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# Successful treatment of disseminated nocardiosis diagnosed by metagenomic next-generation sequencing

A case report and literature review

Ting Li, Yi-Xin Chen, Jia-Jia Lin, Wei-Xian Lin, Wei-Zhen Zhang, Hang-Ming Dong, Shao-Xi Cai, YING MENG

**Abstract**

BACKGROUND

*Nocardia paucivorans* is an infrequently found bacterium with the potential to cause severe infection, with a predilection for the central nervous system, both in immunocompromised and immunocompetent individuals. Rapid etiological diagnosis of nocardiosis can facilitate timely and rational antimicrobial treatment. Metagenomic next-generation sequencing (mNGS) can improve the rate and reduce the turnaround time for the detection of *Nocardia*.

CASE SUMMARY

A 49-year-old man was admitted to hospital with cough and hemoptysis. Imaging revealed pulmonary consolidation as well as multiple brain lesions. *Nocardia asiatica* and *Nocardia beijingensis* were rapidly detected by mNGS of bronchoalveolar lavage fluid (BALF) while bacterial culture of BALF and pathological biopsy of lung tissue were negative. In early stages, he was treated with trimethoprim–sulfamethoxazole (TMP-SMZ) and linezolid by the implementation of individual dose adjustment based on serum concentrations and the adverse effects of thrombocytopenia and leukopenia. The treatment was replaced by TMP-SMZ and ceftriaxone or minocycline. He was treated with 8 mo of parenteral and/or oral antibiotics with resolution of pulmonary and brain lesions on repeat imaging revealed in a clear clinical improvement.

CONCLUSION

mNGS provided fast and precise pathogen detection of *Nocardia.* In disseminated nocardiosis, Linezolid is an important alternative that can give a better outcome with the monitoring of linezolid serum concentrations and platelet count.

**Key Words:** Disseminated nocardiosis; Metagenomic next-generation sequencing; Linezolid; Thrombocytopenia; Case report; Literature review

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**Core Tip:** Early detection of *Nocardia paucivorans* can optimize antibiotic management, shorten hospital stays and improve survival rates. We report rapid detection of *N. paucivorans* by metagenomic next-generation sequencing (mNGS) of BALF. The patient was treated with trimethoprim–sulfamethoxazole (TMP-SMZ) and linezolid by implementation of individual dose adjustment based on serum concentration and thrombocytopenia and leukopenia, then replaced by TMP-SMZ and ceftriaxone or minocycline. This case suggests that mNGS is a convenient and efficient technique for detecting *Nocardia*, especially suitable for rare, novel and atypical etiologies of complicated infectious diseases. Linezolid may be an important alternative in disseminated nocardiosis.

## INTRODUCTION

*Nocardia paucivorans* is a Gram-positive aerobic bacterium of the order Actinomycetales and has become an increasingly important opportunistic pathogen, mostly in immunocompromised individuals[1]. It causes a wide range spectrum of illness, include pneumonia, cutaneous or subcutaneous infections, brain or other solid organ abscesses, thus resulting in high mortalitys[2]. Early detection of *N. paucivorans* can optimize antibiotic management, shorten hospital stays, improve survival rates and reduce medical costs. Delaying diagnosis may impede targeted therapies and lead to poor prognosis. However, the definitive diagnosis of nocardiosis still depends on the isolation and identification of organisms from the infected site, which may take days to weeks and the positive rates of these methods are very low. As these methods cannot meet the current demand for rapid and accurate diagnosis, metagenome next generation sequencing (mngs) came into being[3].mNGS also known as shotgun deep-sequencing, is a high-throughput sequencing approach with more rapid and accurate diagnostic advantages than traditional methods, especially in culture-negative samples[4, 5]. The detection and identification of pathogens by mNGS is an emerging clinical practice, which can simultaneously detect and identify pathogens by extracting only a small amount of DNA or RNA from samples. mNGS can theoretically detect all pathogens in clinical samples, especially for rare, novel, and atypical etiologies of complex infectious diseases[6]. Here, we describe a case of disseminated nocardiosis in a 49-year-old man diagnosed by mNGS of bronchoalveolar lavage fluid (BALF) rather than bacterial culture of BALF and pathological biopsy of lung tissue. He was successfully treated with parenteral or oral antibiotics for 8 mo with resolution of pulmonary and brain lesions on repeat imaging revealed.

