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【 CASE REPORT 】

Adult T Cell Leukemia/Lymphoma Becoming Apparent during Treatment of Pulmonary Abscess and Empyema Caused by *Nocardia asiatica*: A Case Report and Review of the Literature

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Abstract:
Nocardia is a Gram-positive bacterium that causes opportunistic infections. *Nocardia asiatica* was newly isolated in 2004, and there have been no case reports describing the empyema caused by *N. asiatica*. Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by human T-cell leukemia virus type 1 (HTLV-1). We herein report a case in which immunosuppression attributable to ATL may have led to pulmonary abscess and empyema caused by *N. asiatica*. Our case demonstrates the need to investigate causes of immunosuppression, including ATL, in patients showing nocardiosis.

Key words: adult T-cell leukemia/lymphoma, human T-cell leukemia virus, nocardiosis, *Nocardia asiatica*

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Introduction

Nocardiosis is an uncommon disease caused by aerobic Gram-positive bacteria in the genus *Nocardia*, which are usually found in soils, water, or air. The genus *Nocardia* is composed of 13 medically important species, of which *N. asteroides*, *N. farcina*, *N. nova*, and *N. abscessus* cause the majority of invasive infections (1). *Nocardia asiatica* was newly isolated by Kageyama et al. from three *N. asteroides-like* strains obtained in Japan and Thailand in 2004 (2). To date, only a few case reports have described *N. asiatica* infections, and details of the nocardiosis caused by this strain are unclear. *Nocardia* species can cause localized or systemic suppurative diseases in humans and animals. The lung is the major target organ involved in *Nocardia* infections because the main portal of entry is inhalation (3). The main risk factor for nocardiosis is immunosuppression, such as that induced by prolonged corticosteroid therapy, malignancy, organ transplantation, or human immunodeficiency virus infection.

Human T-cell leukemia virus type 1 (HTLV-1) was identified as the first human oncogenic retrovirus 30 years ago (4). In southern Japan, the prevalence of HTLV-1 in the general population is more than 10%, making it the area with the highest HTLV-1 prevalence worldwide (5). Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by HTLV-1 that is characterized by clonal proliferation of CD4-positive T cells containing randomly integrated HTLV-1 provirus (6). Patients with ATL are often immunosuppressed and are at risk of developing opportunistic infections (5).

We herein report a case showing pulmonary abscesses and empyema caused by *N. asiatica* under ATL-induced immunosuppression. In addition, we provide a review of the literature on *N. asiatica* cases.

Case Report

A 78-year-old Japanese man visited a hospital with general malaise in March 2020. Chest computed tomography (CT) showed massive and multilocular left pleural effusion. He was suspected of having empyema and was admitted to our hospital. His medical history included bladder cancer (cTaN0M0, cStage 0a) and prostate cancer (cT4N1M1b, cStage IV). He had no history of pulmonary disease or drug

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abuse. He had smoked approximately 25 cigarettes a day for 58 years until admission. He had been previously employed as an electric mechanic. He had been born in Nagasaki Prefecture, located on the northwest side of Kyushu, southwest of the four major Japanese islands. His family history included no remarkable disease-related findings.

A physical examination revealed multiple untreated dental caries and stumps but no skin lesions. His vital signs were as follows: body temperature, 38.1 °C; heart rate, 92 beats/min; respiratory rate, 25 breaths/min; blood pressure, 179/100 mmHg; and oxygen saturation, 85% on room air. Auscultation of his left lung revealed decreased breath sounds. The main results of the laboratory examinations are shown in Table 1. His white blood cell count was 13,700/μL, and his C-reactive protein level was 36.9 mg/dL. Chest radiography and CT showed large and multilocular left pleural effusions with a rightward shift of the mediastinum and trachea (Fig. 1, 2).

Table 1. Main Laboratory Results on Admission.

