CASE REPORT

Pneumococcal Pneumonia Co-infection with Mycobacterium avium and Nocardiya cyriacigeorgica in an Immunocompetent Patient

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Abstract:
A 61-year-old woman was transferred with a complaint of a fever and productive cough. She had tested positive for Mycobacterium avium and Nocardiya cyriacigeorgica at least twice, and Streptococcus pneumonia (PISP) was isolated (+) from her purulent sputum. As radiological findings, a lower lung field-dominant infiltration shadow and nodular shadow with cavity were recognized in the bilateral lung fields. We diagnosed her with pneumococcal pneumonia co-infection with M. avium and N. cyriacigeorgica. She was treated with MEPM for pneumococcal pneumonia, a standard regimen containing clarithromycin for pulmonary MAC disease, and sulfamethoxazole/trimethoprim for pulmonary nocardiosis. She improved with appropriate treatment.

Key words: Pneumococcal pneumonia, Mycobacterium avium, Nocardiya cyriacigeorgica, Co-infection

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Introduction

Nocardiya species is an aerobic Gram-positive actinomycetes commonly found in soil and water. Pulmonary nocardiosis occurs mainly as an opportunistic infection in immunocompromised patients with human immunodeficiency virus (HIV) infection or receiving immunosuppressive treatments (1, 2). However, it sometimes occurs in immunocompetent patients with chronic pulmonary disease, such as chronic obstructive pulmonary disease (COPD) or bronchiectasis (3, 4).

Cases of pulmonary Mycobacterium avium complex (MAC) disease have recently increased in Japan (5), and it sometimes occurs in immunocompetent hosts without underlying diseases (6). There have been two reports of immunocompetent patients with pulmonary MAC disease complicated with pulmonary nocardiosis (7, 8).

To our knowledge, this is the first report of an immunocompetent patient with pulmonary MAC disease complicated with pulmonary nocardiosis caused by Nocardiya cyriacigeorgica in the presence of pneumococcal pneumonia.

Case

A 61-year-old woman was transferred for investigation and treatment from another hospital (the second hospital she visited) with complaints of a fever and a productive cough. She had visited the first hospital with mild symptoms two months earlier, and a sputum culture examination of common bacteria and acid-fast bacilli had led to the isolation of M. avium and M. avium by MAC-polymerase chain reaction (PCR). However, her clinical symptoms of a fever, productive cough, and general fatigue had worsened one week ago, she was introduced to our hospital (the third hospital she visited) for an investigation and treatment.

She was then introduced to a second hospital for an investigation and treatment one month ago, and another sputum culture examination of common bacteria and acid-fast bacilli had led to the isolation of M. avium and Nocardiya species in that hospital. Because her clinical symptoms of a fever, productive cough, and general fatigue had worsened one week ago, she was introduced to our hospital (the third hospital she visited) for an investigation and treatment.

She had been administered ceftriaxone (CTRX) at 2 g/day for pneumonia and trimethoprim/sulfamethoxazole (TMP/
Table 1. Laboratory Data on Admission.

|          | Periperal blood | Chemical screening |
|----------|----------------|--------------------|
| WBC      | 13,520 /μL†    | TP 7.0 g/dL        |
| Neutrophils | 83.1 % †     | Glu 106 mg/dL      |
| Lymphocytes | 12.9 % †     | PaCO₂ 35.8 mmol/L  |
| Monocytes | 3.8 %         | PaO₂ 84.3 mmol/L   |
| Basophils | 0.2 %         | Cho 23.2 mmol/L    |
| RBC      | 398×10⁶ /μL   | γ-GTP 35 U/L†      |
| Hb       | 12.0 g/dL      | Lactate 1.97 mmol/L|
| Ht       | 35.4 %         | Serology           |
| Platelets | 34.1×10⁹ /μL  | Glb 4.0 g/dL†     |
| PT       | 11.4 sec       | Procalcitonin 0.25 ng/mL†|
| APTT     | 28.8 sec       | β-D-glucan <6.0 pg/mL†|
| Fibrinogen | 624 mg/dL†  | Cryptococcus antigen (-) |
|          |                | Aspergillus antigen (-) |
|          |                | T-SPOT.TB (-)      |
|          |                | MAC antibody 4.67 U/mL† |
|          |                | Urea 2.6 mg/dL     |
|          |                | CRP 9.56 mg/dL†   |
|          |                | Sodium 134 mmol/L  |
|          |                | Potassium 4.4 mmol/L|
|          |                | Chloride 96 mmol/L |