## CASE PRESENTATION

### *Chief complaints*

A 49-year-old Chinese man had symptoms of cough and hemoptysis for 2 mo.

### *History of present illness*

A 49-year-old Chinese man presented to the hospital with 2 month of cough and hemoptysis, but without fever or chest pain. It is estimated that the daily blood loss was 20–30mL. During a visit to a different hospital on 10 March 2020, chest computed tomography (CT) demonstrated a mass and atelectasis in the right upper lobe (Figure 1A). The chief physician of the Center for Respiratory Endoscopy performed bronchoscopy to obtain BALF, however, the bacterial culture of BALF was negative. The patient was diagnosed with pulmonary infection and treated with oral cefixime capsules (0.2g every 12h) and azithromycin (500 mg/d) for 1 wk. However, there was no improvement and a poor general status. He had dyspnea when walking hastily or going up stairs and had chest pain. Chest CT on 23 April 2020 showed aggravation of the original lesion, especially in the right upper lobe (Figure 1B). He was admitted in our respiratory department for further evaluation on 25 April 2020.

***History of past illness***

The patient had a free previous medical history. No history of drug allergy.

***Personal and family history***

The patient worked as a welder and lived with his wife and children. He had no history of cigarette smoking or alcohol abuse. There was no family history to note.

***Physical examination***

On admission, the patient was afebrile and vital signs were normal. Breath sounds were decreased in the right lung, and neurological examination was unremarkable.

***Laboratory examinations***

The oxygenation index of blood gas is 265mmHg (Table 1) .Laboratory studies revealed leukocytosis of 14.36 × $10^9$/L, C-reactive protein 117.50 mg/L, procalcitonin 0.126 ng/mL and normal liver and kidney function. GeneXpert MTB/RIF, quantitative immunoglobulins, 1-3-β-D-glucan, galactomannan (GM), cryptococcal and deep sputum bacteriological culture antigen were negative.

***Imaging examinations***

Positron emission tomography (PET)–CT was ordered on the suspicion of lung cancer. PET–CT showed that most of the mass lesions in the posterior segment of the right

upper lobe had significantly increased glucose metabolism inhomogeneously with peripheral exudative changes, which were suspicious for infection on 27 April 2020 (Figure 1C).

***Further diagnostic work-up***

The patient was inhaled oxygen 4L/min and treated empirically with simultaneous cefoperazone–tazobactam and teicoplanin for 7 d but he continued to experience cough and hemoptysis with elevated C-reactive protein (109.92 mg/L) and procalcitonin (0.189 ng/mL). Then, treatment with meropenem and teicoplanin was administered. Besides, bronchoscopy was performed to obtain specimens including BALF and lung tissue. Transbronchial biopsy of soft tissue of the right upper lung showed chronic inflammation with acute activity and fibrous tissue hyperplasia with focal necrosis (Figure 3). GeneXpert MTB/RIF, GM, fungi and acid-fast bacillus stains, and BALF culture for bacteria were negative. However, mNGS analysis of BALF detected *N. asiatica* and *N. beijingensis*. The patient developed a new symptom of headache at the same time. Cranial enhanced MRI was ordered on the suspicion of intracranial *Nocardia* infection and MRI showed multiple lesions in the left occipital lobe, right cerebellar hemisphere and left frontal lobe on 13 May 2020 (Figure 2A). Cerebrospinal fluid (CSF) obtained by lumbar puncture identified no white or red blood cells, glucose 3.42 mmol/L and protein 0.54 g/L. The bacterial culture, cryptococcal antigen, virus DNA and exfoliative cell examination of CSF were all negative, as was NGS analysis of CSF.

