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Case Report

Metagenomic next-generation sequencing for diagnosis of severe pneumonia caused by *Nocardia otitidiscaviarum*

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Abstract

Introduction: *Nocardia spp.* are Gram-positive, aerobic actinomycetes, which can cause pulmonary, primary cutaneous, and lymphocutaneous infections. However, severe pneumonia caused by *Nocardia otitidiscaviarum* has rare reported.

Patient concerns: In this case report, a 73-year-old female presented with a 7-day history of fever, cough, followed by a 1-day history of dyspnea. Both lungs showed patchy shadows on a chest CT scan. Bronchoalveolar lavage and mNGS were performed for the rapid diagnosis of the *Nocardia otitidiscaviarum* induced infection.

Diagnosis: Community-acquired pneumonia was diagnosed following clinical assessment, including characteristic physical examination findings, abnormal laboratory results, and consolidations observed on CT imaging. And the evidence of pathogen was supplied by mNGS.

Interventions: The anti-infection therapy regimen was: trimethoprim-sulfamethoxazole (1.44 g q6h) for 3 months according to the detection of the *Nocardia otitidiscaviarum.*

Outcomes: After 3 months of follow-up, the patient has a good outcome and chest CT suggested that the inflammation in the lungs had been almost absorbed.

Conclusions: Rapid pathogen identification is pivotal for enhancing clinical outcomes and survival in severe pneumonia patients. This case report presents an exceptional case of severe pneumonia caused by *Nocardia otitidiscaviarum* and the uncommon potential occurrence of human-to-human transmission. mNGS could help avoid misdiagnosis and mistreatment in clinical practice.

Key words: Atypital pneumonia; *Nocardia otitidiscaviarum*; nocardiosis; metagenomic next-generation sequencing; case report.

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Introduction

Community-acquired pneumonia is a major healthcare problem, affecting millions of people in different countries each year, and severe CAP is a common cause for Intensive Care Unit (ICU) admission. Despite the remarkable development in rapid diagnostic techniques, innovative therapeutic approaches, and strategic vaccination initiatives, severe CAP remains a leading cause of mortality from infectious diseases globally.

Accurate pathogen identification and prompt antimicrobial therapy are pivotal for enhancing clinical outcomes and survival in severe pneumonia patients. Despite the implementation of comprehensive diagnostic methodologies, the detection rate of pathogens in pneumonia patients remains sub-optimal, which resulted in delayed and inadequate treatment, extended hospital stays, and heightened mortality rates. Compared with the traditional microbiological assays, such as culture techniques, polymerase chain reaction tests, and enzyme immunoassay, metagenomic next-generation sequencing has advantages in high-throughput processing, swift pathogen detection, improved diagnostic accuracy, and the capacity to track antimicrobial resistance in infectious diseases [1].

Nocardia spp. are Gram-positive, aerobic actinomycetes known for decomposing organic matter in soil, and they are commonly found in soil, air, and water [2,3]. *Nocardia* infections are more commonly acquired through environmental exposure. Inhalation of aerosolized spores or mycelia can cause respiratory infections, manifesting as fever, cough, and expectoration. *Nocardia* infections can also manifest as primary skin infections, typically arising from traumatic injuries or surgical wounds. However, human-to-human transmission of *Nocardia spp.* was rarely reported. The precise incidence of nocardiosis is not well-established in the current literature. The estimated annual cases range from 500 to 1,000 in the United States [4,5]. In China, a total of 441 cases were

documented between 2009 and 2021, indicating an escalating trend in morbidity during the initial decade. Therefore, *Nocardia spp.* are often overlooked and not immediately considered during the etiological examination of pneumonia. The difficulty in early identification frequently leads to missed opportunities for timely and appropriate treatment, resulting in the potential for disease progression and worsening outcomes. mNGS is particularly advantageous in diagnosing rare, novel, and atypical etiologies of complicated infectious diseases, such as *Nocardia spp.*, thereby enabling a more precise clinical management. Given the limitations of traditional diagnostic methods and the potential for mNGS to improve diagnostic accuracy, it is crucial to explore its application in cases involving less common pathogens such as *Nocardia spp.*, which can cause severe pneumonia and pose unique diagnostic and therapeutic challenges.

