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Case report

Persistent *Nocardia beijingensis* infection in a patient with postoperative abscess and misuse of antibiotics in China

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ABSTRACT

Here we describe the first case of abscess infection caused by *Nocardia beijingensis* in China. The patient was immunocompetent but suffered from postoperative abscess for 6 years. This study highlights the necessity of long-term infected foci to be thoroughly examined to identify the pathogen, as well as the importance of accurate *Nocardia* identification and antimicrobial susceptibility tests for understanding the pathogen's epidemiology, clinical significance, and treatment strategy.

1. Case

A 57-year-old female was admitted to our hospital with a chief complaint of chest incision fluid with empyema for 6 years. The patient was treated with surgeries including mitral valve replacement, atrial fibrillation radiofrequency ablation, and mediastinal tumor resection for rheumatic heart disease 6 years ago in a local hospital. Two weeks after the operation, she had a fever of up to 40 °C with chills, and her incision showed fluid and poor healing. During the past 6 years, she received surgeries for sternal abscess scavenging in the local hospital twice while the situation did not improve. She also repeatedly changed medication and oral antibiotics on her own but received no significant improvement. The patient was referred to our hospital for further evaluation. On admission, her blood and wound secretion samples were collected for bacterial culture. The initial cultivation of clinical specimens was carried out using Columbia blood agar plate, China blue lactose agar plate, and Sabouraud dextrose agar with chloramphenicol at 37 °C for 48 hours. The blood failed to yield bacterial growth while the secretion samples showed mixed growth of multiple bacteria. No significant growth of clinically common pathogen was observed. Since the wound cleanliness was poor on admission, her first secretion sample was considered contaminated.

Laboratory test results were shown in Table 1: hemoglobin 118 g/L, leukocyte count 9.49×10^9/L, neutrophils 8.7×10^9/L (91.1%), lymphocytes 0.7×10^9/L (7.2%), and platelets 305×10^9/L. Physical examination revealed a 20 cm-long surgical scar in the middle of her chest. A peanut-sized ulcer was on the lower end of the scar, deep to the clavicle. There was a smelly, yellowish pus overflow, with surrounding tissue slightly red, swollen, and tender. Heart examination revealed a heart rate of 101 bpm and no abnormal symptoms. Computed tomography of her chest showed a dense shadow in the lower margin of the sternum (Fig. 1A) and slightly enlarged lymph nodes in the mediastinum and the left axillary. Tests for human immunodeficiency virus (HIV) and hepatitis B and C viruses were negative.

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Table 1
Laboratory test results of the patient.

Clinical indicators	Results	Normal ranges
Hemoglobin (g/L)	118	110–150
Leukocyte count (/L)	9.49×10^9	$3.5–9.5 \times 10^9$
Neutrophils (/L)	8.7×10^9	$2.0–7.5 \times 10^9$
Lymphocytes (/L)	0.7×10^9	$0.8–4.0 \times 10^9$
Neutrophils %	91.1	50–75
Lymphocytes %	7.2	20–40
Platelets (/L)	305×10^9	$100–350 \times 10^9$

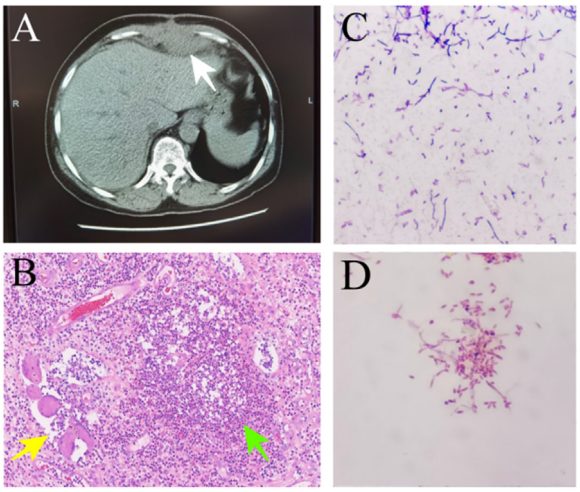

Fig. 1. (A) Computed tomography of the patient's chest, revealing a dense shadow in the lower margin of the sternum. (B) Histological features of the infected foci, showing fibrous tissue with nonspecific inflammatory changes indicated with green and yellow arrows. (C) Gram's staining. (D) Ziehl-Neelsen staining.