Table 2. Antimicrobial Susceptibilities of Nocardia Cyriacigeorgica Isolated from Sputum Culture.

| Antibiotics                      | MIC (μg/mL) |
|----------------------------------|-------------|
| Amikacin                         | 1           |
| Ceftriaxone                      | 4           |
| Ciprofloxacin                    | >4          |
| Imipenem                         | 1           |
| Linezolid                        | 2           |
| Minocycline                      | 2           |
| Trimethoprim/Sufametoxazole      | <0.75/0.25  |
| Cefotaxime                       | 4           |
| Cefpirome                        | 4           |
| Gentamicin                       | <0.5        |
| Ampicillin                       | >8          |
| Clarithromycin                   | >8          |
| Erythromycin                     | >2          |

SMX at 8 g/day for pulmonary nocardiosis at the second hospital. However, because adverse reactions (gastrointestinal symptoms and eruption) appeared, the treatment was stopped three days later, and afterwards, she was followed up.

Her occupation was a healthcare worker, and she had not had any marked exposure to environments rich in soil. She had no smoking history. She had a history of pulmonary MAC disease 12 years ago and had received chemotherapy for 1 year. Afterwards, because her condition had improved and she had no symptoms, sputum culture examinations were not performed, and no follow-up had been conducted. She had no history of human immunodeficiency virus (HIV), diabetes mellitus, or solid organ transplantation. She had not received inhaled or systemic corticosteroids or any immunosuppressive agents.

On a physical examination, her body weight and height were 42 kg and 156 cm. Chest auscultation revealed coarse crackles in the right lower lung field. Regarding laboratory findings, the inflammatory response was positive, her white blood cell count was 13,520/μL, and her C-reactive protein level was 9.56 mg/dL. Although mild hypalbuminemia was noted, her serum globulin level was slightly elevated. Mild liver dysfunction was recognized. Procalcitonin showed mild elevation to 0.25 ng/mL, and a urinary pneumococcal antigen test showed a positive response. MAC antibody showed a positive response (4.67 U/mL), but an interferon-gamma release assay (IGRA) showed a negative response (Table 1).

Gram staining of the sputum showed branching Gram-positive filaments, and the culture grew Nocardia species several times at the previous hospital and our hospital. The isolates were identified as N. cyriacigeorgica using 16S ribosomal RNA gene sequencing by the Medical Mycology Research Center of Chiba University. Minimal inhibitory concentrations (MICs) for selected antimicrobial agents were determined by the broth microdilution method following the guidelines of the Clinical and Laboratory Standard Institute (9) (Table 2); the isolates were susceptible to TMP/SMX. However, Gram staining of the sputum showed Gram-positive cocci, and the purulent culture grew Streptococcus pneumoniae (3+). Because S. pneumoniae isolated from this patient showed intermediate resistance to penicillin G (MIC: 0.5 μg/dL), we judged Penicillin-intermediate S. pneumoniae (PISP) according to the CLSI definition of susceptibility. Acid-fast staining of the sputum was positive, and M. avium (CAM MIC: 0.25 μg/dL) was identified several times by DNA-DNA hybridization (DDH) methods.

