibiotics. Concurrently, the corticosteroid dosages were decreased, and cytotoxic agents were discontinued in some cases. It was suggested that antibiotics should be administered for a minimum of 6 to 12 months; however, the length of therapy should be modulated according to the underlying immunosuppressive conditions and the antinocardial therapeutic effectiveness.^{4–7} Because nearly all of our cases had been receiving immunosuppressant therapy before the diagnosis of nocardiosis, they were administered antibiotics for 10 to 12 months. Although Cercenado et al suggested that prolonged low-dose maintenance therapy may be prescribed for those who must be maintained on steroid or cytotoxic therapy, none of our cases received continuous antibiotics.³⁶

Most cases with skin and/or brain abscesses underwent surgical incision and drainage. None of our enrolled cases underwent thoracic surgery. Of the 2 deceased patients, 1 had disseminated nocardiosis and the other was co-infected with *Aspergillus*. Because disseminated nocardiosis was common in our study, we could not establish the relationship between the death rate and the underlying condition, the species involved, or the antimicrobial treatment. However, nearly all of our enrolled cases underwent modulation of immunosuppressive therapy for their autoimmune disease before they were diagnosed with nocardiosis.

Our retrospective study had several limitations. First, all enrolled cases had a definite microbiological diagnosis, and all of them had an autoimmune disease before they were infected with *Nocardia*, which may have resulted in selection bias. Second, molecular technology was not available for our study, and only the traditional microbiological notation system was used in our study. It was reported that the agreement between molecular techniques and conventional methods ranged from 70 to 90%.³⁷ Molecular methods for identifying *Nocardia* at the species level will be suggested to our microbiological colleagues to facilitate a better understanding of the characteristics of patients with nocardiosis. Third, the lymphocyte subtype analysis was not available for all enrolled cases at the time they were diagnosed with nocardiosis, and it was not repeated regularly during the antinocardial treatment. However, our retrospective study appeared to be the largest analysis of autoimmune cases complicated by pulmonary nocardiosis. This study may help clinicians to better understand the risk factors and clinical characteristics of these unique patients and to improve their prognosis.

CONCLUSIONS

Pulmonary nocardiosis in patients with an underlying autoimmune disease showed a female predominance and presentation at younger age. Immunosuppressant therapy, lymphocytopenia, particularly low CD4⁺ T-lymphocyte counts, and low serum albumin levels may be the primary susceptibility factors. Air-space opacities and nodules were the most common chest imaging features. Disseminated nocardiosis with lung and skin involvement was common among our cohort. Early

diagnosis and antinocardial therapy with modulation of the basic immunosuppression therapy were important for these individuals.

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