The patient subsequently underwent infected-sternum radical operations and bilateral ecto pectoralis transfer plasty. During the operations, abscess cavities and liquor puris were found spread all over the incision. A huge string-of-beads-like abscess cavity was found on the sternum and retrosternal sinus. A 3 cm-long pacing traverse was found in the abscess cavity and was completely removed. Biopsy specimens of the tissue under incision were obtained. Pathological examination showed dermal and subcutaneous suppurative inflammation and focal polykaryocyte infiltration (HE staining, Fig. 1B). Incisional secretion was collected for bacterial culture.

Within 3 days of incubation at 37 °C, the isolates revealed only small, chalky white, dome-shaped, rough colonies on blood agar and Sabouraud agar plates. The strain showed Gram-positive short filaments, coccoid forms, and branching rods in Gram's stain, and partially acid-fast in the modified Ziehl-Neelsen stain (Fig. 1C and D). This specimen was collected after the wound was thoroughly cleaned. Only bacteria in such form grew after cultivation. Therefore, it was considered the causative etiological agent. The isolate was further identified as *Nocardia beijingensis* (*N beijingensis*) through 16S rRNA sequencing. Phylogenetic trees based on the 16S rRNA sequences (Fig. 2) showed that the isolate exhibited some differences with *N beijingensis* isolates in GenBank. Sensitivity tests were completed using Sensititre Susceptibility plates for Rapidly Growing Mycobacteria (Thermo Scientific, Trek Diagnostic Systems Ltd, United Kingdom). The isolate showed resistance to moxifloxacin and ciprofloxacin, and susceptibility to other tested antibiotics (Table 2).

Table 2
N beijingensis isolate antimicrobial susceptibility results.

Antibiotic	MIC (μg/mL)	Susceptibility
Amikacin	< 1	S
amoxicillin-clavulanic acid	≥ 64/32	R
Ceftriaxone	< 4	S
Ciprofloxacin	≥ 4	R
Clarithromycin	0.5	S
Imipenem	< 2	S
Linezolid	< 1	S
Minocycline	< 1	S
trimethoprim/sulfamethoxazole	< 0.25/4.75	S
Tobramycin	< 1	S
Doxycycline	< 0.12	S
Moxifloxacin	≥ 8	R

MIC, minimum inhibitory concentration; R, resistant; S, sensitive.

Empirical treatment with cefotaxime and vancomycin was initiated during the hospitalization. According to the national guidelines for antimicrobial treatment, compound sulfamethoxazole is the preferred choice for primary cutaneous nocardiosis. The treatment course is 3 months for immunocompromised individuals and 6 months for immunosuppressed individuals [1]. Upon diagnosis of nocardiosis, vancomycin was replaced with trimethoprim-sulfamethoxazole. After 2 weeks of treatment, the incision healed well, and the patient showed no abnormal symptoms or discomfort. She was then discharged from the hospital but continued taking the medication for 3 months without any recurrence.

2. Discussion

Nocardiosis is a rare but life-threatening infectious disease which can be caused by inhalation or direct contact with bacteria via a cut or scratched skin [2]. *N beijingensis* was first isolated from a soil sample at Xishan Mountain in Beijing in 2001 [3]. Since 2004, infections with this pathogen have been reported in Thailand, Japan, France, and the United States [4–6]. *N beijingensis* was rarely reported as a pathogenic bacterium in China except for 3 isolates from sputum samples reported by Wei et al. [7] in 2017. Up to one-third of patients with nocardiosis are immunocompetent [8]. According to our literature review, the site of infection with *N beijingensis* in immunocompetent patients includes lung, central nervous system, eye, and adrenal. Table 3 summarizes reported cases of *N beijingensis* in immunocompetent patients. In this case, we reported a persistent abscess infection caused by *N beijingensis*. The patient was immunocompetent and had no sign of respiratory or bloodstream infection but suffered from postoperative abscess infection for up to 6 years. She

