Heliyon 9 (2023) e17183

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Pathogenic *Nocardia amamiensis* infection: A rare case report and literature review

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A R T I C L E I N F O

Keywords:
Nocardia
Nocardia amamiensis
Pulmonary infection
Clinical characteristics
Diagnosis
Therapy

A B S T R A C T

Background: To date, only six cases of *Nocardia amamiensis* infection have been reported, including two ocular cases, three pulmonary cases, and one disseminated case. However, no *Nocardia amamiensis* pulmonary infection cases have been reported in immunocompetent patients without structural pulmonary disease. This study describes a rare case and provides a detailed review of all previous cases.
Methods: A pulmonary infection caused by *Nocardia amamiensis* in a 64-year-old man with low-grade fever, night sweats, and weight loss was reported. All previously reported cases of *Nocardia amamiensis* infection were searched and reviewed.
Results: The pathogen was identified as *Nocardia amamiensis* using bronchoalveolar lavage fluid (BALF) mNGS, and the current case was successfully treated with trimethoprim-sulfamethoxazole (ST) monotherapy. mNGS and 16S rRNA PCR are standard tests to identify *Nocardia*.
Conclusion: mNGS has high diagnostic performance for *Nocardia amamiensis*. Further studies are needed to clarify the clinical characteristics and explore more effective treatment protocols for this rare pathogen.

1. Introduction

Nocardia species are Actinomycetales and aerobic gram-positive bacteria that cause opportunistic infections. They can be found ubiquitously in water, soil, dust, decaying vegetation, and animal waste [1]. *Nocardia* can infect various organs, including the lungs, skin, eyes, and central nervous system. Ongoing studies on the taxonomy of the genus *Nocardia* have identified 54 categories associated with human infections out of the 119 known *Nocardia* categories with valid names [2,3]. To date, 120 *Nocardia* category names have been published and corrected [4]. *Nocardia* infection poses a significant threat to human health, and the diagnosis and etiology of this disease are of great importance.

Despite the severity of *Nocardia* infections, reports and research remain scarce, and large-sample epidemiological studies are lacking. Many important clinical questions regarding the treatment and management of nocardiosis remain unanswered [5]. However, the isolation rate of *Nocardia* is increasing with the growing number of immunocompromised hosts and advancements in diagnostics and identification of *Nocardia* [6,7].

In 2007, a novel species called *Nocardia amamiensis* was discovered in the soil of a sugarcane field in Japan [8]. o date, only six cases

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https://doi.org/10.1016/j.heliyon.2023.e17183
Received 15 December 2022; Received in revised form 6 June 2023; Accepted 9 June 2023
Available online 16 June 2023

of *N. amamiensis* infection have been reported [9–13]. However, no cases have been reported in patients with normal immune function and without structural pulmonary disease. Therefore, it is crucial to present additional cases to explore the clinical characteristics and therapy of *N. amamiensis*. In this study, we report the first *N. amamiensis* pulmonary infection case in an immunocompetent patient without structural pulmonary disease and review previous *N. amamiensis* infection cases.

2. Case presentation

A 64-year-old man with a functioning immune system and no chronic lung diseases was admitted to the hospital with symptoms of pneumonia. He had been experiencing low-grade fever, weakness, night sweats, and weight loss for one year before admission. Chest computed tomography (CT) revealed sporadic high-density shadows (Fig. 1a). Blood tests showed an elevated erythrocyte sedimentation rate (ESR) of 19 mm/h, and the T-cell detection for tubercle bacillus spot (T-Spot) test was negative. The sputum smear for tuberculosis bacteria was normal, and no tuberculosis bacteria were detected in the sample.

A percutaneous lung biopsy guided by CT was performed on the right lung, and the pathological result revealed fibrous tissue and gland hyperplasia with leukomonocytes, oat cells, neutrophil granulocytes, slightly broadened alveolar wall, and pulmonary vesicle epithelial hyperplasia. The patient initially received ten days of moxifloxacin therapy, but the anti-infective treatment was ineffective. Subsequently, the patient underwent diagnostic anti-tuberculosis treatment for approximately ten months. Isoniazid (0.45 g/day), rifampicin (0.6 g/semiweekly), pyrazinamide (2.0 g/semiweekly), and ethambutol hydrochloride (2.0 g/semiweekly) were administered for six months, followed by isoniazid (0.45 g/day) and rifampicin (0.6 g/semiweekly) for four months.