Hematology	
White blood cells	13,700 /μL
Neutrophil count	83.8 %
Lymphocyte count	14.4 %
Atypical lymphocyte count	0.5 %
Red blood cells	276×10^4 /μL
Hemoglobin	8.6 g/dL
Platelets	43.8×10^4 /μL
Blood chemistry	
Aspartate aminotransferase	37 U/L
Alanine aminotransferase	14 U/L
Lactate dehydrogenase	277 U/L
Alkaline phosphatase	287 U/L
γ-Glutamyltranspeptidase	30 U/L
Albumin	3.9 g/dL
Blood urea nitrogen	60.7 mg/dL
Creatinine	2.08 mg/dL
C-reactive protein	36.9 mg/dL
Infection	
T-SPOT®	-
HIV Ag/Ab	0.06 S/CO
HTLV-1,2	107.72 S/CO
Tumor marker	
PSA	0.317 ng/mL
sIL2-R	6,005 U/mL

HIV: human immunodeficiency virus, HTLV: human t-cell leukemia virus, PSA: prostate specific antigen, sIL2-R: soluble interleukin-2 receptor

We inserted two chest drainage tubes: one in the left upper chest and the other in the lower chest. He was diagnosed with empyema due to purulent drainage.

Laboratory results for the pleural effusions are shown in Table 2. Gram staining and Kinyoun's acid-fast staining from pleural effusions were performed, but both showed negative results. We administered ampicillin/sulbactam (ABPC/SBT) and intrathoracic lavage with saline and intracavitary instillation of urokinase through both chest tubes several times, promoting drainage of pus. On day 7, cultures from pleural effusions were grown, and *N. asiatica* was identified using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS). An *in vitro* drug susceptibility analysis could not be performed because of the small number of colonies.

Trimethoprim-sulfamethoxazole (TMP-SMX) was added to the treatment regimen. Two sets of blood cultures were negative, and there were no lesions in the central nervous system on brain magnetic resonance imaging (MRI). On day 13, *N. asiatica* was cultured again from follow-up pleural effusions, so we changed the antibiotics from ABPC/SBT to minocycline (MINO) and imipenem/cilastatin (IPM/CS) in addition to TMP-SMX. Laboratory examinations revealed that the proportion of atypical lymphocytes ("flower cells") among white blood cells had increased from 0.5% (day 1) to 30.3% (day 15). Antibodies against HTLV-1 were detected in the serum using an enzyme-linked immunosorbent assay (ELISA). Biclonal bands for HTLV-1 provirus DNA were observed in peripheral blood specimens by a Southern

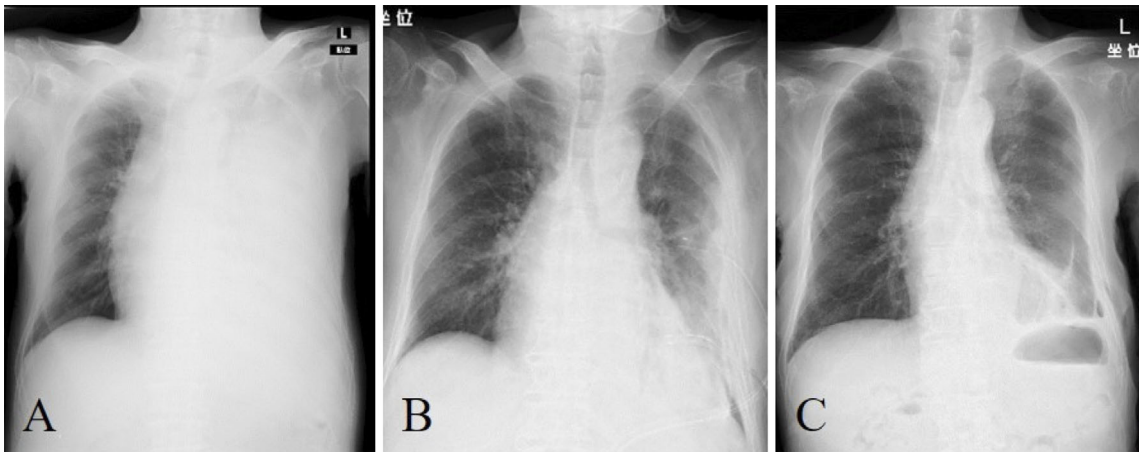

Figure 1. Time course of chest radiography findings showed the improvement of empyema. (A) On admission, (B) after insertion of two chest drainage tubes, and (C) at the time of discharge.

