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CASE REPORT

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Treatment of refractory localized pulmonary nocardiosis caused by *Nocardia mexicana* with a combination of medication and surgery

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Abstract

Pulmonary nocardiosis is a rare disease that is often difficult to cure because of its tendency to recur. Here, we report a case of refractory localized pulmonary nocardiosis caused by *Nocardia mexicana*. A 60-year-old Japanese woman had recurring pulmonary nocardiosis four times previously and each time she was treated with antibiotics for a sufficient duration; nevertheless, the disease continued to recur, probably because of resistance to antibiotics. As a fifth treatment, we performed middle lobe resection and pre- and post-operative antimicrobial therapy for 6 months. The combination of medication and surgery was useful for treating refractory localized pulmonary nocardiosis

KEYWORDS

medication, *Nocardia mexicana*, pulmonary nocardiosis, refractory, surgery

INTRODUCTION

Nocardiosis is an opportunistic disease caused by *Nocardia* species, Gram-positive, filamentous bacteria that affect the lungs, skin, and central nervous system.[1,2] General antimicrobial therapy for nocardiosis includes trimethoprim/sulfamethoxazole (TMP/SMX), imipenem (IPM), amikacin (AMK), minocycline (MINO), and linezolid (LZD).[1] Generally, *Nocardia* species have variable resistance to antibiotics,[1] and coverage with a few agents for 6–12 months is recommended, although this has not been well established.

The first report of *Nocardia mexicana* isolated from pus samples of Mexican patients with mycetomas was in 2004.[3] We reported the first case of pulmonary nocardiosis caused by *N. mexicana* in 2016.[4] Subsequently, our patient had recurring pulmonary nocardiosis. Here, we report the successful treatment of pulmonary nocardiosis caused by *N. mexicana* using a combination of medication and surgery as a fifth treatment.

CASE REPORT

A 60-year-old Japanese woman visited another hospital with a cough that persisted for 6 months. Chest roentgenogram revealed infiltration in the right lower area and left middle area. The patient was diagnosed with pneumonia and treated with garenoxacin mesylate hydrate. However, the cough worsened and the patient presented at our hospital for further investigation. Chest computed tomography (CT) showed infiltration in the middle lobe and lingula (Figure 1A). She had a history of well-controlled dyslipidaemia. Smoking history was 20 pack years. At presentation, her vital signs were: body temperature, 36.8°C; percutaneous oxygen saturation, 96% in room air; and breath sound, no rales. The laboratory findings were: C-reactive protein 1.33 mg/dL and white blood cell count, 15,190/μL. Because she did not produce sputum, she underwent bronchoscopy and *N. mexicana* was identified by Gram staining and bacterial cultivation of the bronchial lavage fluid performed in the middle lobe (Table 1 and