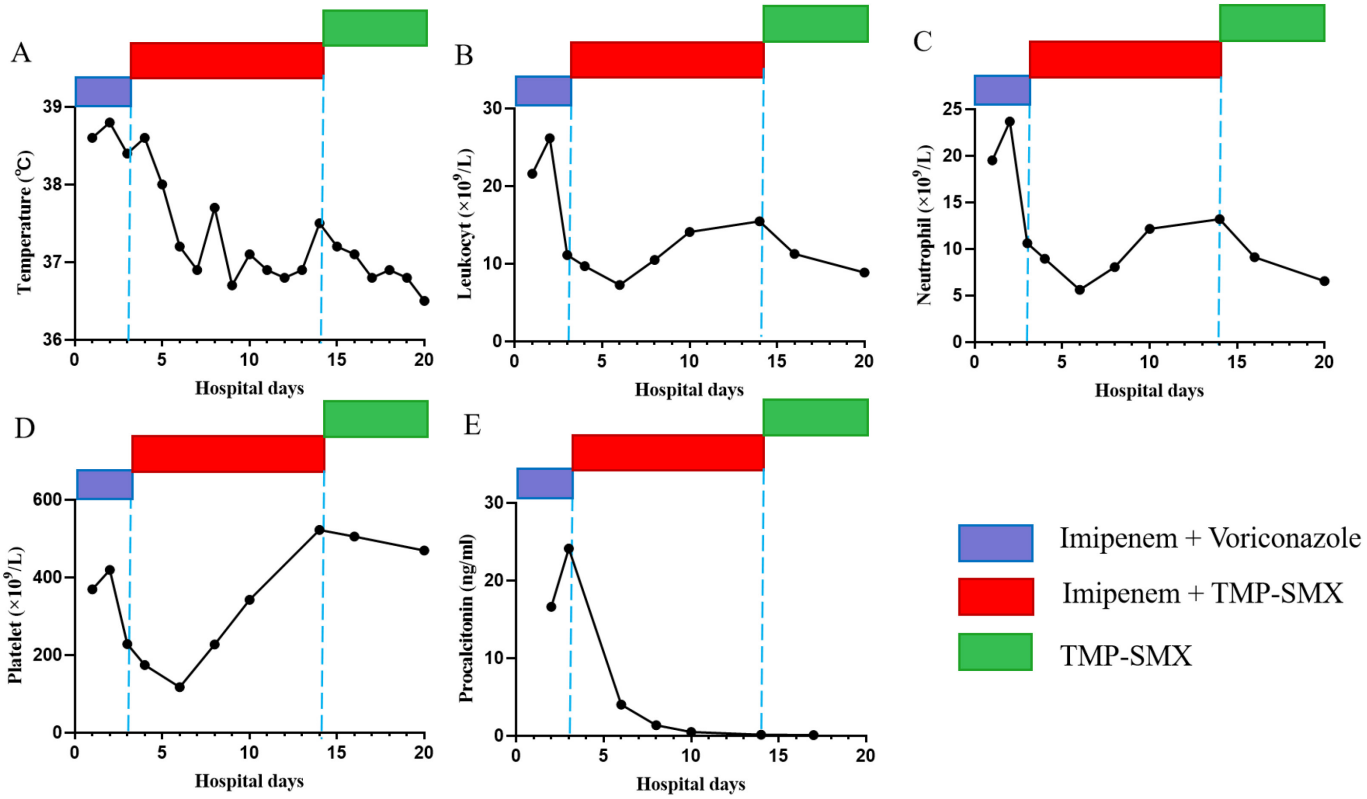
Among the various *Nocardia spp.*, *Nocardia otitidiscaviarum* is relatively rare, accounting for 3%-5.9% of cases [6,7]. This case report presents an exceptional case of severe pneumonia caused by *Nocardia otitidiscaviarum*, hinting at the possibility of human-to-human transmission. The uniqueness of this case report lies in its documentation of a rare case of severe pneumonia caused by *Nocardia otitidiscaviarum* and the uncommon occurrence of human-to-human transmission. Additionally, this case report further underscores the significant advantages and promising prospects of mNGS in the early identification of *Nocardia* pneumonia infections.

