An Autopsy Case Of Disseminated Nocardiosis Involving Multiple Organs Associated With Chemotherapy-induced Lung Damage Following Lung Cancer Surgery

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Abstract
The patient was a 71-year-old man. Two months after using prednisolone at a dose of 80 mg/day for the treatment of drug-induced interstitial pneumonia induced by chemotherapy following lung cancer surgery, his chest x-ray film showed cavitary shadows, and Nocardia farcinica was detected from subcutaneous abscess, sputum, urine, and blood cultures. Thus, disseminated nocardiosis involving multiple organs was diagnosed. Despite treatment with a combination of trimethoprim-sulfamethoxazole and imipenem/cilastatin, the patient died of alveolar hemorrhage. In cases with steroid-induced immunosuppression, caution is necessary for the prevention of not only tuberculosis and pneumocystis jirovecii pneumonia, but also other infectious diseases including nocardiosis.

Key words
disseminated nocardiosis, brain abscess, renal abscess, subcutaneous abscess, intramuscular abscess, autopsy

Introduction
Nocardia species are aerobic gram-positive bacilli widely distributed in soil. Infection with Nocardia is classified into the cutaneous type caused by bacterial invasion from a wound area or the visceral type caused by infection via the respiratory route. Visceral nocardiosis usually occurs as an opportunistic infection in states of compromised cellular immunity (malignancies, use of steroids, organ transplantation, HIV infection, etc.)¹. The primary focus of infection develops in the lung and hematogenously disseminates to the central nervous system (CNS) and organs throughout the body including the skin, subcutaneous tissues, the eye (particularly the retina), kidneys, joints, bones, and heart². When lesions form in two or more organs, the disorder is termed disseminated nocardiosis. It is common for multiple organs to be involved, and the prognosis is poor, particularly in immunocompromised patients³⁻⁴. As the causative bacterium, Nocardia asteroides accounts for 70–90% of all cases⁵.

We report herein our recent experience with a rare case of disseminated nocardiosis, focusing on the following features: [1] the infection was associated with chemotherapy-induced lung damage following lung cancer surgery; [2] there were lesions in multiple organs including the brain, subcutaneous, lung, renal, and intramuscular abscesses; [3] Nocardia farcinica (N. farcinica) was the causative bacterium; and [4] autopsy data were obtained with the family’s permission.

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Case report

The patient was a 71-year-old man with a smoking history of 20 cigarettes/day for 50 years. He underwent resection of primary adenocarcinoma of the left upper lobe (pT2aN1M0) in another hospital. The patient received 3 courses of postoperative chemotherapy with cisplatin (CDDP) + docetaxel (TXT), and TS-1 was introduced as second-line treatment. Thereafter, he developed drug-induced interstitial pneumonia due to the TS-1 and began to receive prednisolone (PSL) 80 mg (1.0 mg/body). After reduction of the PSL dose by 60 mg, chest computed tomography (CT) revealed abnormal shadows, and the patient was referred to our department. Although he returned home with a prescribed combination drug of trimethoprim-sulfamethoxazole (ST) at a dose of 1 g/day for prophylaxis of Pneumocystis jirovecii pneumonia, he soon suffered leg weakness. He visited the emergency and critical care center of our hospital and was admitted for detailed examination and treatment.

On admission, consciousness was clear, blood pressure was 144/90 mmHg, pulse rate was 133/min, body temperature was 37.8 degrees C, respiratory rate was 28 breaths/min, and percutaneous oxygen saturation was 93% (room air). Auscultation of the chest revealed dry rales in the bilateral lung fields. Indurated red nodules were observed on the skin of the entire body (Figure 1).

A blood examination showed impaired liver functions and increased inflammatory reaction (Table 1). Arterial blood gas analysis revealed that the patient was in respiratory distress accompanied by hypocapnia. CT on admission showed cavitary lesions with irregular borders surrounded by mild groundglass opacification at a site in the right upper lobe and at 2 sites in the left lower lobe, as well as postoperative changes in the left upper lobe (Figure 2A, B). There were subcutaneous nodules localized in the left cervical region (Figure 2C), a shadow indicative of a soft tumor mass in the right axilla (Figure 2D), and subcutaneous nodules localized in the left thoracic region (Figure 3A). In addition, nodular shadows were found in the kidneys (Figure 3B), and lesions that had low density in the interior portion and high density in the periphery were found in the right iliopsoas muscle, lateral rectus muscle of the left thigh, and the rectus muscle of the right thigh (Figure 3C). Magnetic resonance imaging (MRI) of the head showed high-intensity lesions in diffusion-weighted images of the brain stem and cerebellum (Figure 3D).