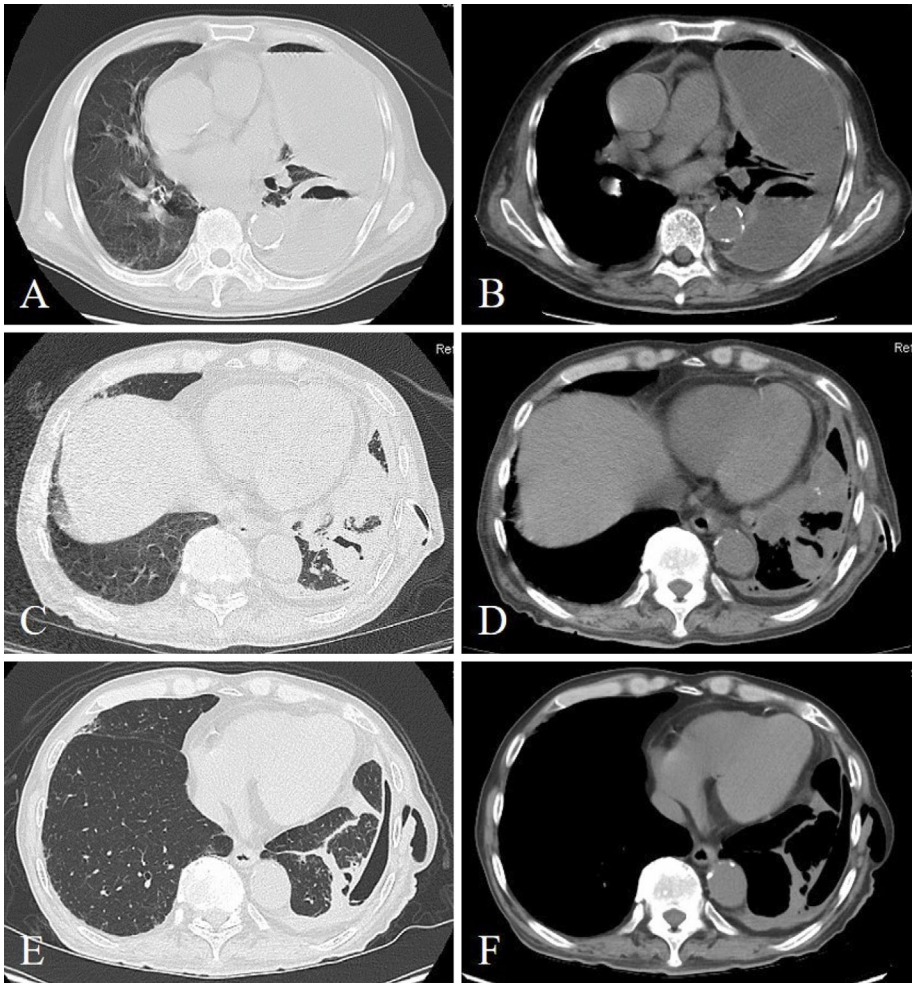

Figure 2. **Time course of chest computed tomography findings showed the improvement of pulmonary abscess and empyema. (A, B) On admission, (C, D) day 6, and (E, F) day 50.**

Table 2. **The Examination Results of Pleural Effusions.**

pH	7.5
White blood cell	2,200 /μL
Neutrophil count	68.1 %
Albumin	2.6 g/dL
Glucose	72 mg/dL
Lactate dehydrogenase	1,283 IU/L
CEA	5.9 ng/mL
Hyaluronic acid	44,000 ng/mL
ADA	60.7

ADA: adenosine deaminase, CEA: carcinoembryonic antigen

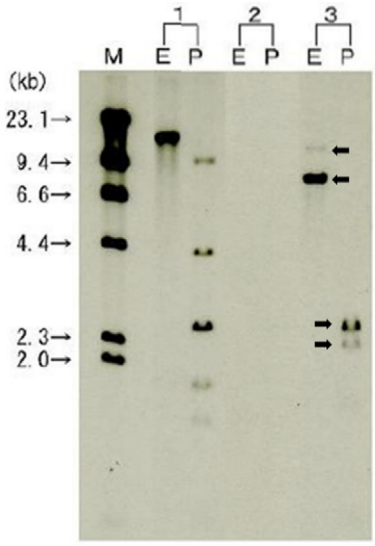

Figure 3. **Southern blot analysis of HTLV-1 provirus DNA depicted two bands (black arrows) after EcoR I digestion and two bands (black arrows) after Pst I digestion indicating biclonality of HTLV-1. M: size marker, 1: positive control, 2: negative control, 3: this patient, E: *EcoR*I (restriction enzyme), P: *Pst*I (restriction enzyme)**

blot hybridization analysis (Fig. 3).

