Case Report

Correspondence

Shigemi Hitomi
shitomi@md.tsukuba.ac.jp

Pulmonary infection due to *Nocardia exalbida* complicated with pneumococcal pneumonia

Yoshihiko Kiyasu, Hiroshi Koganemaru, Yoko Kurihara and Shigemi Hitomi

Department of Infectious Diseases, University of Tsukuba Hospital, Tsukuba, Ibaraki Prefecture 305-0005, Japan

Introduction: *Nocardia exalbida* is an uncommon *Nocardia* sp., first described in 2006. We report a case of pulmonary infection due to this organism, which became evident after treatment of antecedent pneumococcal pneumonia.

Case presentation: A 68-year-old man was hospitalized because of pneumococcal pneumonia. Although his symptoms improved immediately after administration of anti-pneumococcal antibiotics, patchy opacity on the chest X-ray remained and pyrexia recurred. Administration of trimethoprim/sulfamethoxazole, given after seropositivity against human immunodeficiency virus type 1 was confirmed and *Nocardia*-like organisms were detected from the sputa, completely resolved his symptoms. The recovered organism was identified as *N. exalbida* by comparison of 16S rRNA gene sequences.

Conclusion: To the best of our knowledge, only six other cases of *N. exalbida* infection have been described. Most of these cases were reported from Japan, suggesting that the organism is more prevalent in this country than in other areas. The present case also highlights that underlying nocardiosis should be considered when an immunocompromised patient with acute bacterial pneumonia demonstrates refractory respiratory manifestations, despite receiving appropriate treatments.

Keywords: Human immunodeficiency virus; *Nocardia exalbida*; pneumonia; *Streptococcus pneumoniae*; trimethoprim/sulfamethoxazole.

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Introduction

Members of the genus *Nocardia*, a group of aerobic actinomycetes forming Gram-positive branching filaments, are widely found in the environment, including in soil and water. They occasionally cause human diseases, especially among immunocompromised hosts, through direct inoculation of the skin or inhalation into the lung (Wilson, 2012). To date, more than 30 *Nocardia* spp. have been described as human pathogens. Taxonomy in the genus through biochemical characterization has been complicated because of technical difficulties. In contrast, recent advance in molecular methodologies, including analyses of 16S rRNA gene sequences, facilitates precise identification of the species (Brown-Elliott *et al.*, 2006).

Nocardia exalbida is a new *Nocardia* sp. first recovered from materials of immunocompromised humans and characterized by Iida *et al.* (2006). Since then, only a few cases of *N. exalbida* infection have been described in the

literature (Mizota *et al.*, 2007; Ono *et al.*, 2008; Imai *et al.*, 2011; Milman *et al.*, 2011). Here, we report a case of pulmonary infection caused by *N. exalbida* in a human immunodeficiency virus type 1 (HIV-1)-infected patient, which became evident after treatment of antecedent pneumococcal pneumonia.

Case report

A 68-year-old Japanese man was admitted to a local hospital because of fever and impaired consciousness. A chest X-ray revealed infiltration of both sides of the lower lung fields (Fig. 1a). Administration of cefazopran and clindamycin promptly improved the manifestations. The antibiotics were switched to cefotiam alone and given for a total of 2 weeks because *Streptococcus pneumoniae* susceptible to the drug was recovered from the blood drawn on the admission. Two weeks after the completion of the anti-pneumococcal treatment, the patient became febrile again. Bronchoscopy was performed on day 28 of admission because patchy opacity remained on segment 9 of the right lobe (Fig. 1b). Bacterial and histopathological examinations of bronchoalveolar lavage fluid

Abbreviations: HIV-1, Human immunodeficiency virus type 1; TMP/SMX, trimethoprim/sulfamethoxazole.

Fig. 1. Chest X-rays taken on admission to the referring hospital (a), 1 day before performing bronchoscopy (b), and 50 days after administration of TMP/SMX started (c). Infiltration initially existing on both sides of the lower lung field [indicated with arrows in (a)] and improved after administration of antibiotics, but patchy opacity remained in the right lower lobe [arrowhead in (b)], which almost disappeared after treatment with TMP/SMX (c).

demonstrated no significant micro-organism but many cells containing intranuclear inclusions, indicating activation of cytomegalovirus. Following a work-up of immunosuppression, HIV-1 infection with a CD4-positive lymphocyte count of $20 \mu\text{l}^{-1}$ and a plasma viral load of 1.2×10^5 copies ml^{-1} was confirmed. Intravenous cefotiam was repeatedly administered immediately after the bronchoscopy until the patient was transferred to our hospital on day 41. No anti-cytomegalovirus agent was given because the patient's respiratory conditions did not deteriorate under the treatment with cefotiam.