Case presentation

A 73-year-old female presented to our emergency department with a 7-day history of fever, cough, followed by a 1-day history of dyspnea. She was treated with moxifloxacin (0.4 g/d) for 4 days in a local hospital, but the symptoms progressively aggravated and she was then sent to the ICU of our hospital, where the initial vital signs were observed as follows: blood pressure, 156/74 mmHg; heart rate, 128 bpm; respiratory rate, 32 bpm; body temperature, 38.6 ℃; and blood oxygen saturation, 93% on high-flow nasal oxygen therapy (HFNO) with a flow rate of 50 L/min and a fractional inspired oxygen (FiO_2) of 60%. An arterial blood gas analysis indicated a pH of 7.28, partial pressure of carbon dioxide ($PaCO_2$) of 43.6mmHg, partial pressure of oxygen (PaO_2) of 80.3 mmHg, an actual bicarbonate level of 4 mmol/L, and a standard bicarbonate level of 7.9 mmol/L (FiO_2 60%). Further physical examination revealed moist rales in both lungs on auscultation.

Given her advanced age and multiple comorbidities, including type 2 diabetes mellitus,

Figure 1. Dynamic changes in the infection indexes of the patient after admission.



hypertension, and a history of cerebral infarction (with no residual neurological deficits), she had been largely confined to her residence and had limited external exposure. The patient disclosed that a close household contact had manifested comparable respiratory symptoms over a 10-day period preceding her presentation, providing epidemiological evidence of a potential human-to-human transmission event. The family member exhibited pyrexia (38.5 °C), persistent dry cough, and exertional dyspnea, with no cutaneous abscesses observed. The symptoms gradually ameliorated over a two-week period without medical treatment. However, additional clinical information and detailed medical history are lacking.

For her epidemic history, the emergency physician immediately prescribed throat swab test for influenza A, influenza B, and COVID-19; however, the results of nucleic acid tests were negative after only 2 hours. Routine laboratory tests showed white blood cell (WBC) of 21.59 × 10^9/L, neutrophil percentage of 90.5%, platelet count of 369 × 10^9/L, C-reactive protein of 479 mg/L, erythrocyte sedimentation rate of 85 mm/H, creatinine of 89 μmol/L, alanine aminotransferase of 16 U/L, aspartate aminotransferase of 15 U/L, lactic acid of 2.3 mmol/L (Figure 1). Subsequently, the patient underwent a chest computed tomography (CT) scan, showing diffuse nodules, mass shadow, and halo sign, especially in the middle and lower lobes of the bilateral lungs (Figure 2A). Based on the findings from the physical examination, laboratory analyses, and CT imaging, a diagnosis of community-acquired pneumonia was established. Given the high CRP and WBC count, a diagnosis of bacterial infection was initially suspected, but the CT images showed lesions suspicious for fungal infection. Sputum smears, sputum cultures and blood cultures were performed before medical treatment, and eventually imipenem-cilastatin (0.5 g q6h) and voriconzale (0.4 g qd) were selected as the antibiotics for empirical antibacterial treatment, for it was difficult to judge whether the pathogen was a Gram-positive or Gram-negative bacterium or fungus.

On the second day of admission, the patient's clinical condition aggravated and she presented with diabetic ketoacidosis (DKA). Arterial blood gas analysis indicated a pH of 7.08, $PaCO_2$ of 16.3 mmHg, PaO_2 of 130.6 mmHg, blood oxygen saturation of 91% (HFNO with a flow of 50 L/min, FiO_2 60%), an actual bicarbonate level of 4.8 mmol/L, and a standard bicarbonate level of 7.5 mmol/L. Additional laboratory findings included WBC of 26.16 × 10^9/L, neutrophil percentage of 90.6%, procalcitonin of 16.6 ng/L, blood glucose of 23.1 mmol/L, urine glucose of 56 mmol/L, and urine ketone of 15 mmol/L. After rehydration, correction of acidosis, and insulin pump-injection, DKA-related performance improved slightly. To expedite the diagnosis, control the primary infection, and prevent the further deterioration of the condition, bronchoalveolar lavage and mNGS were performed for the rapid diagnosis of the pathogen. One day later, mNGS revealed the relative abundance of *Nocardia otitidiscaviarum* was 99.8092%, with the sequence number was 148900; *Candida albicans*, the sequence number being only 549. No other pathogens or antimicrobial resistance gene was detected (Table 1).

