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CASE REPORT

Diagnostic Challenges of *Nocardia beijingensis* Pneumonia: a Microbiological and Multidisciplinary Analysis in an Immunocompetent Patient

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ABSTRACT

Background: **Nocardia species are ubiquitously distributed in natural environments and typically cause opportunistic infections through inhalation into the respiratory tract or invasion of damaged skin or mucosal barriers. The clinical manifestations and imaging findings of Nocardia infections often lack specificity, which can lead to misdiagnosis or delayed diagnosis. However, etiological examinations (e.g., microbiological culture, PCR, or metagenomic sequencing) can facilitate accurate diagnosis and prompt therapeutic intervention.**
Methods: **In November 2024, a 74-year-old female presented with a cough and sputum production. Sputum and bronchoalveolar lavage fluid (BALF) samples were collected by the Department of Respiratory and Critical Care Medicine and subjected to Gram staining, modified acid-fast staining, and cultured on blood agar plates at a constant temperature of 35°C with 5% CO_2. Gram staining of sputum smears revealed Gram-positive bacilli with right-angle branching, which were also positive on modified acid-fast staining. After 48 hours of culture on blood agar, dry, white colonies were observed. Finally, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) identified the isolate as *Nocardia beijingensis* (*N. beijingensis*), which was further confirmed by targeted next-generation sequencing (tNGS).**
Results: **The patient was definitively diagnosed with Nocardia pneumonia and achieved complete recovery following antibiotic therapy. After hospitalization, the patient was treated with piperacillin sodium-tazobactam sodium (4.5 g, Q8h) combined with compound sulfamethoxazole (2 tablets, Q6h), along with adjunctive symptomatic and supportive management such as antitussive agents and gastric protection.**
Conclusions: **Nocardia pneumonia remains a clinical challenge due to its rarity and nonspecific symptoms. A systematic analysis of laboratory findings, definitive pathogen identification, and therapeutic interventions in this case offers valuable insights to improve diagnostic proficiency for Nocardia-related pulmonary infections and enhance patient prognosis.**
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KEYWORDS

Nocardia beijingensis, pneumonia, infection, modified acid-fast staining

INTRODUCTION

Nocardia, a genus of aerobic actinomycetes, is ubiquitously distributed in natural environments, particularly in water and soil [1]. These microorganisms can cause localized or disseminated infections in humans [2,3]. Notably, Nocardia infections predominantly affect immunocompromised individuals, but immunocompetent hosts may also develop infections, albeit less frequently [4,5]. This phenomenon warrants particular clinical attention, as delayed diagnosis in immunocompetent patients often leads to poorer outcomes due to atypical presentations. Pulmonary nocardiosis exhibits the most prevalent clinical manifestations, which include persistent fever, production of purulent sputum, progressive dyspnea, and pleuritic chest pain [2,6,7]. However, these clinical manifestations lack distinctive specificity when compared with other infectious diseases such as tuberculosis or bacterial infections, posing significant diagnostic challenges in clinical practice [8]. To augment the existing evidence on *N. beijingensis* pathogenicity, this study presents a clinically confirmed case of pulmonary nocardiosis treated at the Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Guilin Medical University in November 2024. This case highlights the importance of analyzing laboratory diagnostic methods to improve detection and clinical understanding of this rare infection.

CASE PRESENTATION

Clinical features

A 74-year-old Asian female was admitted to the hospital with a 3-month history of progressively worsening shortness of breath, cough, and sputum. The patient presented with progressive dyspnea following physical exertion, accompanied by a paroxysmal cough that is more prominent in the morning and produces small amounts of white mucoid sputum. Blood is occasionally observed in the sputum, episodes of paroxysmal headaches, and dizziness when the patient breathes or coughs. She denied chest tightness, chest pain, or fever. The patient had a history of chronic gastritis and cataract but no known hypertension, diabetes mellitus, coronary artery disease, hepatitis, and tuberculosis. She denied any tobacco or alcohol use. Her family history showed no notable genetic disease. She came to The First Affiliated Hospital of Guilin Medical University (Guangxi province, China) for medical consultation and treatment. After admission, the patient's initial vital signs were as follows: blood pressure, 118/61 mmHg; heart rate, 71 beats/minute; respiratory rate, 20 breaths/minute; body temperature, 36.3°C.

Laboratory examinations

Laboratory findings are shown in Table 1. The patient's elevated white blood cell count, elevated fibrinogen, elevated D-dimer, decreased albumin, elevated globulin, a reduced albumin-to-globulin ratio, and elevated ultrasensitive C-reactive protein. Electrolytes, lactate, interleukin 6, and cardiac enzymes were within normal limits. These abnormalities suggest an active infection (potentially bacterial in origin) or inflammatory triggers, along with systemic inflammation involving both acute-phase responses and chronic inflammatory pathways.

