Case Report

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Pulmonary nocardiosis in patients with connective tissue disease: A report of two cases

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Summary **Reported here are 2 patients with connective tissue disease who developed pulmonary nocardiosis. Case 1 involved a 73-year-old man with malignant rheumatoid arthritis treated with prednisolone 25 mg/day. Chest X-rays revealed a pulmonary cavity and bronchoscopy detected *Nocardia* species. The patient was successfully treated with trimethoprim/sulfamethoxazole. Case 2 involved a 41-year-old woman with systemic lupus erythematosus. The patient received remission induction therapy with 50 mg/day of prednisolone and tacrolimus. Six weeks later, a chest CT scan revealed a pulmonary cavity; bronchoscopy resulted in a diagnosis of pulmonary nocardiosis. The patient had difficulty tolerating trimethoprim/sulfamethoxazole, so she was switched to and successfully treated with imipenem/cilastatin and amikacin.**

Keywords: Connective tissue disease, immunosuppressive therapy, nocardia, pulmonary nocardiosis

1. Introduction

Nocardia is an aerobic gram-positive bacillus belonging to the family Nocardiaceae within the order Actinomycetales. It is weakly acid-fast and is widely distributed in soil. *Nocardia* species are usually considered to be opportunistic pathogens. A previous report showed that more than half of 1,000 patients with nocardiosis were immunosuppressed (*1*). Risk factors for nocardiosis include corticosteroid treatment, lymphoma, solid tumors, stem-cell or organ transplantation, human immunodeficiency virus (HIV) infection, and diabetes (*2*).

Connective tissue disease (CTD) is typically treated with corticosteroids and immunosuppressants and biologics. Nocardiosis is an occasional, but potentially serious, infection for immunosuppressed patients. Reported here are cases of 2 patients with CTD who developed pulmonary nocardiosis during immunosuppressive therapy.

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2. Case reports

2.1. *Case 1*

A 73-year-old Japanese man was admitted to this hospital in May 2012 for polyarthritis. He tested positive for anti-citrullinated peptide antibody (anti-CCP antibody) and rheumatoid factor (RF) and he met the 2010 rheumatoid arthritis (RA) classification criteria (American College of Rheumatology/European League Against Rheumatism) (*3*). The patient was diagnosed with rheumatoid arthritis, and this condition was highly active. The patient had difficulty tolerating methotrexate (MTX) and corticosteroids presumably due to renal dysfunction and diabetes. Therefore, he was treated with adalimumab (ADA), which was subsequently switched to etanercept (ETN) because of primary failure (Figure 1A).

In September 2012, the patient was again admitted to this hospital because his arthritis had worsened. Blood examinations at admission showed decreased