Regarding the radiological findings, chest computed tomography (CT) one month ago at the second hospital had
shown small nodular shadows with bronchiectatic changes in the right middle and lower lobes and cavity lesions in the right S₆ segment (Fig. 1A and 1B). Chest X-ray and chest CT on admission showed the deterioration of small nodular shadows with bronchiectatic changes in the right middle and lower lobes and left lingula lobes but similar findings for cavity lesions in the right S₆ segment. Furthermore, a new infiltration shadow appeared in the right lower lung field on chest X-ray and in the right S₆ segment on chest CT on admission (Fig. 2A, 3A and 3B). Finally, we diagnosed her with pneumococcal pneumonia co-infected with *M. avium* and *N. cyriacigeorgica* in combination with the information from the previous hospital.

Regarding the treatment in our hospital, because she showed adverse reactions to CTRX and/or TMP/SMX in the previous hospital, we initiated treatment using meropenem (MEPM) at 3 g/day for pneumococcal pneumonia and pulmonary nocardiosis and combined chemotherapy using rifampicin (RFP) at 300 mg/day, ethambutol (EB) at 500 mg/day, clarithromycin (CAM) at 600 mg/day, and streptomycin (SM) at 0.5 g/3 times per week for pulmonary MAC disease. Because her clinical symptoms of a fever and productive cough and the inflammatory response were improved 14 days after admission, we completed the treatment with MEPM and added treatment using a decreased dose of TMP/SMX at 6 g/day for pulmonary nocardiosis, consider-
Figure 3. Chest CT on admission revealed small nodular shadows with bronchiectatic changes in the right middle and lower lobes and left lingula lobes and a cavity lesion in the right S6 segment (A) and an infiltration shadow in the right lower lobe (B). Chest CT one year after the initiation of treatment showed an improvement of small nodular shadows and infiltration shadows containing the cavity lesion, except for bronchiectatic changes (C, D).

Discussion

Nocardia species are Gram-positive aerobic bacilli that cause respiratory tract infections in around 50% to 70% of nocardiosis patients [9]. Pulmonary nocardiosis most frequently occurs in immunocompromised patients with solid organ transplantation, hematopoietic stem cell transplantation, HIV infection, or corticosteroid treatment (1, 2). However, it is also known to occur in immunocompetent patients with underlying pulmonary diseases, such as chronic obstructive pulmonary disease and bronchiectasis (3, 4). In our case, because N. cyriacigeorgica had been simultaneously isolated several times from the bronchiectatic or cavity lesion formed by pulmonary MAC disease, and because S. pneumoniae had infected these lesions, a diagnosis of pneumococcal pneumonia co-infection with pulmonary nocardiosis and pulmonary MAC disease in an immunocompetent patient was made. Such bronchiectatic and cavity lesions due to MAC cause respiratory immune defense system dysfunction and facilitate lower respiratory tract infections and bacterial colonization. Furthermore, bacterial colonization alters ciliary motility, causes epithelial damage, and facilitates nocardia infection (10).

Nocardia species were recently classified into several different species by 16S ribosomal RNA sequencing. N. cyriacigeorgica was the first to be identified and classified as a new species by Yassin et al. in 2001 (11). According to a recent study using 16S ribosomal RNA sequencing, although N. asteroides is the most frequently isolated in Australia (12), N. cyriacigeorgica was the most frequently isolated strain in Taiwanese and Spanish patients with pulmonary nocardiosis (13, 14). A difference in the local distribution of Nocardia strains may exist. Because pulmonary N. cyriacigeorgica disease shows a notable pattern compared with other nocardia infections (13), a large-scale world population study of pulmonary N. cyriacigeorgica disease should be performed to examine the clinical characteristics in the future.