Although the sample test result was positive for *Candida albicans*, it was considered a contamination because of the low count. Therefore, voriconazole was switched to imipenem-cilastatin (0.5 g q6h) and trimethoprim-sulfamethoxazole (TMP-SMX, 1.44 g q6h) for infection control. On day 7 of admission, the patient's condition improved significantly and the patient was transferred from the ICU to the emergency ward. On day 12 after admission, bacterial cultures remained negative. Imipenem-cilastatin was discontinued on day 14 of admission, and the TMP-SMX dosage was adjusted to 1.44 g, q12h. Finally, her infection-related lab tests returned to normal and CT scans demonstrated absorption of the pulmonary pathological changes, and she was discharged on day 20 of admission.

Long-term follow-up is currently in progress to monitor changes in the lung lesion of the patient. At one-month follow-up, the patient rejected the use of TMP-SMX because of adverse effects of nausea and decreased appetite. The chest CT images revealed obvious inflammation absorption (Figure 2C). At 3-month follow-up, the patient exhibited no apparent lung symptoms and CT scans indicated that exudation was almost absorbed (Figure 2D).

Table 1. Metagenomic next-generation sequencing analysis of bronchoalveolar lavage fluid.

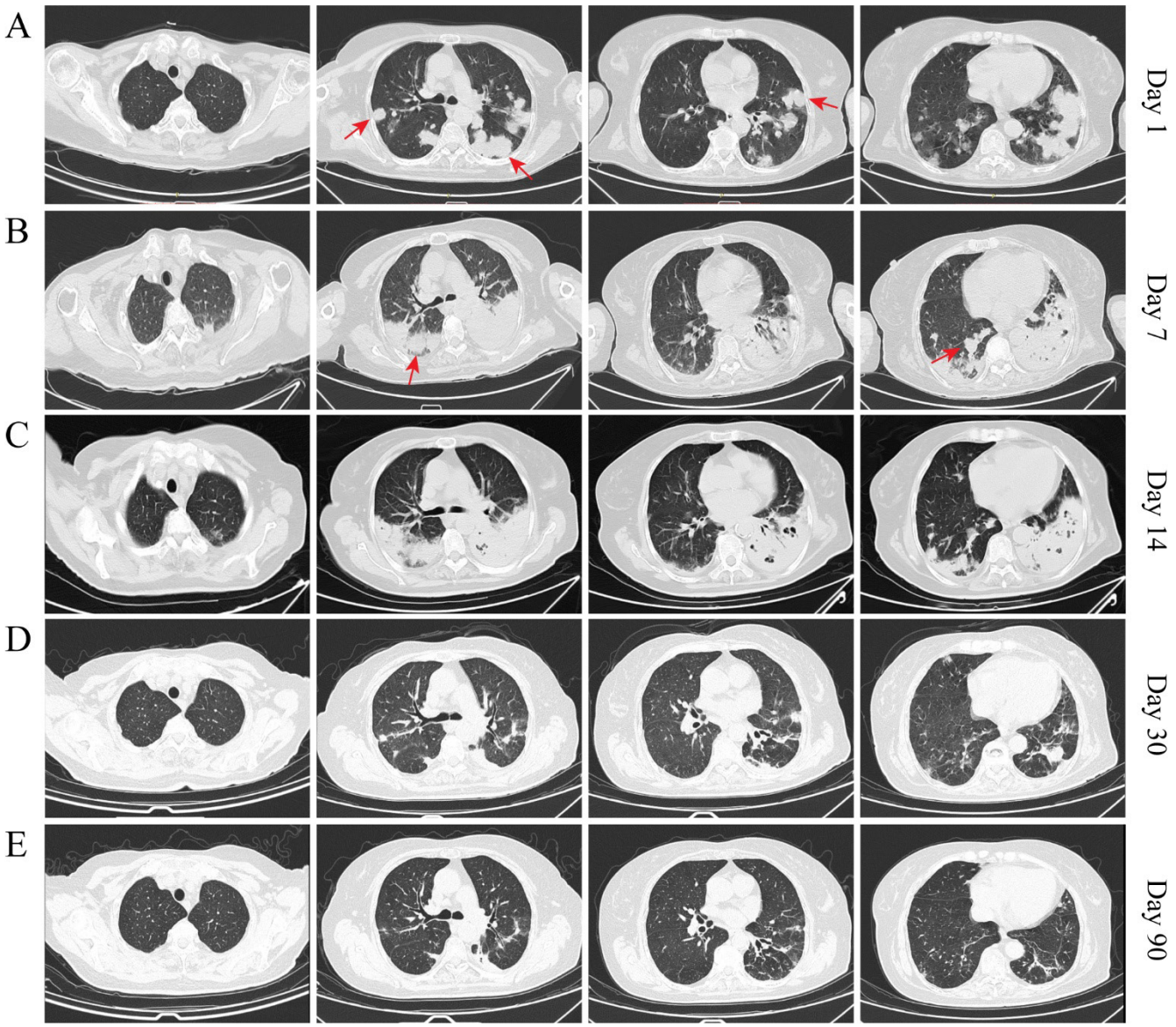
Type	Latin name	Sequence Number	Relative abundance
G^+ bacteria	*Nocardia otitidiscaviarum*	148900	99.8092%
Fungus	*Candida albicans*	549	100%