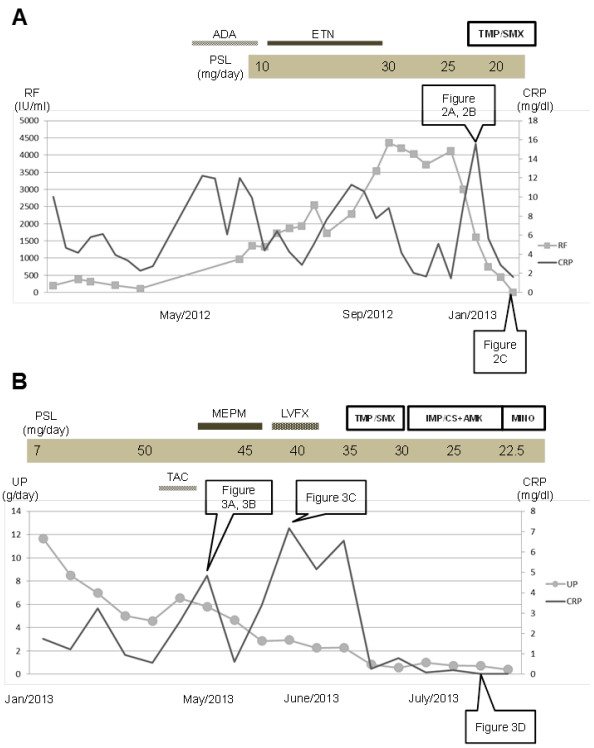

Figure 1. Clinical courses. (A) Case 1: Treatments and changes in levels of serum C-reactive protein (CRP) and rheumatoid factor (RF) are shown along with the timing of chest X-rays and computed tomography (CT) scans (*Abbreviations*: ADA, adalimumab; ETN, etanercept; PSL, prednisolone; TMP/SMX, trimethoprim/sulfamethoxazole; CRP, C-reactive protein; RF, rheumatoid factor; Sep, September; Jan, January); **(B)** Case 2: Treatments and changes in levels of serum C-reactive protein (CRP) and proteinuria are shown along with the timing of chest X-rays and computed tomography (CT) scans (*Abbreviations*: PSL, prednisolone; TAC, tacrolimus; MEPM, meropenem; LVFX, levofloxacin; TMP/SMX, trimethoprim/sulfamethoxazole; IPM/CS, imipenem/cilastatin; AMK, amikacin; CRP, C-reactive protein; UP, urine protein; Jan, January).

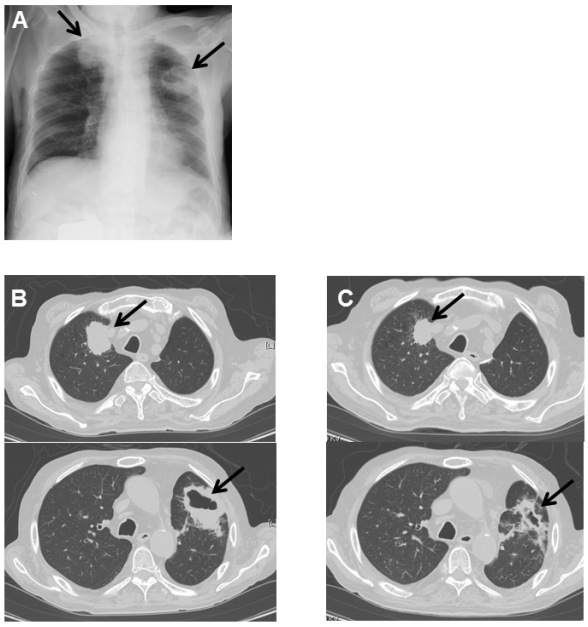

Figure 2. Chest X-ray and computed tomography findings in case 1. On admission, chest X-rays **(A)** and computed tomography (CT) **(B)** revealed a cavity in the upper left lung lobe and a mass lesion in the upper right lung lobe (indicated by arrows). Two weeks after initiation of trimethoprim/sulfamethoxazole (TMP/SMX), a chest CT **(C)** scan revealed marked reduction in the size of both the cavity and the mass lesion (indicated by arrows). **(A)** Chest X-ray on admission (January 2013). **(B)** Chest CT scan on admission (January 2013). **(C)** Chest CT scan 2 weeks after initiation of trimethoprim/sulfamethoxazole (TMP/SMX).

complement levels (CH50: < 10 U/mL; C3 75: mg/dL; and C4 7: mg/dL) as well as marked elevation of RF (4,356 IU/ml). Moreover, chest X-rays revealed bilateral pleural effusion, and thoracentesis confirmed exudative pleurisy without infection. Consequently, the presence of definite RA, low complement levels, and high titers of RF led to a diagnosis of malignant rheumatoid arthritis (MRA). The patient was treated with 30 mg/day (0.6 mg/kg/day) of oral prednisolone (PSL), and ETN was discontinued. His arthritis improved markedly, as did his pleurisy (Figure 1A).

In January 2013, he complained of general fatigue and fever, and he was admitted to this hospital, where he was treated with 25 mg/day of oral PSL. Chest X-rays and computed tomography (CT) revealed a cavity in the upper left lung lobe as well as a mass lesion in the upper right lung lobe (Figure 2A, 2B). Because pulmonary tuberculosis and mycosis were suspected, sputum and gastric fluid were cultured for *Mycobacterium* species and levels of beta-D-glucan in serum were determined. The results of these examinations were all negative. Therefore, bronchoscopy was performed to diagnose these lung lesions. *Nocardia* species were found in cultured bronchoalveolar lavage fluid (BALF) but not malignant cells. A systemic examination revealed no involvement of the brain or skin. Ultimately, lung nocardiosis was diagnosed. Moreover, the 16S ribosomal RNA genes of the recovered organisms were amplified using a polymerase chain reaction (PCR) as described previously (*4*), and the 1,367-nucleotide product was sequenced with an ABI PRISM 3130 genetic analyzer (Applied Biosystems Japan, Tokyo, Japan). Analyses with the Basic Local Alignment Search Tool showed that the sequence had 99.9% similarity to that of *Nocardia farcinica* ATCC 3318^T (GenBank accession number: Z36936).