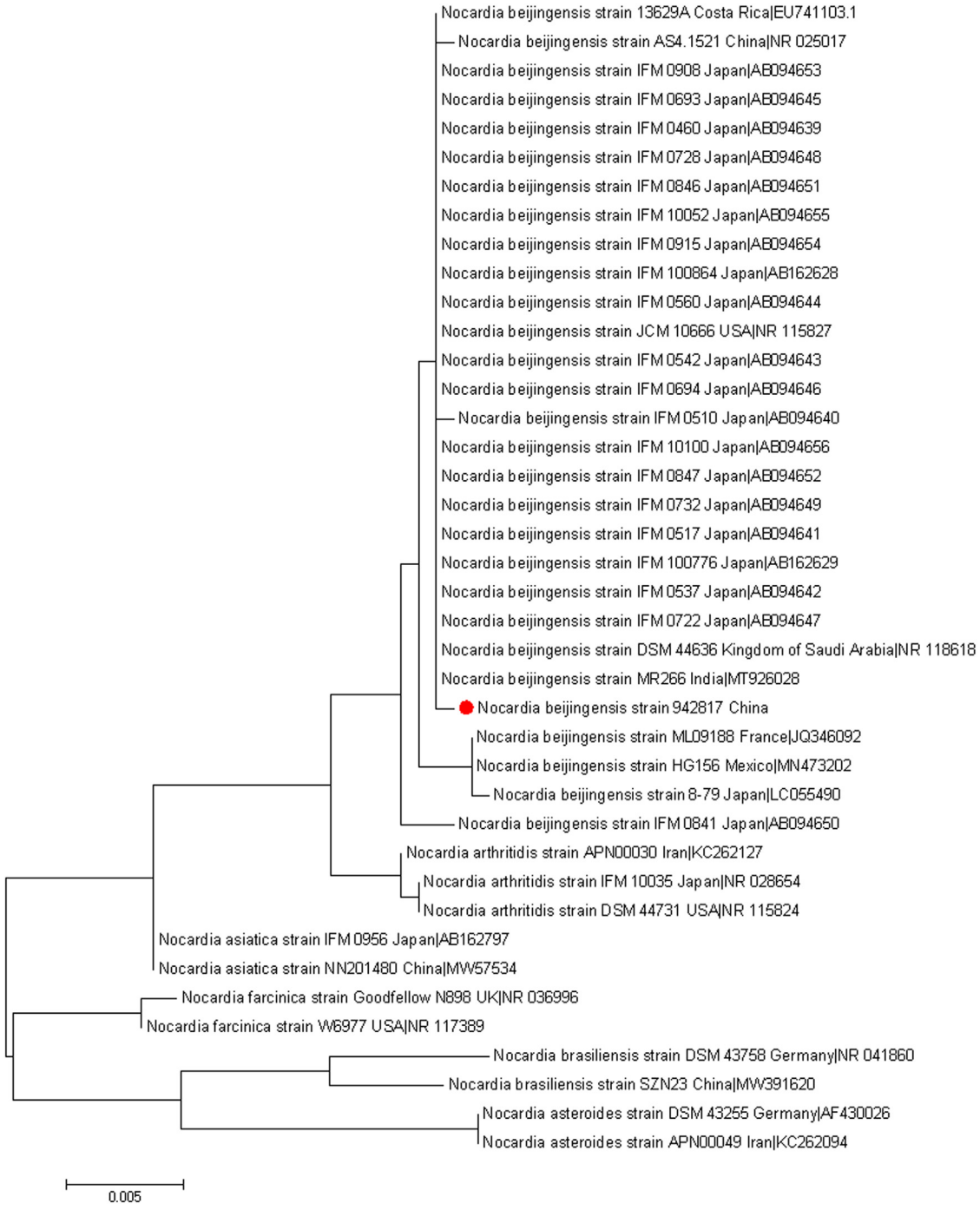

Fig. 2. Phylogenetic relationships of the isolate (*Nocardia beijingensis* strain 942817 China, highlighted in red) compared with reference strains. Trimmed 16S rRNA were aligned using MEGA 7.26 software. The strain ID, country source, and GenBank accession number are indicated. The scale bar indicates the nucleotide substitutions per site.

was finally cured by surgical abscess removal in a combination of sulfonamides treatment.