Cough index : 0 : NO cough ; 1: Occasionally have a cough; 2: Frequent cough, mild impact on daily life; 3: Frequent cough, serious impact on daily life. Hemoptysis volume: small amount:＜100 mL/24h; moderate amount:100-500 mL/24h; massive amount:＞500 mL/24h or ＞100 mL at one time. Dyspnea index: 0: Asymptomatic while climbing stairs; 1: Symptomatic while climbing stairs; 2: Symptomatic after walking 100 m on flat ground; 3: Symptomatic with the least effort (e.g., talking, getting dressed); 4: Symptomatic in bed, at rest. Oxygenation index: partial blood oxygen divided by oxygen concentration.

## FINAL DIAGNOSIS

Disseminated nocardiosis affecting the CNS and lungs.

## TREATMENT

The patient was immediately treated with oral TMP-SMZ 0.96g every 8 h and intravenous linezolid 600mg every 12h from 9 May 2020. After 2 wk of combined antibiotic therapy, he improved and pulmonary CT showed an obvious reduction in consolidation in both lung fields on 23 May 2020 (Figure 1D). The oxygenation index of blood gas is 388mmHg (Table 1) . Platelet count showed thrombocytopenia ($171 \times 10^9$/L *vs* normal $233 \times 10^9$/L). After 3 wk, because of the higher dose of linezolid in the plasma (9.36 mg/L) and reduction of hemamebas ($3.34 \times 10^9$/L) and platelets ($122 \times 10^9$/L), we adjusted the dose of intravenous linezolid (600 mg/d) and oral TMP-SMZ (0.96 g every 12 h) on 31 May 2020 (Table 2). The patient's blood count recovered gradually, and at the same time he continued to have definite clinical improvement. After 5 wk and improvement of his brain lesions on repeat MRI (Figure 2B), as the dose of linezolid was still high (6.38 mg/L), it was replaced by ceftriaxone (2 g/d) on 16 June 2020 (Table 2). After 1 wk of treatment with ceftriaxone (2 g/d) and TMP-SMZ (0.96 g every 12 h), we shifted the antibiotic therapy to oral minocyline (100 mg every 12 h) and TMP-SMZ (0.96 g every 12 h) for 6.5 mo (Table 2). He completed nearly 8 mo of antibiotic therapy, with resolution of his pulmonary and brain lesions (Figure 1E–1J), and complete cure was achieved (Figure 2C–2D).

## OUTCOME AND FOLLOW-UP

He completed nearly 8 mo of antibiotic therapy, with resolution of his pulmonary and brain lesions (Figure 1E–1J), and complete cure was achieved (Figure 2C–2D).

## DISCUSSION

Disseminated nocardiosis may affect many organs, especially the lungs, CNS, skin and even the pericardium. Among disseminated infections, 44% of patients had CNS

involvement, highlighting the neurotrophic features of Nocardia spp. CNS manifestations of Nocardia infection can include isolated or multifocal brain abscesses and meningitis[9]. Consistent with these reports, our patient presented with disseminated disease from a primary pulmonary infection with spread to the central nervous system. He had a neurological symptom of headache and MRI revealed multiple lesions in the left frontal lobe, occipital lobe and right cerebellar hemisphere. Although bacterial culture and NGS analysis of CSF were both negative, his headache disappeared and MRI showed that the craniocerebral lesions were significantly reduced or even disappeared after antibiotic therapy, which confirmed that he had cerebral nocardiosis.