Oral administration of trimethoprim/sulfamethoxazole (TMP/SMX) (960-4,800 mg/day) was started for lung nocardiosis, and symptoms such as fatigue and fever improved. Two weeks after the initiation of TMP/SMX, a marked reduction in the cavity and in the mass lesion in the lungs was noted on a chest CT scan (Figure 2C). TMP/SMX administration was continued for 6 months (Figure 1A).

2.2. *Case 2*

The patient in the second case was a 41-year-old woman who had been diagnosed with systemic

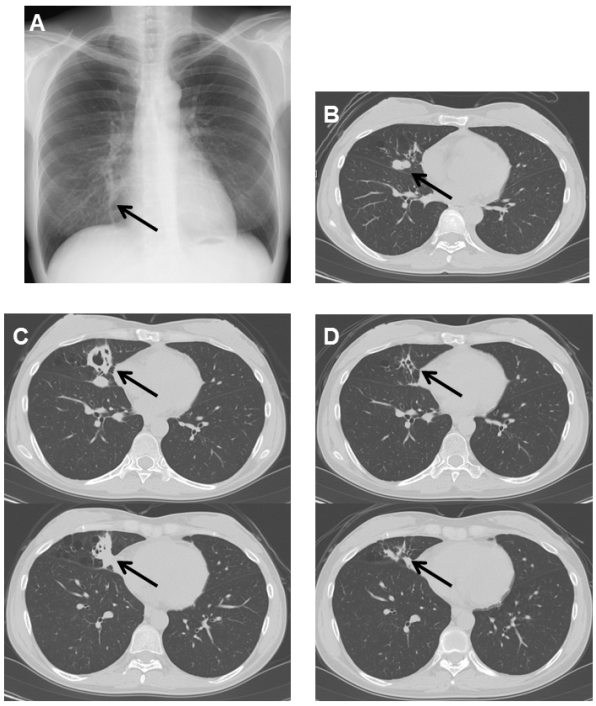

Figure 3. Chest X-ray and computed tomography findings in case 2. Two weeks after the initiation of remission induction therapy for systemic lupus erythematosus (SLE), chest X-rays **(A)** and computed tomography (CT) **(B)** revealed nodules in the middle right lung lobe (indicated by arrows). One month after the first chest CT scan, a second chest CT scan showed that the nodules had enlarged and formed a cavity **(C)** (indicated by arrows). After 6 weeks of treatment for nocardiosis, a chest CT scan **(D)** revealed that the cavity (indicated by arrows) was less opaque. **(A)** A chest X-ray 2 weeks after initiation of remission induction therapy. **(B)** Chest CT scan 2 weeks after initiation of remission induction therapy. **(C)** Chest CT scan 1 month after the first chest CT scan. **(D)** Chest CT scan after 6 weeks of treatment for nocardiosis.

lupus erythematosus (SLE) along with nephritis and serositis. The onset of SLE occurred at the age of 19, and the patient had received continued maintenance therapy with 7 mg/day of oral PSL for several years (Figure 1B).

In June 2012, proteinuria appeared, and edema in both legs gradually worsened. As a result, the patient was admitted to this hospital in January 2013. Proteinuria of 6 - 12 g/day, pericardial effusion, a high anti-DNA antibody titer according to radioimmunoassay (90 IU/mL), and a low white blood cell (WBC) count ($3,100/mm^3$) were observed. On the basis of these findings, a flare-up of SLE was diagnosed. She was again given remission induction therapy with 50 mg/day (1 mg/kg/day) of oral PSL and tacrolimus (TAC). Two months later, the proteinuria had decreased to 1 - 2 g/day (Figure 1B).

After TAC was started, a blood examination showed increased levels of C-reactive protein (CRP). Moreover, chest X-rays and CT scans showed nodules in the middle right lung lobe (Figure 3A, 3B). Her respiratory symptoms were very mild, and the sputum culture results were negative. Although antibiotics (meropenem and levofloxacin) were administered and TAC was discontinued, the CRP increased again after occasionally decreasing. One month after the first chest CT scan, a second chest CT scan was performed and showed that the nodules had enlarged and formed a cavity (Figure 3C). Bronchoscopy was performed, and *Nocardia* species were identified in the BALF culture. Thus, pulmonary nocardiosis was diagnosed (Figure 1B). Furthermore *Nocardia* species were identified as *Nocardia farcinica* by sequencing analysis of the 16S ribosomal RNA genes as was done in case 1.