Imaging examination

High-resolution computed tomography (HRCT) from the hospital showed a partial solid nodule and was identified in the posterior basal segment of the left lower lobe (Lung-RADS Category 4) (Figure 1). Bilateral pulmonary inflammation was observed, characterized by mild dilation and infection of multiple bronchi in both lungs, along with evidence of mucus plug formation in some bronchi. A small amount of pericardial effusion was observed. Short-term follow-up or consultation with a thoracic surgeon is recommended post-treatment. Combined with the patient's elevated inflammatory indexes and chest CT manifestations suggestive of pulmonary infection, due to suspected typical bacterial pneumonia, the physician empirically administered piperacillin sodium tazobactam sodium 4.5 g Q8h for anti-infective treatment, and recommended further sputum smears, sputum cultures, and other etiological examination for diagnostic clarification, and promptly adjusted the treatment plan according to the results.

The distribution of pulmonary vessels in both lungs was regular, and multiple bronchial dilatation with wall thickening was seen in both lungs, surrounded by multiple patchy and flaky hyperdense shadows with fuzzy margins, and some bronchial tubes seemed to be filled with hyperdense shadows. The posterior basal segment of the lower lobe of the left lung showed a partially solid nodular shadow, with a size of about 12 mm x 12 mm, with signs of lobulation, burr, pleural depression, and thin-walled central vacuole. The trachea and bronchi were patent, and no enlarged lymph node shadows were seen in the hilum or mediastinum.

Etiological examination

A deep sputum specimen was collected from the patient and subjected to etiological examination. Gram staining of the smear revealed Gram-positive bacilli arranged in right-angled branching structures under microscopy (Figure 2A). Acid-fast staining (Figure 2B) yielded negative results, while weak acid-fast staining demonstrated red-stained bacilli (Figure 2C). Deep sputum specimens from the patient were aseptically inoculated onto blood agar plates, chocolate agar plates, and Mac Conkey agar plates using a sterile inoculation loop. The cultures were incubated at 35°C under 5% CO_2 condi-

Table 1. Abnormal laboratory indicators in the patient.

Laboratory indicators	Measurements	Reference range
White blood cell count	11.640 x 10^9/L	3.5 - 9.5 x 10^9/L
Fibrinogen	4.59 g/L	2.0 - 4.0 g/L
D-dimer	0.62 μg/mL	< 0.5 μg/mL
Albumin	39.00 g/L	40 - 55.00 g/L
Globulin	42.10 g/L	20 - 40 g/L
Albumin-to-globulin ratio	0.93 ratio	1.2 - 2.4 ratio
Ultrasensitive C-reactive protein	8.82 mg/L	0 - 3 mg/L

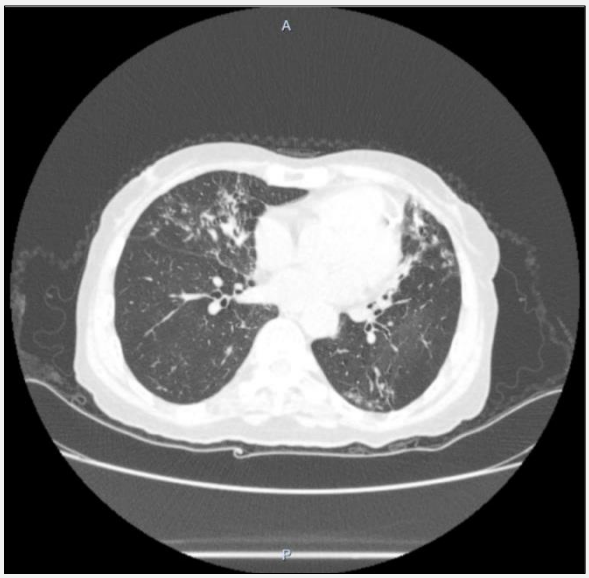

Figure 1. HRCT scan of the chest.

tions. Following 48 hours of incubation, white, dry surface colonies were observed on the blood agar plates (Figure 2D). Subsequent analysis of the sputum identified *N. beijingensis* through culture. Meanwhile, the same bacteria were also identified from the bronchoalveolar lavage fluid (BALF) in the patient. Further confirmation was achieved through tNGS, where the results showed that it was *Nocardia* with a sequence number of 23495, corroborating the microbiological diagnosis.

Treatment and outcome

The doctor adjusted the medication regimen and continued to give piperacillin sodium, tazolol Bactam sodium 4.5 g Q8h for anti-infection, and added compound Sulfamethoxazole 96 mg Q6h for Nocardia infection. After a period of treatment, the patient improved and was discharged from the hospital. After discharge, the patient should continue to take two tablets of compound sulfamethoxazole every six hours. During the treatment period, blood count, liver function and kidney function indicators should be checked weekly and the treatment plan evaluated based on the results and the patient's condition. One month after discharge, the patient should return to our outpatient clinic for a chest CT scan to assess lung function and adjust the medication if necessary.

