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 lungs; 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 hydroxyclo-roquine. 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.

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 transplantation10–12 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
defined as a serum albumin level a lymphocyte count and a lymphocyte count when Nocardia infection was suspected or diagnosed. Globulin analysis was performed for most of the enrolled cases during the first 3 weeks of the diagnosis of acquired nocardiosis. The immune system was stimulated by flow cytometry analysis, 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 days. The lymphocyte subset 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 less than 120 g/l for women and less than 120 g/l for men, (2) neutropenia was defined as a neutrophil count less than 1.5 × 10⁹/L, (3) lymphocytopenia was defined as a lymphocyte count less than 1 × 10⁹/L, and (4) hypoalbuminemia was defined as a serum albumin level less than 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 ± 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 polyaniglitis (3 cases, 12.5%), idiopathic thrombocytopenic purpura (ITP) (3 cases, 12.5%), Henoch–Schönlein purpura nephritis (2 cases, 8.3%), inflammatory myositis (1 case, 4.2%), rheumatoid arthritis (1 case, 4.2%), rheumatoid arthritis and secondary Sjögren’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 hemoptyis (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 × 10⁹/ l to 22.88 × 10⁹/ l (mean, 9.67 × 10⁹/ l), with neutrophils comprising the largest portion (mean, 78.2%; range, 61.4–94.7%). Peripheral lymphocyte counts ranged from 0.29 × 10⁹/ l to 3.41 × 10⁹/ l (mean, 1.13 × 10⁹/ l). Only 1 case exhibited neutropenia (1.24 × 10⁹/ l), and in 12 cases (50%), the lymphocyte counts were < 1 × 10⁹/ 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/μl in 5 cases (31.25%); however, the CD4⁺ T-cell counts were normal ([561–1137]/μl) in only 3 cases (18.75%). Moreover, the CD4⁺ T-cell counts were < 200/μl 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
The Involved Lesions of These 24 Cases

| 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 + pleural 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 | Plural effusion | Cefoperazone + Ciprofloxacin | Died |
| 5  | 15/F        | HSPN                | 60 m                 | CTX + HCQ      | Lung + skin       | Sputum + skin      | TMPco     | Recovered|
| 6  | 31/F        | ITP                 | 24 m                 | No             | Lung + skin + pleura | Skin + pleural effusion | TMPco | Recovered|
| 7  | 28/M        | ITP                 | 3 m                  | VCR            | Lung + pleura + skin | Sputum | TMPco + Co-amoxiclav + Amikacin | Recovered|
| 8  | 20/F        | HSPN                | 5 m                  | CTX            | Lung + brain + pleura | Lung | TMPco | Recovered|
| 9  | 54/M        | RA                  | No                   | No             | Lung + skin       | Lung                | TMPco, Levofloxacin | Recovered|
| 10 | 45/F        | Myotitis            | 2 m                  | No             | Lung + skin + pleura | Lung | TMPco | Recovered|
| 11 | 58/F        | DM                  | 4 m                  | AZA            | Lung + skin       | Lung                | TMPco + Minocycline | Recovered|
| 12 | 62/F        | ITP                 | 2 m                  | No             | Lung + skin       | Sputum | TMPco | Recovered|
| 13 | 61/F        | RA, SS              | 1 m                  | CTX + LEF      | Lung + skin       | Lung                | 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 + skin       | Lung | TMPco + Co-amoxiclav | Recovered|
| 16 | 47/F        | Evans               | 23 m                 | CTX            | Lung + brain + skin + pleura | Sputum + pus | TMPco + Co-amoxiclav | Recovered|
| 17 | 72/M        | MPA                 | 4 m                  | TII            | Lung + skin       | Sputum | TMPco, Co-amoxiclav + Amikacin | 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 + skin       | Lung | Ceftriaxone + TMPco | Recovered|
| 21 | 40/F        | SLE, Evans          | 1 m                  | CTX            | Lung + skin       | Lung | TMPco | Recovered|
| 22 | 56/F        | MPA                 | 2 m                  | CTX            | Lung + skin       | Lung | TMPco | Recovered|
| 23 | 57/M        | SLE, RA             | 1 m                  | MTX + LEF      | Lung + skin       | Lung | TMPco + Minocycline | Died |
| 24 | 64/F        | MPA                 | 24 m                 | AZA            | Lung + skin       | Lung + 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?lein purpura nephritis, ITP = idiopathic thrombocytopenic purpura, LEF = leflunimide, M = male, MPA = microscopic polyangiitis, MTX = methotrexate, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, SS = Sjögren syndrome, THA = thalidomide, TII = tripterygium wilfordii, TMPco = co-trimoxazole, VCR = vincristine.

Pus in this table was from cutaneous abscesses.

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...
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.3–6 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 jiroveci 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

### 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.
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 al5 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 cytoytic 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.3,4 In our cohort, there was only 1 case of neutropenia (1.24 × 109/l); however, in 12 cases (50%), the lymphocyte counts were < 1 × 109/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 × 109/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
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 10^7/l were at the highest risk. 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. However, most of the patients in the present study had hypoalbuminemia, in contrast to the results of Yamagata’s study. Hypoalbuminemia was not analyzed in many other large studies on nocardiosis.

Lung consolidation and nodules were the most common CT findings in Kanne’s cohort, and these were also the main CT findings in our study and most recent analyses of pulmonary nocardiosis. However, in Chen’s study (Zhejiang), nodules and cavitations were the most common chest CT findings,24 which were similarly reported by Smilack. Although many of our cases had lymphocytopenia and low CD4+ T-cell counts, cavitations were not as common in our cohort, especially low peripheral CD4+ T-cell counts, may be a risk factor in patients with autoimmune disease complicated by pulmonary nocardiosis.

Thus, pulmonary nocardiosis should be considered in the differential diagnosis of autoimmune diseases when new airspace 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) 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 Martinez and Chen (Zhejiang), 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, 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 Martinez and Chen (Zhejiang), 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

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

| Ref Characters | Martinez2 | Chen’s23 | Kurahara’s22 | Chen’s24 | 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%) | Cough (80%) | Cough (76%) | Cough (94%) | Fever (71%) |
| 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+ cavititation | Air-space opacities+ nodules |
| Positive sputum results | 20/77% | 2/10% | NA          | 12/70.6% | 13/54.2% |
| Disseminated cases (n%) | 11/35.5% | 13/65% | 3/18.8%     | 15/88.2% | 23/95.8% |
| Died cases (n%) | 12/39% | 13/65% | NA          | 3/18.8%  | 2/8.3% |

CT = computed tomography, NA = not applicable.
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.³ 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%.⁵⁷ 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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