Figure 4 shows the clinical course of this patient. He went into shock after admission, necessitating artificial ventilation control. On admission, sputum quality was classified as poor (Geckler class 1), and gram staining detected no bacteria. Clinical findings of multiple subcutaneous nodules suggested

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Table 1. Laboratory Data on Admission to Our Hospital

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry/Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 8100 /μl</td>
<td>T-bil 1.3 mg/dl</td>
</tr>
<tr>
<td>RBC 389 x 10^6 /μl</td>
<td>AST 68 IU/l</td>
</tr>
<tr>
<td>Hb 13.4 g/dl</td>
<td>ALT 94 IU/l</td>
</tr>
<tr>
<td>Ht 40.7 %</td>
<td>LDH 776 IU/l</td>
</tr>
<tr>
<td>Plt 107 x 10^5 /μl</td>
<td>ALP 380 IU/l</td>
</tr>
<tr>
<td>Fe 10.7 x 10^5 /μl</td>
<td>γ-GTP 120 IU/l</td>
</tr>
<tr>
<td>P</td>
<td>TP 5.4 mg/dl</td>
</tr>
<tr>
<td>BUN 18.3 mg/dl</td>
<td>Cr 0.84 mg/dl</td>
</tr>
<tr>
<td>pH 7.533</td>
<td>Na 138 mEq/l</td>
</tr>
<tr>
<td>pO2 72.9 torr</td>
<td>Cl 103 mEq/l</td>
</tr>
<tr>
<td>pCO2 29.3 torr</td>
<td>K 4.2 mEq/l</td>
</tr>
<tr>
<td>HCO3^- 24.6 mEq/l</td>
<td>Glu 92 mg/dl</td>
</tr>
<tr>
<td>CRP 19.38 mg/dl</td>
<td>β-D-glucan 2.77 μg/ml</td>
</tr>
</tbody>
</table>

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Figure 1. Dermal findings on admission
The entire body had red indurations.
subcutaneous abscesses, and aspiration biopsy specimens were cultured. Abscesses were also suspected from imaging findings of the kidneys and muscles. MRI findings of the head were regarded as being indicative of hematogenous lesions based on multiplicity and the distribution pattern, suggesting a diagnosis of cerebral infarction or cerebral abscesses. Taking these findings together with those of chest imaging, we suspected a generalized infection with common bacteria (including *Staphylococcus aureus*), tubercle bacillus, fungi, or Methicillin-resistant *Staphylococcus aureus* (MRSA) and initiated therapy with tazobactam/piperacillin (TAZ/PIPC) 9 g/day, voriconazole (VRCZ) 400 mg/day, and teicoplanin (TEIC) 400 mg/day after submitting the specimens for various culture studies. On the third hospital day, a gram-positive bacillus was detected from a blood culture of the specimen collected on admission. On the eleventh hospital day, *N. farcinica* was detected from cultures of subcutaneous abscesses, sputum, urine, and blood. These results pointed to a diagnosis of disseminated nocardiosis involving multiple organs as reflected by brain, subcutaneous, lung, renal, and intramuscular abscesses. As antimicrobial therapy, the ST dose was increased to achieve a therapeutic dose of 14 g/day and was later replaced by combination therapy with imipenem/cilastatin (IPM/CS) at a dose of 1 g/day. Subsequent drug sensitivity testing revealed that antimicrobial agents used in the present patient were effective in the treatment of nocardiosis. The dose of PSL, 60 mg/day at the time of admission, was reduced to 50 mg/day, and further reduced by 10 mg every 5 days. The patient was once weaned from artificial ventilation because his condition showed improvement, but diffuse ground-glass opacification appeared on the 21st hospital day with worsening of respiratory status, and artificial ventilation control was again required. KL-6 and surfactant protein (SP)-D, tested for the first time in this patient, were high at 1690 IU/l and 567 ng/ml, respectively. This worsening was attributed to exacerbation of drug-induced interstitial pneumonia due to the steroid tapering, and the dose of PSL was increased to 60 mg/day after administration of steroid pulse therapy. However, disseminated intravascular coagulation syndrome progressed to multiple organ failure on the 32nd hospital day, and the patient died of respiratory deterioration on the 38th hospital day. Pathological autopsy, excluding the brain, was carried out with consent from the patient’s family.