Sequence number: higher sequence number typically indicates a greater abundance of the microorganism in the sample, while a lower read count may suggest a lower abundance or fewer detected sequences. Relative Abundance: proportion of sequences of a particular microbial species within a corresponding major category of species (typically divided into four major categories: bacteria, fungi, viruses, and parasites) after the removal of host sequences. A higher proportion indicates a greater dominance of that microorganism, and thus a relatively higher likelihood of pathogenicity.

Discussion and conclusions

This case report documents an instance of severe pneumonia attributable to *Nocardia otitidiscaviarum* infection. As saprophytic microorganisms, *Nocardia spp.* are pervasive in the environment, with an estimated 60% of infection cases occurring in immunocompromised hosts. However, the patient reported herein was immunocompetent with negative HIV antibody and TSPOT test results, and there was no history of immunosuppressive medication use. *Nocardia spp*. are transmitted in two dominant ways: cutaneous infections from contaminated soil and pulmonary infection from inhalation of aerosolized spores or mycelia [8,9]. Primary cutaneous infections may present as a spectrum of manifestations, including superficial, lymphocutaneous, ulcers, cellulitis, and abscesses, which can disseminate systemically to cause systemic nocardiosis. Primary pulmonary nocardiosis typically presents with symptoms such as cough, fever, and dyspnea, accompanied by clinical signs like elevated CRP and leukocytosis. Radiographic tests often reveal nonspecific findings such as one or more lung nodules, cavitation, or lobar consolidation [10,11]. Differential diagnoses for pulmonary nocardiosis include tuberculosis, various fungal and bacterial infections, sarcoidosis, and malignancy. Studies have shown that CT manifestation of multiple nodules in bilateral lungs accounts for about 13.8%, which is hard to be differentiated from fungal infection and malignancy [10]. The CT manifestations in this patient

Figure 2 A. Serial chest CT scans on day 1; **B.** day 7; and **C.** day 14 after admission, and subsequent follow-up images at **D.** 1 month; and **E.** 3 months post-discharge. Arrows indicate diffuse nodules, mass shadow, and halo sign.



were presented as diffuse nodules which were suspected as being caused by fungal infection, and therefore voriconazole was used. Although inhalation of aerosolized spores or mycelia may cause pulmonary nocardiosis, human-to-human transmission is rarely to be reported [4]. Due to her advanced age, the patient had been housebound for a long time, without any external engagement. Her similar symptoms were closely followed by her inmate family member, who had the same symptoms as the patient. These findings raised suspicion for person-to-person transmission of pulmonary nocardiosis in this case. Notwithstanding the absence of definitive evidence for human-to-human transmission—which attenuates the conclusiveness of our epidemiological linkage—this investigation provides novel insights into *Nocardia otitidiscaviarum* potential transmissibility, thereby advancing surveillance framework of Nocardiosis in the future. To our knowledge, this constitutes the first documented hypothesis of possible interpersonal dissemination in *Nocardia otitidiscaviarum* infections. Due to limitations in methods and patient privacy concerns, we were unable to further investigate, including sampling the patient's living environment for the presence of *Nocardia otitidiscaviarum*, the possibility of aerosol transmission, and ruling out transmission through water or food. We should also track the condition of the patient's relatives, test their respiratory-related specimens, and if *Nocardia otitidiscaviarum* is detected, conduct further sequencing to prove the homology of the pathogens between the two patients.