Although the proportion of atypical lymphocytes increased rapidly at first, lymphocytosis stabilized thereafter. A cytological assessment of the pleural effusions showed no atypical lymphocytes. Body CT and brain MRI did not reveal any organ involvement. Based on these findings, we diagnosed the patient with chronic-type ATL with no unfavorable prognostic factors, such as a low serum albumin level, high lactate dehydrogenase level, or high urea nitrogen con-

Table 3. Literature Review of *N. asiatica* Infections.

Case no./ reference	Age/sex	Site(s) of infection	Underlying disease(s)	Diagnostic method(s)	Treatment(s)	Outcome
1/(20)	45/M	Skin	HIV	16S rRNA	TMP-SMX	Recovered
2/(21)	57/F	Lung	Asthma	16S rRNA	TMP-SMX MEPM AMK LZD	Recovered
3/(22)	60/M	Lung	DM	16S rRNA	TMP-SMX MEPM Operation	Recovered
4/(23)	49/M	Mediastinal	MG	Unknown	IPM AMK TMP-SMX	Recovered
5/(24)	66/M	Lung	AIP	16S rRNA	AMK IPM AMPC/CVA MINO	Recovered
6/(25)	66/M	Elbow	None	16S rRNA	LZD	Recovered
7/(11)	64/F	Lung	Old Tb	16S rRNA	TMP-SMX	Recovered
8/(26)	76/M	Lung	AAV Old Tb	16S rRNA	TMP-SMX DRPM	Recovered
9/(27)	65/M	Brain Lung	AIHA	16S rRNA	TMP-SMX	Recovered
10/(28)	51/M	Brain	SLE	16S rRNA	TMP-SMX CTRX MINO AMPC/CVA	Died
11/(29)	37/M	Disseminated	HIV	16S rRNA	MEPM AMK TMP-SMX	Recovered
12/(12)	40/F	Brain Mediastinal	HIV	16S rRNA	TMP-SMX CTRX AMK Operation	Recovered
13/(30)	53/M	Brain	HIV	MALDI-TOF-MS 16S rRNA	TMP-SMX	Recovered
14/(31)	61/F	Brain	Malignancy DM	Metagenomics next-generation sequencing	Linezolid TMP-SMX Operation	Recovered
15/(32)	33/M	Skin	None	Bacterial culture	AMK	Recovered
16/Our case	78/M	Lung	ATL Malignancy	MALDI-TOF-MS	TMP-SMX MINO IPM/CS AMPC/CVA	Recovered

AAV: antineutrophil cytoplasmic antibody associated vasculitis, AIHA: autoimmune hemolytic anemia, AIP: autoimmune pancreatitis, AMK: amikacin, AMPC/CVA: amoxicillin/clavulanate, ATL: adult T-cell leukemia/lymphoma, CTRX: ceftriaxone, DM: diabetes mellitus, DRPM: dripenem, HIV: human immunodeficiency virus, IPM/CS: imipenem/cilastatin, LZD: linezolid, MALDI-TOF-MS: matrix-assisted laser desorption ionization-time of flight mass spectrometry, MEPM: meropenem, MG: myasthenia gravis, MINO: minocycline, Tb: tuberculosis, TMP-SMX: trimethoprim-sulfamethoxazole, 16S rRNA: 16S ribosomal ribonucleic acid

centration. Therefore, we decided to follow-up the ATL without active treatment.

Drug-induced kidney dysfunction was detected after the onset of TMP-SMX treatment; therefore, the patient was treated with a combination of MINO and amoxicillin/clavulanate (AMPC/CVA). After chest CT, the empyema improved, and his left lung expanded again. There were three cavitary nodules in his re-expanded left lung, indicating the presence of pulmonary abscesses in addition to empyema (Fig. 2). Two chest drainage tubes were removed on days 3 and 15, respectively. His condition gradually improved, resulting in the disappearance of his fever and malaise and a reduction in the serum C-reactive protein (CRP) level. Since the prolonged treatment deteriorated his activities of daily living (ADL), he was transferred to another hospital for rehabilitation.

Discussion

The specific feature of the present case was the presence

of pulmonary abscess and empyema caused by *N. asiatica*, and the concomitant occurrence of ATL during the treatment of nocardiosis. In this case, although Gram staining and Kinyoun's acid-fast staining from pleural effusions both showed negative findings, we identified *N. asiatica* using colonies cultured from pleural effusions by MALDI-TOF-MS.