Reports on *Nocardia* infection in humans are limited [2]. To our knowledge, the identification of *Nocardia* in many Chinese hospitals is often limited at the genus level. *Nocardiosis* is always diagnosed via morphological consideration, including acid-fast stain, Gram stain, and pathogen colony morphology rather than molecular analysis. Thus, cases of infection caused by *N beijingensis* might be underestimated. The species is also considered underreported due to the lack of gene sequencing performed outside Asia [9]. Since each species of *Nocardia* has different clinical features and mortality rates, and displays variable antimicrobial susceptibility patterns, accurate identification of *Nocardia* isolates at the species level is important for patient's diagnosis and treatment. It is also important for further understanding the epidemic situation of *Nocardiosis* and enriching information on *No-*

Table 3
Reported cases of *N beijingensis* in immunocompetent patients.

Serial no.	Year	Age/Sex	Site of infection	Presenting symptoms	Duration of symptom	Antibiotics used	Author/Ref.
1	2013	75/M	Fascia	Back pain	10 weeks	Imipenem, amikacin, cotrimoxazole	Rigotti et al. [10]
2	2014	48/F	Lung	Cough	1 month	Ceftriaxone, TMP-SMX	Crozier et al. [5]
3	2015	55/F	Lung	Fever, haemoptysis	6 months	TMP-SMX, ceftriaxone	Abdel-Rahman et al. [11]
4	2016	52/F	Sclera	Right eye redness, pain, photophobia	4 weeks	TMP-SMX, amikacin, polymyxin	Gonzalez et al. [12]
5	2019	58/M	CNS	Headache, progressive right hemiparesis	6 months	Meropenem, amikacin, TMP-SMX	Solano-Varela et al. [13]
6	2020	68/M	CNS	Headache, vomiting, disturbance of consciousness	1 month	Meropenem, TMP-SMX	Tanaka et al. [14]
7	2020	57/F	Lung, CNS	Acute seizure		TMP-SMX	Roy et al. [15]
8	2021	58/M	Lung, CNS	Headaches, aphasia, lethargy	2 weeks	TMP-SMX, ceftriaxone	Diioia et al. [16]
9	2021	47/M	Lung	Lung mass identified on imaging	–	TMP-SMX, doxycycline	Raslan et al. [17]
10	2022	57/M	Adrenal gland	Abdominal pain, fevers, nausea, weight loss	1 month	Linezolid, TMP-SMX	Pender et al. [18]
11	2022	63/M	Lung, CNS	Dyspnea, cough, malaise	2 months	TMP-SMX, ceftriaxone/ doxycycline	Lam et al. [19]
12	2022	49/M	Lung	Cough, hemoptysis	2 months	TMP-SMZ, linezolid/ceftriaxone/minocycline	Li et al. [20]

CNS, central nervous system; F, female; M, male; TMP-SMX, trimethoprim-sulfamethoxazole.

cardia clinical isolates in the literature. Currently, only molecular analysis can accurately identify *Nocardia*at the species level. Molecular analysis mainly includes gene sequencing (16S rRNA, hsp65, secA1, gyrB, and rpoB), multilocus sequence analysis (MLSA), and Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) techniques. The 16SrRNA gene sequencing is the earliest and most widely used target fragment, which has good identification accuracy for common *Nocardia*. However, in some rare *Nocardia* species, accurate identification cannot be achieved due to the presence of multicopy of genes [21]. Compared with 16SrRNA, hsp65, secA1, gyrB, rpoB have higher gene sequence polymorphism, making them a good supplement for identifying rare and closely related *Nocardia* [22,23]. MLSA involves sequencing 3–5 of the above-mentioned genes and concatenating them together to construct a phylogenetic cluster, identifying strains based on their phylogenetic relationships, which has a higher resolution than sequencing a single gene [21]. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) may be a more rapid and cost-efficient test for *Nocardia* identification. It can accurately identify *Nocardia* species though hinges on the availability of a well-developed and validated database to compare isolate profiles [23].