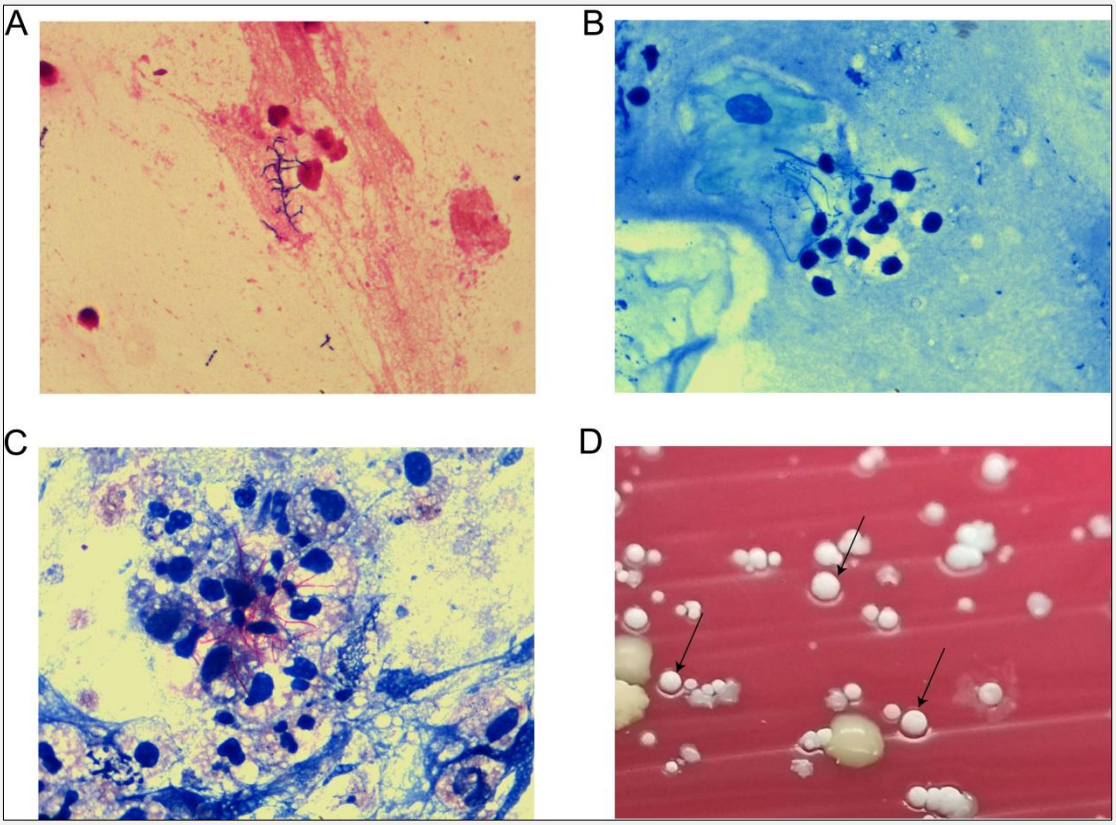

Figure 2. Sputum specimen status, smear, and cultured colony morphology.

A: Gram-stained sputum smear (oil, 100 x). B: Acid-fast stained sputum smear (oil, 100 x). C: Modified acid-fast stained sputum smear (oil, 100 x). D: Colony morphology on blood agar after 48 hours of sputum culture (Black arrows suggest colony morphology of suspected *Nocardia spp.*).

DISCUSSION

Currently, Nocardia species have been identified, of which 54 have been identified as clinically important pathogens [9]. In 2001, researchers first isolated *N. beijingensis* from soil samples in Beijing, China. Pulmonary infection represents the most common clinical manifestation, where the pathogen enters the respiratory tract and causes pulmonary nocardiosis [10]. Typically, Nocardia infections predominantly affect immunocompromised individuals. Current evidence has identified diabetes mellitus, HIV infection, autoimmune diseases, and smoking as established risk factors for *N. Beijingensis* infections [6]. The diagnostic challenge lies in the nonspecific clinical presentation and radiographic features. This diagnostic ambiguity frequently leads to delayed antimicrobial therapy.

In the present study, etiological identification confirmed that the pulmonary infections were caused by *N. beijingensis*. The patient in this case was immunocompetent, with no prior history of immunosuppressive medication use or underlying immunodeficiency disorders. The accurate microbiological diagnosis was achieved through an integrated approach utilizing sputum smear microscopy, culture techniques, MALDI-TOF MS, and tNGS. These findings underscore the critical role of etiological diagnostic methods in differentiating nocardiosis from more prevalent pulmonary infections, such as tuberculosis or bacterial pneumonia.