During the first three weeks of the diagnostic anti-tuberculosis treatment, the patient's low-grade fever subsided slightly, and the high-density shadows in the lung showed some improvement. However, later in the treatment, the patient's temperature fluctuated between 36.0 °C and 37.6 °C, and the body weight decreased by 14 kg. Chest CT showed progression compared to the previous scan (Fig. 1b).

After admission to our hospital, the patient underwent a series of medical tests. The physical examination revealed stable blood pressure and heart rate. No abnormal findings were observed on the skin or mucous membranes. Slightly weak breathing sounds were heard in both lungs. Abdominal and cardiac examinations showed no abnormalities.

Blood tests showed a high percentage of neutrophils (75.5%), high levels of ESR (62 mm/h), and positive results for T-Spot (A-antigen 13.0 and B-antigen 11.0). Liver and kidney function, as well as infection-related indicators (including calcitonin, high-sensitivity C-reactive protein, blood, sputum, and alveolar lavage fluid microbiological culture, smear test for bacilli, epiphyte, and mycobacterium), were within normal ranges.

Fiberoptic bronchoscopy revealed an unobstructed tracheal lumen and a few white secretions with mucosal hyperemia observed in each bronchial tree segment. Forty milliliters of alveolar lavage fluid were collected from the patient's right middle bronchus, and four brushed slides were obtained. The fluid was used for microbiological culture, smear tests for bacilli, epiphyte, mycobacterium, and gram staining.

On the fifth day, the microbial culture dish showed an alarm, and similar specimens were sent to a commercial company (Vision Medicals Research Center) for metagenomic next-generation sequencing (mNGS).

The mNGS analysis revealed the presence of *Nocardia amamiensis* with a sequence number of 22 and an identification confidence of 99.0%. Other pathogenic bacteria identified were *Lactobacillus fermentum,* with a sequence number of 3, and *Aspergillus nidulans,* with a

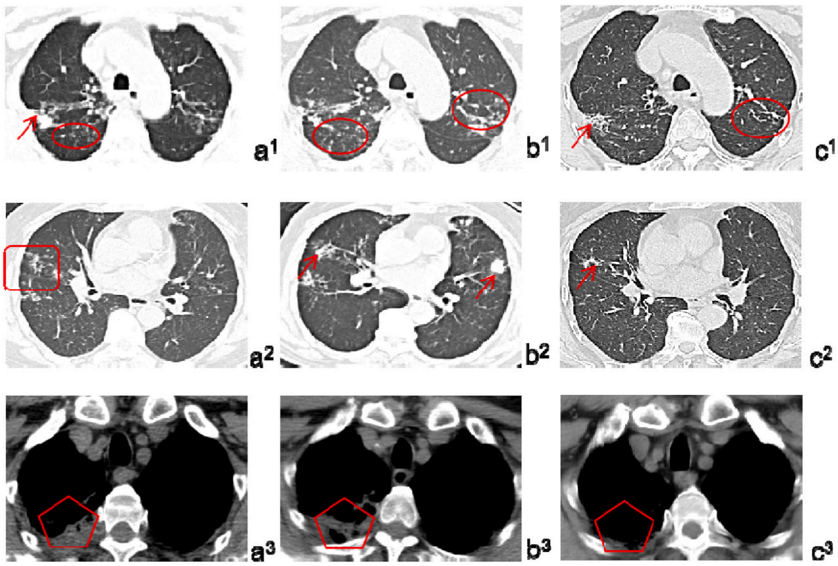

Fig. 1. Chest CT of the current case.

sequence number of 14 (Table 1). Lactobacillus fermentum is typically found in the non-nasal and intestinal tracts and rarely causes pulmonary infections. The patient's symptoms and the characteristics of the lung shadows did not support the presence of Aspergillus nidulans, which was consistent with *Nocardia* infection.

The antibiotic susceptibility of *N. amamiensis* was determined using the broth microdilution method (Table 2). It was found that ST trimethoprim-sulfamethoxazole) was sensitive to *N. amamiensis*. Therefore, the patient's treatment was initiated with ST (7.5 mg/kg, as trimethoprim). On the third day of ST administration, the patient's temperature remained below 37 °C and did not recur.