Oral administration of TMP/SMX (1,440-7,200 mg/day) was started for pulmonary nocardiosis. The treatment with TMP/SMX was effective, and the serum CRP decreased dramatically after initiation of TMP/SMX. However, 2 weeks later, the TMP/SMX was switched to imipenem/cilastatin (IPM/CS) and amikacin (AMK) because the patient had hyponatremia. The treatment with IPM/CS and AMK was continued for 4 weeks, following oral administration of minocycline (MINO). Serum CRP remained low during these treatments (Figure 1B). After 6 weeks of the treatment (2 weeks with TMP/SMX and 4 weeks with IPM/CS and AMK), a chest CT scan showed a reduction in the pulmonary cavity (Figure 3D).

3. Discussion

Patients with CTD undergoing immunosuppressive therapy are at risk of acquiring various opportunistic infections, such as mycosis, *Pneumocystis jiroveci* pneumonia, and mycobacteriosis. Although nocardiosis is infrequent, some reports have noted nocardiosis in patients with CTD (*5,6*).

Pulmonary nocardiosis is the most common clinical presentation of nocardiosis. The onset of symptoms includes a productive or nonproductive cough, shortness of breath, chest pain, hemoptysis, fever, night sweats, weight loss, and progressive fatigue (*7*). Because nocardiosis does not have any specific symptoms, whether nocardia is present must be determined, such as by a culture test, in high-risk patients. Indeed, Martínez Tomás and colleagues showed that the mean time to diagnosis for nocardiosis was 42 days (*8*). Although a chest CT scan is useful at diagnosing pulmonary nocardiosis, a cavity opacity may not necessarily be observed. As potential findings include pleural effusion, multiple nodules, and chest wall extension (*9*).

Nocardia species must be identified for a definitive diagnosis of nocardiosis. Generally, a sputum culture or bronchoscopy (obtaining BALF) is performed to diagnose pulmonary nocardiosis. In the 2 current cases, *Nocardia* species were not detected in sputum cultures but were detected in BALF cultures. Importantly, a previous report showed that specimens obtained by invasive methods were required for definitive diagnosis in 47% of patients

with pulmonary nocardiosis (*8*). Moreover, Scott and colleagues reported that percutaneous transthoracic needle biopsy (PTNB) was useful at diagnosing patients with acquired immunodeficiency syndrome (AIDS) (*10*).

General treatment recommendations for nocardiosis are hindered by the lack of prospective controlled trials. Optimal antimicrobial treatment regimens have not been firmly established (*7*). TMP/SMX is most commonly used to treat nocardiosis (*7*,*11*). Alternative antimicrobial agents with activity against *Nocardia* species include AMK, IPM, meropenem, ceftriaxone, cefotaxime, MINO, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin-clavulanic acid (*7*). Combination therapy with IPM and cefotaxime, AMK and TMP/SMX, IPM and TMP/SMX, AMK and cefotaxime, or AMK and IPM may provide increased effectiveness (*7*). Both of the current patients responded well to TMP/SMX monotherapy, but the patient in case 2 had to be switched from TMP/SMX to IPM/CS and AMK because of an adverse reaction following oral administration of MINO. Interestingly, that patient did not respond sufficiently to meropenem or levofloxacin.

When treating nocardiosis, drug resistance and the duration of the treatment are also important points to consider. Recent reports showed that 2% to 43% of *Nocardia* species were resistant to TMP/SMX (*11*). The duration of treatment is generally prolonged to minimize the risk of disease relapse. Immunocompetent patients with pulmonary or multifocal (non-central nervous system, CNS) nocardiosis may be successfully treated with 6 to 12 months of antimicrobial therapy. Immunosuppressed patients and those with CNS disease should receive at least 12 months of antimicrobial therapy with appropriate clinical monitoring (*7*).

The findings reported here indicate that if patients with CTD who are receiving immunosuppressive therapy have abnormal findings in the lungs (including pulmonary cavities), then the possibility of nocardiosis should be considered in addition to mycosis and mycobacteriosis. If patients have negative sputum cultures, bronchoscopy may need to be performed to obtain BALF in order to detect *Nocardia* species.

In conclusion, pulmonary nocardiosis is one of the important differential diagnoses for pulmonary lesions (including pulmonary cavities) as well as mycobacteriosis and mycosis in patients with CTD undergoing immunosuppressive therapy.

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