At the transfer, the patient was afebrile but slightly disoriented with a blood pressure of 96/60 mmHg and arterial oxygen saturation in room air of 98 %. Laboratory findings included hypochromic anaemia (erythrocytes: $2.45 \times 10^6 \mu\text{l}^{-1}$; haemoglobin: 7.1 g dl^{-1}), elevation of the C-reactive protein level (3.98 mg dl^{-1}) and positive results for rapid plasma reagin (46.8 RPR units) and *Treponema pallidum* latex agglutination. Computed tomography revealed no remarkable findings on the brain. A lumbar puncture indicated no increased intracranial pressure or the presence of pleocytosis, *Cryptococcus* antigens and syphilitic reactions in the cerebrospinal fluid. From day 4 of the transfer, intermittent fever up to 39°C reappeared. Although oral amoxicillin-clavulanate was given because aspiration pneumonia was suspected and serum syphilitic reactions were positive, his productive cough worsened. The fever gradually subsided after one single-strength tablet of trimethoprim/sulfamethoxazole (TMP/SMX) day^{-1} was given for prophylaxis of pneumocystosis on day 14. The daily dose of TMP/SMX was increased to six tablets (approx. $12 \text{ mg (kg body weight)}^{-1}$ for the TMP

component) on day 21 because Gram-positive, acid-fast (with the modified Kinyoun method) branching filamentous bacteria, suggesting *Nocardia* spp., were detected from the sputum but was reduced to three tablets on day 27 because severe appetite loss emerged. Thereafter, his productive cough and intermittent fever disappeared and the size of the patchy opacity on the chest X-ray diminished (Fig. 1c). The patient was transferred to a long-term care facility on day 84, at which point the plasma HIV-1 load decreased to an undetectable level under antiretroviral therapy with zidovudine, lamivudine and raltegravir. The same dose of TMP/SMX was administered for a total of 12 months, followed by a prophylactic dose against pneumocystosis (one single-strength tablet day^{-1}). On a follow-up one and a half years after the discharge from our hospital, the patient showed no recurrence of nocardiosis, although the TMP/SMX prophylaxis was still given.

The organism suspected of being *Nocardia* sp., recovered from the sputum on day 21, was further examined. The 16S rRNA gene of the organism was amplified by PCR (Lane, 1991) and a 1392 nt product was sequenced with the ABI PRISM 3130 Genetic Analyzer (Applied Biosystems Japan). An analysis with BLAST showed that the sequence was 100 % nucleotide identity to that of *N. exalbida* IFM 0803? (GenBank accession no. AB187522). MICs against the organism, measured with the broth microdilution method described by the Clinical and Laboratory Standards Institute (CLSI, 2011) using a DryPlate (Eiken Chemical), were as follows: TMP/SMX, $0.25/4.75 \mu\text{g ml}^{-1}$; imipenem, $<0.5 \mu\text{g ml}^{-1}$; cefotiam, $4 \mu\text{g ml}^{-1}$ cefepime, $2 \mu\text{g ml}^{-1}$; ceftazidime, $2 \mu\text{g ml}^{-1}$; ciprofloxacin, $2 \mu\text{g ml}^{-1}$.

Table 1. Summary of human *N. exalbida* infection reported in English literature

AMK, amikacin; DM, diabetes mellitus; EM, erythromycin; F, female; GRNX, garenoxacin; HB, hepatitis B; HIV, human immunodeficiency virus infection; IMP, imipenem; M, male; MEPM, meropenem; NR, not reported; TMP/SMX, trimethoprim/sulfamethoxazole.

Case	Age/sex	Reported country	Disease	Underlying condition	Treatment	Outcome	Reference
1	43/NR	Japan	Pneumonia	NR	NR	NR	Iida <i>et al.</i> (2006)
2	60/NR	Japan	NR	Pemphigus vulgaris	NR	NR	Iida <i>et al.</i> (2006)
3	38/F	Japan	Keratitis	None	EM + topical agent	Survived	Mizota <i>et al.</i> (2007)
4	63/M	Japan	Brain abscess	Lymphoma	TMP/SMX + MEPM	Survived	Ono <i>et al.</i> (2008)
5	47/M	Japan	Pneumonia	HIV, DM, HB	TMP/SMX, IMP + AMK, GRNX	Survived	Imai <i>et al.</i> (2011)
6	56/M	USA	Endophthalmitis	None	Enucleation, TMP/SMX	Survived	Milman <i>et al.</i> (2011)
7	68/M	Japan	Pneumonia	HIV	TMP/SMX	Survived	Present case