During the treatment with ST, the patient's symptoms of fever, weakness, weight loss, and night sweats were effectively controlled. Additionally, the sporadic high-density shadows in both lungs gradually reduced. After seven weeks of ST treatment, the patient developed gastrointestinal symptoms (nausea, loss of appetite), so the medication dosage was reduced to 5.0 mg/kg as trimethoprim. In the fourth month of ST administration, due to a reduced white blood cell count (2.1 × 10ˆ9/L), the treatment was switched to minocycline (MINO) monotherapy. However, liver dysfunction was observed during MINO administration, leading to the selection of clarithromycin therapy (CAM, 200 mg every 12 h) as the final choice. Long-term CAM therapy was continued for three months without any relapse.

After approximately five months of treatment, the sporadic high-density shadows in the lungs were significantly reduced and absorbed, as shown in Fig. 1c. The density of the shadows was also reduced. The total treatment duration was eight months. The patient was followed up for about one year after discontinuing the treatment, and no recurrence of the symptoms mentioned above was observed during regular telephone and outpatient follow-ups.

3. Discussion

To identify previously reported cases of *Nocardia amamiensis* infection, a comprehensive search was conducted using the PubMed and Chinese National Knowledge Infrastructure (CNKI) databases. The search terms used were "*Nocardia amamiensis*" and "N. *amamiensis*". Furthermore, the reference lists of previously published reports were examined for additional relevant studies. To compare *N. amamiensis* with more commonly encountered *Nocardia* species, a thorough investigation was conducted on the clinical characteristics, diagnosis, and treatment protocols of all *Nocardia* species.

3.1. Incidence of N. amamiensis

With the increasing number of immunocompromised hosts and advancements in molecular-level diagnostic methods, the incidence of *Nocardia* species infections has risen in recent reports [7,14]. *N. amamiensis*, identified as a novel species, was first isolated from a sugarcane field in Japan in 1997 by Yamamura H. et al. [8]. However, only six cases of nocardiosis caused by *N. amamiensis* have been reported to date, with detailed descriptions available for just three of those cases [9,10,13]. Furthermore, previous reports or studies on the epidemiology of nocardiosis have rarely included cases caused by *N. amamiensis*. As a result, information regarding the response to *N. amamiensis* infection is limited, and the incidence trends remain unclear due to the rarity of this disease.

Overall, *N. amamiensis* is an extremely uncommonly isolated pathogen, and the incidence of *N. amamiensis* infection is presumed to be very low. However, it poses a significant public health threat due to its underdiagnosis and the lack of adequate understanding [4].

3.2. Clinical characteristics of N. amamiensis

Nocardiosis is primarily an opportunistic infection commonly detected in immunocompromised patients, although it can also occur in immunocompetent individuals. Among immunocompromised hosts, solid organ transplant (SOT), hematopoietic stem cell transplantation (HSCT), and immunosuppression for autoimmune diseases and cancer have been associated with nocardiosis. Lung and heart transplant recipients are particularly susceptible to nocardiosis, with a higher incidence observed in hosts with significant immunosuppression [5,15].

Recent studies have shown that immunocompetent individuals, including those with comorbidities associated with impaired immunity, such as alcoholism and diabetes, accounted for 18–45% of all nocardiosis cases [16–18]. Chronic lung diseases have also been reported in 10–58% of infected patients, indicating them as potential risk factors [19,20]. Inhalation is the primary route of exposure to *Nocardia*, making pulmonary nocardiosis the most common type of infection [21]. Other *Nocardia*l infections include systemic/disseminated, extrapulmonary, and central nervous system infections.

To date, rare cases of *N. amamiensis* infection have been documented (Table 3). It appears that patients with underlying diseases or

Table 1
The mNGS of alveolar lavage fluid indicated nocardia amamiensis, lactobacillus fermentum and aspergillus nidulans. The sequence numbers were 22, 3 and 14 respectively.

List of bacteria						
Genericity				Species		
Type	Generic name	Relative abundance	Sequence number	Specific name	Identification confidence	Sequence number
–	Nocardia	4.3%	91	Nocardia amamiensis	99.0%	22
G^+	Lactobacillus	2.8%	16	Lactobacillus fermentum	99.0%	3
Epiphyte	Aspergillus	22.1%	17	Aspergillus nidulans	99.0%	14

Table 2
Susceptibility testing of the *Nocardia amamiensis* strain isolated in the current case.