If the primary infection is not under good control, *Nocardia otitidiscaviarum* can disseminate anywhere in the body including skin, lungs, central nervous system, kidney, and heart. Studies have shown that the crude mortality rate for pulmonary nocardiosis is about 55.4%, and patients presenting with bacteremia reached a mortality rate ranging from 40% to 85% [4,10]. Prolonged latency in diagnosis is associated with adverse clinical outcomes and higher mortality. mNGS has been used increasingly in infectious diseases in recent decades due to its fast and accurate detection, as well as its high throughput. It has been documented that the average turnaround time for conventional culture methods is approximately 7.5 ± 1.92 days, which is significantly longer than the 48h of the mNGS group [12]. In our case, routine culture methods failed to detect the infection of *Nocardia otitidiscaviarum*, whereas mNGS found the evidence of *Nocardia otitidiscaviarum* only in one day. This earlier diagnosis facilitated the implementation of an evidence-based treatment regimen and avoided endotracheal intubation in this patient. The decision to withdraw broad-spectrum Gram-positive/Gram-negative and antifungal therapy in this case averted potential antibiotic-induced adverse events. In addition, given the rarity of pulmonary nocardiosis in CAP and the nonspecific nature of its clinical signs, the advantage of mNGS in detecting rare and atypical bacteria brings patients more benefits, enhancing the precision of treatment and patient outcomes [13].

In our case, *Nocardia otitidiscaviarum* consistently exhibited resistance to moxifloxacin, a finding supported by other case reports, and conversely, it showed sensitivity to imipenem [4,14]. Laboratory tests showed that WBC count in our case was markedly decreased on day 3 of imipenem administration before the application of TMP-SMX and bronchoalveolar lavage. Although no standard treatment for nocardiosis is recommended currently, TMP-SMX is a first line therapy with a low resistance rate [15]. In severe cases, empiric multi-drug therapy is recommended, and the treatment for pulmonary infections should last between 6 and 12 months [16]. Laboratory susceptibility testing is crucial for guiding appropriate antimicrobial therapy, though it is often time-consuming, leading to potential delays in optimal treatment initiation.

A comprehensive long-term follow-up was conducted for the patient. The patient was in a good condition when she was discharged after 20-day hospitalization. However, she experienced nausea and decreased appetite one month after oral administration of TMP-SMZ, and therefore rejected medical advice. Nevertheless, we still persuaded her to undergo regular CT re-examination and seek medical advice in time if uncomfortable symptoms occurred after discharge. Three months later, her CT scans showed that the exudation was almost absorbed. Considering patient’s compliance and the quite long time in treatment duration, we should have patience to take time for communication and use specialized knowledge to tell patients the importance of complying with medication regimen. Adverse reactions to certain medications can be alleviated through symptomatic treatment, thereby enhancing patient compliance. *Nocardia* spp. colonized in the respiratory tract is reported in many asymptomatic patients, especially in patients with lung diseases, such as cystic fibrosis. Hence, in addition to chest CT, special importance should be given to pathogen detection, which can give more solid evidence to the therapy recommendation. Currently, there are no commercially available detection kits for *Nocardia*, such as qPCR. However, some literature has reported specific sequences for the detection of *Nocardia*.

In summary, diagnosis and treatment of rare and atypical pathogens are usually difficult, especially when empiric therapy is inefficient. In our patient, the clinical signs and auxiliary examination of pneumonia caused by *Nocardia otitidiscaviarum* are nonspecific, making differential diagnosis difficult. Therefore, mNGS technology was applied for etiological detection, which is faster and more accurate than the conventional lab tests. Quick pathogen identification by mNGS helped us make correct treatment. Interestingly, the source and transmission route of such infections remain subjects for further investigation. Further discussion is required regarding the optimal duration of the subsequent treatment regimen that should be maintained.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, further inquiries can be directed to the corresponding authors.

Ethical approval and consent to participate

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article. The authors would like to thank the patient involved in this article.

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Author Contributions

SW and XZ collected and analyzed the data and wrote the manuscript. YL and MW designed the study and revised the manuscript. All authors have reviewed and approved the final manuscript.

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Conflict of interests

No conflict of interests is declared.

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