Discussion

In the present case, the patient's illness was first diagnosed as pneumococcal pneumonia because of typical findings on the chest X-ray and recovery of *S. pneumoniae* from the blood. However, administration of anti-pneumococcal antibiotics incompletely ameliorated the patient's symptoms. The residual manifestations resolved after administration of TMP/SMX, following detection of *Nocardia*-like organisms in the sputum. The recovered organism was identified as *N. exalbida* by molecular analysis. These results showed that the patient in the present case contracted pulmonary infection due to both *S. pneumoniae* and *N. exalbida*, the latter of which became evident afterwards.

To date, six other cases of *N. exalbida* recovery from human materials have been described in the English literature (Table 1): two from patients with pulmonary infection (Iida *et al.*, 2006; Imai *et al.*, 2011), one each with endogenous endophthalmitis (Milman *et al.*, 2011), keratitis (Mizota *et al.*, 2007) and brain abscess (Ono *et al.*, 2008), and one with an undescribed location (Iida *et al.*, 2006). Interestingly, five of the six cases were reported from Japan, suggesting that *N. exalbida* is more prevalent in this country than in other areas (Ono *et al.*, 2008). Detailed clinical courses have been described in four cases, in which three patients were favourably managed with antimicrobial therapies only, but the other, suffering from endophthalmitis, received enucleation followed by antibacterial treatment (Milman *et al.*, 2011). *In vitro* studies demonstrated that all examined *N. exalbida* strains, including the one in the present case, were susceptible to TMP/SMX, the drug most commonly used for treatment of nocardiosis (Wilson, 2012). In addition, several other antibiotics, including cefotaxime, imipenem, minocycline and amikacin, showed good activity against the examined strains, indicating that these agents may be used in place of TMP/SMX for treatment of *N. exalbida* infection. Indeed, pulmonary *N. exalbida* infection occurring in an HIV-1-infected patient having hypersensitivity to TMP/SMX was successfully treated with intravenous imipenem plus amikacin and subsequent oral garenoxacin (Imai *et al.*, 2011).

Because of the indolent onset and chronic progression, pulmonary nocardiosis has occasionally been complicated with other pulmonary infections, including pneumocystosis, tuberculosis, aspergillosis and cytomegalovirus infection. In contrast, co-infection with pathogens causing acute pneumonia in communities has rarely been reported (Brown *et al.*, 1986; Wilson *et al.*, 1989; Javaly *et al.*, 1992; Peleg *et al.*, 2007; Ambrosioni *et al.*, 2010). In the present case, anti-pneumococcal treatments eliminated most manifestations of pneumonia on the chest X-ray but disclosed patchy opacity in the right lower lung lobe, which diminished after TMP/SMX was given. Thus, we consider that the residual lesion was caused by nocardial infection, which was obscured during the treatment of pneumococcal pneumonia. The present case illustrates that underlying nocardiosis should be considered when pulmonary symptoms of patients with acute bacterial pneumonia are recurrent, despite administration of appropriate treatments.

In the present case, it was approximately 2 months after the initial presentation that diagnosis of nocardiosis was made. One reason for the delay in diagnosis was the fact that *Nocardia*-like organisms were not detected in the bronchoalveolar lavage fluid examined in the referring hospital. We consider that the negative result may have been due to antecedent administration of anti-pneumococcal agents, especially cefazopran and cefotiam. According to the breakpoints for pulmonary infection published by the Japanese Association of Chemotherapy (Saito, 1995; Saito *et al.*, 1999), the MICs for cefazopran and cefotiam against the recovered *N. exalbida* strain were in the range of susceptibility. However, the drugs were only given for a total of 2 weeks, a duration long enough to treat pneumococcal pneumonia but insufficient to prevent relapse of pulmonary nocardiosis (Wallace *et al.*, 1982; Uttamchandani *et al.*, 1994). Susceptibility of nocardiae to antibiotics other than TMP/STX varies in their species (Wilson 2012). Thus, physicians should be aware of the possibility that preceding uses of certain antibiotics unexpectedly interfere with diagnosis of nocardiosis.

In conclusion, we have described a case of *N. exalbida* infection, which was complicated with pneumococcal pneumo-

nia. Underlying nocardiosis should be considered when an immunocompromised patient with acute bacterial pneumonia demonstrates refractory or recurrent respiratory manifestations, despite receiving appropriate treatments.

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