Antimicrobial agent	Typical value	Interpretation	MIC (ug/ml) for category	
			S	I
AMC	32	R	≤8	≥32
ST	0.25	S	≤2	≥4
CRO	10	I	≤8	≥64
AMK	4	S	≤8	≥16
IMI	2	S	≤4	≥16
MINO	1	S	≤1	≥8
CAM	0.8	S	≤2	≥8
LZD	0.5	S	≤8	–

S, susceptible; I, intermediate; R, resistant; MIC, minimum inhibitory concentration(ug/ml); AMC, amoxicillin-clavulanic acid; ST, trimethoprim–sulfamethoxazole; CRO, ceftriaxone; AMK, amikacin; IMI, imipenem; LZD, linezolid; CAM,clarithromycin; MINO, minocycline.

those undergoing treatment with immunosuppressive agents are more susceptible to *N. amamiensis* pulmonary infection. The first report of pulmonary infection caused by *N. amamiensis* was published by Martinez-Gamboa A. et al., in 2016 [10]. The current case represents only the fourth reported case and is the first to be reported in an immunocompetent patient without structural pulmonary disease. Incidences of *N. amamiensis* infection have been observed in the lungs and eyes.

Radiological characteristics of chest CT images in nocardiosis include ground-glass opacities (GGOs), centrilobular nodules, nodules/masses, interlobular septal thickening, bronchial wall thickening, mucoid impaction, cavitation, intralobular reticular opacity, pleural effusion, and enlarged hilar/mediastinal lymph nodes [22,23]. Studies have shown that the most common combination of lung imaging findings in nocardiosis is nodules/masses and interlobular septal thickening (77.8%), while bronchial wall thickening and centrilobular nodules are less commonly observed [1,24]. Consolidation, mass, or nodule shadows are frequently seen, and approximately one-third of patients may present with cavitation [24]. The lung imaging characteristics of *N. amamiensis* lack specificity, and cavitation or pleural effusion tends to be more common in immunosuppressed patients. Fever and cough are the most common symptoms reported in pulmonary *N. amamiensis* infection cases.

In conclusion, the clinical manifestations and lung imaging characteristics of *N. amamiensis* lack specificity [22]. Due to the limited number of reports on *N. amamiensis* infection, it is often underdiagnosed and lacks sufficient understanding, leading to misdiagnosis as tuberculosis in some patients.

3.3. Identification of *N. amamiensis*

Sputum microbial culture is a repeated, cost-effective, and effective method, but the long culture time may result in delayed diagnosis [5,23]. In addition, the positive rate of bacterial smear and pathological examination of lung tissue remains low.

Table 3
Summary of data concerning all patients with *Nocardia amamiensis* infection and clinical characteristics.

Study name	Age/ gender	Comorbid conditions	Clinical presentation	Site	Treatment	White cell (10^9/L)	Specimen	Method	Outcome	State
Case	64/M	None	Fever, weakness, night sweats, weight loss	P	ST	5.37	BALF	mNGS	Cured	China
Anyuan et al. [9]	43/F	Nocardia Pneumoniae, bronchiectasia	Fever, cough, panting	P	LZD + IPM + ST	11.34	BALF	mNGS	Cured	China
Martinez et al. [10]	43/F	Primary glomerulonephritis Prednisone, tacrolimus,	Fever, weight loss, cough	P	IPM + ST	13.8	BALF	16sRNA	Cured	Mexico
Rudramurthy et al. [12]	64/F	–	Cough, dyspnea	P	–	–	Sputum	16sRNA	Cured	India
Reddy et al. [11]	–	–	–	E	–	–	Corneal scrapings	16sRNA	–	India
Reddy et al. [11]	–	–	–	E	–	–	Corneal scrapings	16sRNA	–	India
Elballat M et al. [13]	57/M	COPD	dyspnea, chills, sweats, cough	P, CE, CU	ST + IPM + AM	–	Sputum	Sputum culture	Died	USA

F, female; M, male; '-', unknown; BALF, brochoalveolar lavage fluid; COPD, chronic obstructive pulmonary diseases; P, pulmonary; E, eye; CE,cerebral; CU, cutaneous; ST, trimethoprim–sulfamethoxazole; LZD, linezolid; IPM, imipenem; AM, amikacin.