The genus *Nocardia* includes more than 80 species, of which at least 33 cause diseases in humans (7, 8). Determination of the *Nocardia* species causing an infection is important because different species vary in their epidemiology, virulence, and antibiotic susceptibility. Traditional methods for the determination of *Nocardia* species include biochemical tests and susceptibility profiling, but the identification of *Nocardia* species in such tests is often difficult. To overcome these limitations, sequencing methods, such as 16S ribosomal ribonucleic acid (16S rRNA) gene sequencing, have been advocated for *Nocardia* species identification, but they remain unavailable in clinical practice. Recently, MALDI-TOF-MS, which can analyze the protein composition of a bacterial cell, has been identified as a rapid and accurate method for the identification of *Nocardia* species in clinical laboratories (9, 10).

N. asiatica is a rare *Nocardia* species that was newly identified in 2004. There are few reports describing *N. asiatica* infections, including respiratory infections such as pneumonia and mediastinal infections (11, 12). We conducted a systematic review of relevant articles in the Medline database using the term "*Nocardia asiatica*." We identified a total of 24 articles, including 15 case reports of *N. asiatica* infections (Table 3). Non-English articles were excluded from this study. With the increasing popularity of MALDI-TOF-MS, *N. asiatica* may be detected as a causative pathogen more frequently, as in this case.

Because *N. asiatica* is a rare species, the most appropriate therapeutic agent, administration route, and treatment duration have not been well established. In general, several drug regimens based on TMP-SMX as a key drug are recommended as first-line therapy for some cases of severe pulmonary nocardiosis (13). Susceptibility tests for all clinically significant *Nocardia* isolates are recommended because antimicrobial susceptibility patterns vary among different studies, countries, and *Nocardia* species. Unfortunately, we were unable to perform a susceptibility test; therefore, based on our literature review, we empirically treated the patient with TMP-SMX, MINO, IMP/CS, and AMPC/CVA. Although we were unable to continue TMP-SMX in this patient due to renal dysfunction, treatment with MINO and AMPC/CVA was successful. Determining the optimal treatment regimen for *N. asiatica* infections will require further study.

One review showed that 64% of 1,050 patients with nocardiosis were immunocompromised (14). The most common causes of immunosuppression were glucocorticoid therapy, malignancy, organ and hematopoietic stem cell transplantation, and HIV infection. In the present case, the patient had bladder cancer (cTaN0M0, cStage 0a) and prostate cancer (cT4N1M1b, cStage IV). Although these cancers may have been responsible for the nocardiosis, both cancers were stable. Furthermore, he was only administered goserelin acetate, which is a hormonal drug, for prostate cancer and had never been treated with chemotherapy. Initially, we were unable to recognize his immunosuppressive status which induced empyema caused by *Nocardia* except for malignancy. Since the numbers of atypical lymphocytes were rapidly increased in his peripheral blood after admission, we were able to detect the presence of ATL during the treatment of empyema.

ATL is a peripheral T-cell malignancy caused by HTLV-1, an oncogenic human RNA retrovirus (15). Southwestern Japan is one of the most endemic areas for its associated malignancy, along with the Caribbean basin, Central and South America, and Western Africa (16). The patient was born in Nagasaki Prefecture on the northwest side of Kyusyu, in southwestern Japan. The frequency of opportunistic infections among HTLV-1 carriers and ATL patients is 1.5% and 6.5%, respectively. The pathogenic microorganisms are diverse, including *Cryptococcus*, *Aspergillus*, *Pneumocystis*, and Cytomegalovirus (17). Although the mechanisms underlying immunosuppression in ATL patients remain obscure, a reduced CD4-positive T-cell function due to HTLV-1 infection has been proposed to be a causative mechanism (18, 19). Aggressive chemotherapy may be required to kill HTLV-1-infected CD4-positive T cells, but this increases the risk of further immunosuppression and opportunistic infections. We were unable to administer treatment for ATL to this patient, since his ADL declined during the treatment of nocardiosis.

In conclusion, we encountered a rare case of ATL that became apparent during the treatment of pulmonary abscess and empyema due to *N. asiatica*. Clinicians should consider the potential of *N. asiatica* to cause pulmonary infections, including empyema, and at the diagnosis of nocardiosis, they should investigate the possibility of disease-producing immunosuppression, including ATL, as in this case.

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

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