A definitive diagnosis of nocardiosis requires the isolation and identification of the organism from a clinical specimen. The traditional detection methods in specimens for microbial culture, histopathology, or smear microscopy, have low yield and are time-consuming; therefore, NGS has emerged [3]. NGS can detect unknown pathogens and a variety of mixed infectious pathogens by one-stop precision sequencing, therefore simplifying the detection process, improving pathogen detection sensitivity, and shortening detection time[4, 5]. In this case, *N. asiatica* and *N. beijingensis* were rapidly detected by the mNGS of BALF, while the bacterial culture of BALF and the pathological biopsy of lung tissue were negative, contributing to prompt and accurate antibiotic treatment, with resolution of pulmonary and brain lesions on repeat imaging revealed in clear clinical improvement. As reported, NGS can enable in-depth identification and classification of pathogens and their abilities to resist current treatment methods. Besides, the analysis of drug genes and virulence factors has an incomparable advantage over traditional detection methods[10]. However, mNGS analysis usually detects more than one pathogen in one test. Therefore, clinicians need to comprehensively evaluate the clinical status and sequencing results of patients to distinguish pathogens, symbiotic flora and pollutants. Although, this method could detect the common resistance genes, but these are limited, not directly provide formation about antibiotic sensitivity. Furthermore, up to now, the high cost and low

accessibility of NGS still limit its utility in general practice. In the future, optimization of sample acquisition, sample preparation and bioinformatics analysis will be essential to the application of mNGS in clinical diagnosis. We hope that in the near future, this technology will serve the clinic more appropriately and benefit more patients.

Treatment of CNS nocardiosis is largely based upon expert opinion. Popular treatment strategies include empirical combination intravenous therapy with agents such as imipenem, TMP-SMZ, linezolid and amikacin for several weeks followed by antibiogram-guided oral therapy[12, 13]. Consistent with these strategies, our patient initiated treatment with parenteral and oral antibiotics for 6 wk and had definite clinical improvement, followed by switching to oral minocyline and TMP-SMZ for 6.5 mo. He completed nearly 8 mo of antibiotic therapy, with resolution of his brain and pulmonary lesions and complete cure was achieved. Furthermore, this successful case confirmed that in some cases of disseminated nocardiosis, linezolid may be an important alternative that can give a better outcome. However, it should be emphasized that the risk of adverse effects might be increased if linezolid were combined with other antibiotics.Postmarketing studies have reported higher rates of linezolid-associated thrombocytopenia, ranging from 15% to 50%[14, 15]. The higher dose of linezolid in the plasma and prolonged duration of therapy have been suggested as more important risk factors[16, 17, 18, 19]. Consistent with these findings, our study identified longer duration of therapy as a risk factor. The first thrombocytopenic platelet count occurred after 14 d of linezolid therapy. The severity of thrombocytopenia increased with the duration of treatment. Similarly, in this case, thrombocytopenia was closely related to the higher dose of linezolid in the plasma. The combined treatment of linezolid and TMP-SMZ may aggravate the myelosuppressive effects of reversible neutropenia and thrombocytopenia. Selection of appropriate antibiotics given at the optimal time is hence crucial for effective therapy. Although NGS can detect the presence of drug resistance genes in pathogens, but it may not be consistent with clinical drug susceptibility results. Furthermore, there are still many drug resistance genes that have not yet been discovered and false negative results may exist.

A PubMed/MEDLINE（(nocardiosis[Title]) AND lung[Abstract]） search of literature tracked a total of seventeen within a decade except for the references already cited in the article (Table 3)[20-36]. Underlying conditions (87.5% in immunocompromised individuals); affected Organ (lung involvement is most common, followed by the brain); Positive Specimens(mosty made by culture and histopathology, not the NGS); TMP-SMZ is the most commonly used and effective drug.

## CONCLUSION

This case illustrates that *Nocardia* may cause severe disseminated infection in immunocompetent patients, which often involves the CNS and lungs. mNGS has more rapid and accurate diagnosis than traditional methods. It is a convenient and efficient technique for the detection of *Nocardia*, and is especially suitable for rare, novel and atypical etiologies of complicated infectious diseases. This successfully treated case confirmed that, in some patients with disseminated nocardiosis, TMP-SMZ is still the first choice of treatment, but linezolid may be an important alternative that can give a better outcome with the monitoring of linezolid serum concentrations and platelet count. Notable risk factors for linezolid-induced thrombocytopenia included high daily weight-based dose and prolonged duration of therapy (some patients experience thrombocytopenia within 14 d of treatment). Clinicians should monitor patients for linezolid-induced thrombocytopenia throughout therapy.

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