Several reports have described Nocardia species co-infection with other microorganisms in immunocompromised hosts or immunocompetent hosts with underlying respiratory disease. Nocardia species co-infection with As-
pergillus species was found to be the most frequent in previous reports (12, 13). In our case, three microorganisms (N. cyriacigeortica, M. avium, and S. pneumoniae) were isolated simultaneously on admission to our hospital. Although the complication rate of pulmonary MAC disease in patients with pulmonary nocardiosis was 6% in previous reports (12), and 5 previous reports described pulmonary nocardiosis co-infected with pulmonary MAC disease in immunocompromised or immunocompetent hosts (7, 8, 15-17), to our knowledge, this is the first report of 3 microorganisms isolated several times simultaneously, necessitating individual treatment for pneumococcal pneumonia, pulmonary nocardiosis, and pulmonary MAC disease. Regarding the radiological findings of pulmonary nocardiosis in an immunocompetent patient, Fujita et al. reported that it often showed a nodular-bronchiectatic pattern resembling typical radiological findings in middle-aged women with pulmonary NTM disease (18). Because pulmonary nocardiosis and pulmonary NTM disease are similar with regard to several clinical findings in immunocompetent patients, pulmonary nocardiosis in an immunocompetent patient might be misdiagnosed as pulmonary NTM disease. We must therefore practice caution in cases showing mixed infection due to multiple microorganisms, especially in immunocompetent patients with underlying respiratory diseases, and perform multiple microbiological examinations to obtain a correct diagnosis.

Concerning the treatment of this patient in our hospital, because clinical symptoms of a fever and productive cough and positive inflammatory response with leukocytosis were recognized, and adverse reactions to CTRX and/or TMP/SMX appeared at the previous hospital, we first performed antibiotic therapy for bacterial infection due to PISP and pulmonary nocardiosis using MEP as carbapenem antibiotics (imipenem/cilastatin was not available in our hospital) for two weeks. Furthermore, as this patient also showed radiological findings of small nodular shadows with bronchiectatic changes leading to the suspicion of progressing pulmonary MAC disease on admission, we initiated combined chemotherapy using CAM, RFP, and EB including SM simultaneously. The clinical symptoms and inflammatory response gradually improved with treatment.

As favorable susceptibility of N. cyriacigeortica to TMP/SMX (Table 2) was obtained, we administered a decreased dose of TMP/SMX for pulmonary nocardiosis, considering future outpatient treatment, and fortunately, no adverse reactions were noted. We selected treatment including SM for pulmonary MAC disease with a cavity according to the guideline of the American Thoracic Society (ATS) (19). TMP/SMX is the first recommended drug therapy for pulmonary nocardiosis. As alternative drugs, amoxicillin/clavulanic acid, minocycline, imipenem/cilastatin, amikacin, and ceftizoxime are effective against Nocardia species (10). However, as drug susceptibilities differ by Nocardia species, we had to identify the specific Nocardia species using molecular and biochemical analyses and drug sensitivity examinations. Sorrell et al. stated that the duration of treatment for pulmonary nocardiosis in an immunocompetent patient with underlying pulmonary disease should be at least six months. We thus administered TMP/SMX 6 g/day for 6 months according to that report (20).

Regarding the prognosis associated with Nocardia species infection, the incidence of death due to pulmonary nocardio-

Figure 4. Clinical course of pneumococcal pneumonia co-infected with Mycobacterium avium and Nocardia cyriacigeortica.
sis was better than that due to disseminated or cerebral nocardiosis with TMP/SMX. Although the present patient had a mixed infection due to N. cyriacigeortica, MAC, and S. pneumonia in an immunocompetent host with underlying respiratory disease, her condition improved with appropriate treatment without marked adverse reactions.

In conclusion, we reported the first case of pneumococcal pneumonia in a patient co-infected with pulmonary MAC disease (M. avium) and pulmonary nocardiosis (N. cyriacigeortica). We must practice care when encountering cases of infectious diseases due to multiple causative microorganisms in immunocompetent patients with underlying respiratory disease, and several microbiological examinations should be conducted in order to obtain a correct diagnosis.

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

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Declaration of competing interests

None.

Compliance with ethical standards

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