Matrix-assisted laser desorption ionization time-of-flight spectroscopy (MALDI-TOF MS) has been reported for identifying *Nocardia* pneumoniae [9] and may have the potential to identify *N. amamiensis* in the future. However, molecular techniques offer rapid and accurate identification of *Nocardia* at the species level. One study indicated that *Nocardia* PCR testing had a specificity of 74% and a sensitivity of 88% for diagnosing nocardiosis [25]. Standard molecular tests include 16S rRNA PCR and sequencing and metagenomic next-generation sequencing (mNGS). Compared to mNGS, 16S rRNA PCR requires clinicians to consider nocardiosis a possibility in advance [26]. However, mNGS has emerged as a promising universal method for pathogen detection in infectious disease diagnostics. This technology allows for the identification and genomic characterization of bacteria, fungi, parasites, and viruses directly from clinical specimens without prior knowledge of a specific pathogen. Chen SL et al. reported a 92% positive detection rate of mNGS for pathogens in bronchoalveolar lavage fluid (BALF) from severely ill or immunocompromised patients with pulmonary infections [27].

Therefore, mNGS can provide more rapid and accurate detection and identification of *N. amamiensis*.

3.4. Antimicrobial susceptibility and treatment of N. amamiensis

According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, the broth microdilution method is recommended for determining the Minimum Inhibitory Concentration (MIC) and conducting antibiotic susceptibility testing (AST) for *Nocardia*. Alternative methods such as Resazurin, Spectrophotometric readings, and microplate Alamar Blue assays have also shown high agreement rates with the broth microdilution method [28–30].

Sulfamethoxazole-trimethoprim (ST) has been the cornerstone of nocardiosis treatment since the 1950s. Other antibiotics, such as amikacin, imipenem, third-generation cephalosporins, and linezolid, have also been identified as effective against most *Nocardia* species [2,5].

Early initiation of appropriate antibiotic therapy is crucial to reduce the mortality rate associated with nocardiosis. Treatment approaches for *Nocardia* vary based on geographical location, species involved, and antimicrobial susceptibility profiles, with consideration given to the patient's condition and antibiotic susceptibility. The antibiotic susceptibility of *N. amamiensis* has primarily been determined using the broth microdilution method.

ST is considered the mainstay of nocardiosis treatment. Limited data exists on the comparative efficacy of monotherapy versus combination antimicrobial therapy for nocardiosis. However, combination therapy is generally preferred for severe cases and immunocompromised patients. In the current case of *N. amamiensis*, monotherapy was successful, although combination therapy has shown success in the other three reported cases of pulmonary *N. amamiensis* infection. Amikacin has demonstrated excellent in vitro activity against *N. amamiensis* eye infections [11]. While studies provide limited information on the response to antimicrobial treatment, ST, carbapenems, and linezolid have been used successfully to treat *N. amamiensis* infections.

In the present case, monotherapy was chosen based on susceptibility analysis; however, treatment had to be discontinued due to drug toxicity. Hence, developing appropriate antimicrobial treatment strategies in the future is crucial.

Studies involving transplant recipients and patients with chronic lung disease have reported relapse rates ranging from 5% to 6.6% [18,31,32]. Due to the low risk of relapse or reinfection following appropriate nocardiosis therapy, secondary prophylaxis is not recommended for immunocompetent individuals [5]. However, selected individuals with permanent immunosuppression may be considered for secondary prophylaxis, although data on the effectiveness of low-dose trimethoprim-sulfamethoxazole in preventing nocardiosis is lacking [33].

Given the scarcity of reported cases, the present study has certain limitations. The clinical characteristics, diagnostic methods, antimicrobial susceptibility, and optimal treatment protocols for *N. amamiensis* are still insufficient and require further information for future clinical practice.

4. Conclusion

When dealing with a complex infection, it is crucial to collect sputum, alveolar lavage fluid, lung tissue, or other specimens promptly and utilize various methods to detect the pathogenic bacteria accurately. mNGS has demonstrated high diagnostic performance for *N. amamiensis*. Further studies are needed to develop more effective treatment protocols for this rare pathogen.

Ethical and waiver of informed consent approval

The study and the request for waiver of informed consent were approved by the first affiliated hospital of Henan University of Science and Technology ethics committee (2021-03-K0002). This retrospective study was conducted using documented and anonymous clinical data and information and didn't involve personal privacy and commercial interests. Waiver of informed consent will not adversely affect the rights and interests of the subjects.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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