At autopsy, foamy bronchial contents with hemorrhagic manifestations were identified in both lung
fields. Microscopically, both lung fields had a dark red color, and there were cavities in the left lower lobe and the right upper lobe. Focal changes were noted around the cavity in the left lung, and diffusely in the right lung (Figure 5A, B). Histologically, there was diffuse alveolar hemorrhage in the bilateral lungs, in addition to the scattered presence of serous exudates, neutrophils, monocytes, and desquamated epithelium in alveoli. The cavities were accompanied by fibrosis and, in some areas, granulomatous lesions (Figure 5C). Branching proliferation of Grocott stain-positive mycelial bodies was observed in the cavities and necrotic foci, and the thin cell bodies were found to be gram-positive, suggesting nocardiosis (Figure 5D). Both lungs showed alveolar collapse and fibrosis extending from the immediate subpleural area, as well as growth of alveolar epithelium. The lesions were macular in the presence of seemingly normal pulmonary tissue, showing a pattern consistent with the most common form of interstitial pneumonia. Other findings included neutrophil infiltration into renal tubules and interstitium of the left kidney and abscess and inflammation in the prostate.

**Discussion**

Lung cancer incidence has been rising in recent years, and along with this increase, anticancer drugs have been used more frequently. Among anticancer drugs, gefitinib and other molecular-targeted agents have often been reported to cause drug-induced interstitial pneumonia, but other anticancer drugs may also cause interstitial pneumonia. Although this condition requires systemic steroid therapy, treatment may necessitate prolonged high-dose administration, which can result in a state of immunosuppression, carrying a high risk of infectious disease. Nocardiosis occurs as an opportunistic infection in patients with decreased defense against infections, such as those on immunosuppressive therapy or prolonged steroid administration. Our present patient was in a markedly immunosuppressed state due to nearly 2 months of high-dose steroid therapy, and therefore it...
An autopsy case of disseminated nocardiosis

was presumed that Nocardia had disseminated to multiple organs including the brain, subcutaneous tissues, lungs, kidneys, and muscles. The mortality rate of disseminated nocardiosis is reportedly 7–44% in immunocompetent persons and 85% in those with decreased cellular immunity. Therefore, prompt diagnosis and treatment are essential.

There is as yet no serological means of diagnosing nocardiosis, and the only available method of definitive diagnosis is isolation and identification of Nocardia. However, Nocardia species require 2 days to 3 weeks to grow, and it is thus not always easy to obtain an early diagnosis. The most useful diagnostic technique is gram staining, a simple and highly specific test. In our patient, the sputum specimen obtained on admission had a poor quality and was classified as Geckler class 1, and early diagnosis was therefore difficult. When sputum is used as a specimen, it is necessary to determine whether the detected bacterium is the pathogen or a normal species comprising the oral flora. Because invasive examination by bronchoscopy is required when sputum fails to lead to a diagnosis, it is important to judge overall data including imaging findings.