The diagnosis of Nocardia infections typically requires isolation and identification of the pathogen from clinical specimens, such as sputum or BALF. Gram staining and modified acid-fast staining play a pivotal role in providing rapid preliminary diagnostic clues during the critical window period [4,11]. These staining techniques demonstrate particular diagnostic value in differentiating Nocardia from morphologically similar microorganisms, including Actinomyces (Gram-positive but non-

acid-fast) and Mycobacterium (acid-fast but with distinct staining characteristics). However, it must be emphasized that microbiological culture remains the gold standard for definitive identification. In a study by Xin Hong [12] et al. investigating Nocardia, it was reported that acid-fast branching filamentous bacteria and Gram-positive branching bacilli were observed in the BALF. Following a 3-day incubation of the patient's BALF specimen on blood agar plates, characteristic white, waxy, and wrinkled colonies were successfully cultured. In the present case, similar phenomena were observed in our experiments, which are consistent with those described in previous literature on Nocardia spp. Gram staining, acid-fast staining, and modified acid-fast staining were performed on direct smears before culture isolation. Microscopic examination revealed filamentous, branching Gram-positive bacilli with partial acid-fast properties, demonstrating morphological features highly suggestive of Nocardia species [13]. Primary isolation on Columbia blood agar demonstrated no visible growth at 24 hours, with small, slow-growing colonies becoming apparent only after 48 hours of incubation. This observation aligns with well-documented characteristics of Nocardia species, which frequently exhibit delayed primary growth on conventional media [11]. It fully demonstrates the significant diagnostic value of combined staining techniques in early clinical decision-making. Notably, the slow growth kinetics and frequent overgrowth by commensal flora in respiratory specimens contribute to significant underdetection rates in routine sputum cultures. Given these diagnostic challenges, clinicians should maintain a high index of suspicion for Nocardia infection (particularly *N. beijingensis*) in patients with compatible clinical manifestations and radiographic findings [14]. To improve detection sensitivity, we recommend extending the incubation period to at least 5 - 7 days for suspected cases, with careful daily examination for subtle colonial growth. The most commonly used methods for identifying Nocardia currently include MALDI-TOF MS and gene sequencing technology [15]. This method is simple to operate, fast, accurate, and has been widely applied. This case observed morphological characteristics highly suggestive of Nocardia through staining techniques under a microscope. This preliminary finding was subsequently confirmed as *N. beijingensis* through culture-based identification combined with MALDI-TOF MS, definitively establishing the taxonomic classification of the pathogen. Microbial cultivation can not only help to conduct a comprehensive analysis of microbial characteristics but also allows for antimicrobial susceptibility testing. The Clinical and Laboratory Standards Institute (CLSI) has formally approved a standardized protocol for antimicrobial susceptibility testing (AST) of Nocardia ssp. specifying broth microdilution as the reference method (CLSI document M24, 3rd edition) [6]. Notably, the CLSI guidelines emphasize testing key agents, including trimethoprim-sulfamethoxazole, amikacin, and linezolid-drugs with clinically proven efficacy against invasive nocardiosis. For infections caused by Nocardia, the choice of treatment plan needs to comprehensively consider the severity of the infection, whether the infection has spread, the host's immune status, potential drug interactions and toxicity, as well as the specific species of Nocardia. Sulfonamide drugs are typically the first-line treatment option for nocardiosis, but emerging surveillance data reveal a concerning trend of increasing resistance rates among Nocardia isolates. Recent multicenter studies demonstrate resistance to sulfonamides in some clinically significant strains, correlating with rising case detection rates and prior antimicrobial exposure [16,17]. In the present case, following a confirmed diagnosis of *N. beijingensis*-induced pneumonia, supported by comprehensive clinical evaluation (including radiographic findings, microbiological assays, and symptomatology), the therapeutic regimen was adjusted to target nocardial infection, with compound sulfamethoxazole tablets administered at 0.96 g Q6h. Integrating the aforementioned findings, advice for doctors to consider when formulating treatment guidelines, for non-severe infection patients with normal immune function, it is recommended to use sulfonamide drugs for treatment; for severe infection patients, it is suggested to empirically use a combination of antibiotics for treatment.

CONCLUSION

In summary, Nocardia infections present with non-specific clinical and radiographic manifestations. When evaluating patients with unexplained pulmonary infections, clinicians should pursue comprehensive pathogen detection strategies, extended culture duration and combined staining techniques should be standard in suspected atypical pneumonia with negative initial cultures. Based on this case report, we hope to raise awareness of nocardiosis within the medical community, thereby reducing the rate of misdiagnosis and improving patient outcomes.

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Informed Consent Statement:
Written informed consent for the publication of this case report, images, and all information was obtained from the patient. A copy of the written consent is available for review by the editor of this journal upon request.

Declarations of Interest:
All authors declare to have no conflict of interest.

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