N beijingensis was reported to be susceptible to imipenem, tobramycin, and kanamycin and could be differentiated from other major *Nocardia* species accordingly [4]. But to some other drugs, the susceptibility patterns of the isolate in this case and those reported in other studies [7,24] were different from each other. We believe it is essential to perform antimicrobial susceptibility testing for *Nocardia* isolated from clinically significant infections to guide clinicians in successfully select proper antimicrobials for treatment. The isolate in this case was susceptible to trimethoprim/sulfamethoxazole. Sulfonamides have been the antimicrobials of choice to treat nocardiosis. For initial treatment, dual coverage with trimethoprim/sulfamethoxazole and another agent are recommended until clinical improvement, and antimicrobial susceptibility is confirmed. For some severe infection cases, a combination of 2 or 3 antibiotics is also recommended. For patients allergic to sulfonamides, alternative antimicrobials may be used. We suggest that the selection of combination and alternative drugs should depend on the results of antimicrobial susceptibility testing. For example, moxifloxacin is recommended as one of the alternative antimicrobial agents with activity against *Nocardia*. However, the isolate in this case was resistant to it. Hence, moxifloxacin could not be used as a combination drug here.

According to previous studies, unlike other forms of nocardiosis, primary cutaneous and soft tissue nocardiosis usually develops in immunocompetent hosts.

While so far, all patients with abscesses caused by *N beijingensis* infection in the literature were immunocompromised because of HIV, systemic lupus erythematosus (SLE), or transplantation [25–30]. Few reports have related nocardiosis to misuse of antibiotics. The patient in this case was immunocompetent. Misuse of antibiotics might be responsible for persistent infection. Instead of frequently changing antibiotics, standardized sampling should be repeated to identify the pathogens first. For long-term infections without clear pathogens, the possibility of *Nocardiosis* should be considered. Nocardiosis is potentially fatal with a significant mortality rate in immunocompromised patients. For infection in immunocompetent patients, *Nocardia* also has a relapsing nature. Therefore, early recognition of the pathogen is impera-

tive for clinically successful treatment. Extrapulmonary nocardiosis often shows abscess formation, which resembles a pyogenic bacterial process or evolves in a chronic granulomatous or mixed progressive inflammatory mass. Such nonspecific symptoms always make nocardiosis diagnosis difficult. *Nocardia* is a slow-growing bacterium, which further increases the difficulty of its detection. In this case, the bacterial culture of the first secretion specimen yielded mixed growth of multiple bacteria while no significant growth of *Nocardia* was observed. We couldn't speculate how long the patient had suffered from *Nocardia* infection. A similar situation might happen before in the local hospital. If the sampling was performed after thorough disinfection, and the specimens were cultured long enough to detect *Nocardia* specifically, the pathogen would have been found earlier. The infection might not last for 6 years.

In conclusion, the present report highlights the necessity of long-term infected foci to be thoroughly examined to identify the pathogen. Missed detection or misuse of antibiotics may lead to *Nocardia* infection and poor therapeutic effect. *Nocardia* identification and antimicrobial susceptibility test are necessary for providing more valuable information for understanding the pathogen's the epidemiology, clinical significance, and treatment strategy.

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Author contributions

Conceived and designed the experiments: W.H.F., L.H.Q., J.L. Performed the experiments: L.H.Q., J.L., J.J.M. Collected and analyzed the data: L.H.Q., H.F.C., D.M.G. Contributed reagents/materials/analysis tools: J.X.X., L.X.Z. Wrote the paper: L.H.Q. All authors read and approved the final manuscript.

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None.

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.

Data available statement

Data archiving is not mandated, but data will be made available on reasonable request.

Ethics statement

Not applicable.

Informed consent

Not applicable.

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