Chest roentgenographic findings of pulmonary nocardiosis are said to be extremely diverse, making differentiation by roentgenographic features difficult. Although lung abscess is a typical finding, various roentgenographic features including evidence of pneumonia, nodular shadows, massive shadows, cavities, miliary shadows, and pleural effusion are reportedly present when pulmonary nocardiosis occurs in patients in an immunocompromised state. Because our patient had multiple cavitary shadows, differentiation from lung tuberculosis, lung abscess, metastatic lung tumor, lung cancer, and mycosis was necessary. N. farcinica was detected by various culture studies, and thoracic findings were consistent with pulmonary nocardiosis. In addition, subcutaneous nodules throughout the body, soft tumor shadows in the right axilla, renal shadows, intramuscular findings, and lesions seen on imaging of the head all

Figure 4. Clinical course

PSL; prednisolone, mPSL; methylprednisolone, TAZ/PIPC; tazobactam / piperacillin, CTRX; ceftriaxone, IPM/CS; imipenem / cilastatin, VRCZ; voriconazole, MCFG; micafungin, F-FLCZ; fosfluconazole, ST; trimethoprim-sulfamethoxazole, TEIC; teicoplanin, CPFX; ciprofloxacin, NAD; noradrenaline, DA; dopamine, DOB; dobutamine, DIC; disseminated intravascular coagulation
indicated abscesses due to *Nocardi*a infection. Thus, a diagnosis of disseminated nocardiosis was established. Infection with *Nocardi*a can occur via the respiratory route or the percutaneous route. In this patient, we speculate that infection developed via the respiratory route because there were no obvious skin wounds. In such cases, nocardiosis reportedly occurs due to inhalation or aspiration of *Nocardi*a and mostly *Nocardi*a *asteroides*; it is rare for *N. farcinica* to be the causative pathogen, as in our case5. *N. farcinica* was reported to constitute 19% of 200 Nocardi*a isolates in a study from the USA15. Bacteraemia due to *N. farcinica* is rarely encountered. A computer-based search (MEDLINE; years, 1966–2005) of the English-language literature identified 13 additional previously reported cases of *N. farcinica* bacteraemia.

A combined ST drug regimen is the first-line therapy. Drugs recommended as second-line therapy include aminoglycoside, carbapenem, tetracycline, penicillin, and quinolone16. In addition, in severe cases or in those with CNS infection, IPM/CS or amikacin is used as monotherapy or combination therapy with the ST drug17. In our present patient, ST drug monotherapy was replaced by combination therapy with the same ST drug plus IPM/CS after a definitive diagnosis was established, and the patient’s condition temporarily improved. However, shortly after reduction of the steroid dose, taking into account immune function, his respiratory status deteriorated, indicating re-exacerbation of drug-induced interstitial pneumonia. To address this problem, steroid pulse therapy was administered and apparently further suppressed the patient’s immune competence.

The clinical issues we focused on at the time of autopsy were as follows: [1] status of progression of
primary lung cancer; [2] extent of Nocardia dissemination; and [3] the pathological condition of ground-glass opacification. There was no pathological evidence of recurrence of the primary lung cancer. Nocardia infection caused no lesions in organs other than the lungs, suggesting that treatment was at least somewhat effective. However, Nocardia cell bodies remained in both lungs. The prostate abscess was attributed to infection resulting from prolonged urethral catheterization and was not considered to be Nocardia infection. Interstitial shadows representing the eventual cause of death were pathologically diagnosed as Nocardia-related hemorrhages. As for the mechanisms producing these hemorrhages, it has been suggested that tissue breakdown associated with chronic inflammation is apt to result in hyperplasia of vulnerable bronchial arteries and a shunt between the bronchial artery and pulmonary artery. Other mechanisms that require differentiation include acute respiratory distress syndrome triggered by the infectious disease and alveolar hemorrhage due to diffuse alveolar damage caused by acute exacerbation of drug-induced interstitial pneumonia. However, at autopsy, there was no hyaline membrane formation, as would be observable in the acute phase, nor the fibroblasts commonly found in the organizing phase of interstitial pneumonia.

In conclusion, high-dose steroid therapy was carried out in a patient with drug-induced interstitial pneumonia caused by chemotherapy following lung cancer surgery. The patient developed disseminated nocardiosis due to N. farcinica, with involvement of multiple organs, including brain, subcutaneous, lung, renal, and intramuscular abscesses. Although the patient partially responded to ST and IPM/CS therapy, the bacterium persisted in the body, and he eventually died of Nocardia-related pulmonary hemorrhage. In cases with steroid-induced immunosuppression, caution is necessary for the prevention of not only tuberculosis and pneumocystis jirovecii pneumonia, but also other infectious diseases including nocardiosis.

References