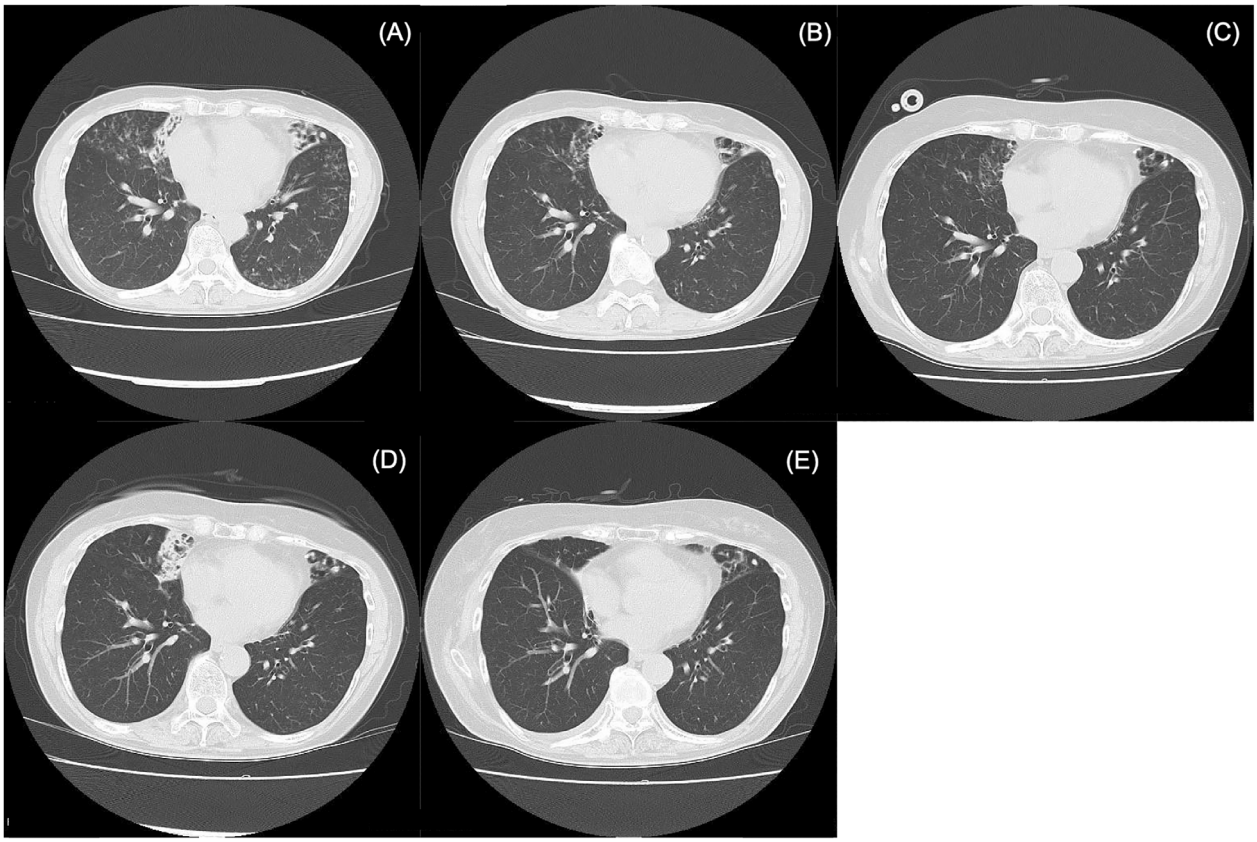

FIGURE 1 Chest computed tomography (CT) of pulmonary nocardiosis caused by *Nocardia mexicana*. (A) First onset. The image shows infiltration in the middle lobe and partially in the lingula with a cavity. (B) CT image after the first treatment. Infiltration in the middle lobe and lingula was reduced. (C) At the end of the fourth treatment, the middle lobe infiltration is not remarkable. The infiltration of the lingula is also as unremarkable as that in (B). (D) Fifth onset. Marked infiltration in the middle lobe is observed. The infiltration of the lingula is unchanged. (E) End of the fifth treatment consisting of combined medication and surgery. The middle lobe was resected and no findings are observed in the area where the middle lobe was originally located

TABLE 1 Susceptibility testing results for *Nocardia mexicana* isolate from bronchial lavage fluid

Antibiotic	MIC (mg/L)	Interpretation[a]
Cefotaxime	8	S
Imipenem	<1	S
Gentamicin	>16	N/A
Amikacin	<4	S
Clindamycin	>8	N/A
Minocycline	4	I
Vancomycin	>8	R
Trimethoprim/Sufamethoxazole	>4/76	R
Ciprofloxacin	>8	R
Levofloxacin	>8	N/A
Ampicillin/Sulbactam	>32	N/A
Meropenem	>0.5	N/A
Piperacillin/Tazobactam	>128	N/A
Azithromycin	>16	N/A
Linezolid	4	S

Abbreviation: MIC, minimum inhibitory concentration.
[a]Resistant (R), Intermediate (I), or Susceptible (S) as per CLSI breakpoints, Not Applicable (N/A).

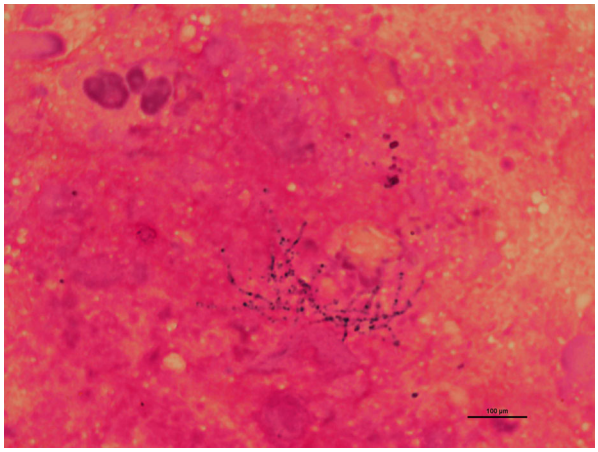

FIGURE 2 Gram stain (×1000) of bronchial lavage fluid showing Gram positive, branching, beaded filaments

Figure 2). This isolate was identified as *N. mexicana* by identification-specific physicochemical characterization and genetic testing. Genotyping tests to identify the species showed the highest homology to *N. mexicana* by sequence

TABLE 2 Treatment details of refractory localized pulmonary nocardiosis caused by *Nocardia mexicana*

Treatment	Treatment details		Total length of treatment period	Time to relapse
1st	BIPM 1 M LZD 2 W, AMK 3 W/5 W/cycle 5 M		6 M	3 M
2nd	BIPM 2 M LZD 2 W, AMK 4 W/6 W/cycle 12 M		14 M	6 M
3rd	BIMP + AMK 2 M LZD 2 W, AMK 3 W/5 W/cycle 9 M		11 M	6 M
4th	IMP + AMK + MINO 2 W, LZD + MINO 2 W/4 W/cycle	6 M	6 M	13 M
5th	IMP + AMK + MINO 2 W, LZD + MINO 2W/4W/cycle Middle lobe resection IMP + AMK + MINO 2 W, LZD + MINO 2 W/4 W/cycle	3.5 M 2.5 M	6 M	None (>30 M)

Abbreviations: AMK, Amikacin; BIPM, Biapenem; IMP, Imipenem; LZD, Linezolid; M, month; MEPM, Meropenem; MINO, Minocycline; W, week.

analysis of the housekeeping genes *16 S rRNA*, *rpoB*, *secA1*, *gyrB*, and *hsp65*. Empirical treatment was started using TMP/SMX and MINO. Then, they were replaced with biapenem (BIPM), because TMP/SMX was resistant and MINO had intermediate susceptibility by antibiotic susceptibility testing. After 4 weeks of treatment with BIPM, she was treated with 2 weeks of LZD and 3 weeks of AMK. Treatment with LZD and AMK was repeated until the total duration of treatment was 6 months (Figure 1B). In general, treatment for more than 6 months is recommended for severe infection with *Nocardia*. We considered the patient had moderate pulmonary disease and was not immunosuppressed. Considering the progress of symptom improvement and decline in the quality of life related to side effects, we decided on 6 months of treatment. We monitored symptoms, antibiotic side effects, and imaging findings at least every month during treatment and every 3 months after treatment ended.

Three months after the first treatment, she started coughing again, and CT showed infiltration in the middle lung lobe in the same area as the first time. Infiltration of the lingula was unchanged after the first treatment. *N. mexicana* was identified by Gram staining and bacterial cultivation of the bronchial lavage fluid performed in the middle lobe. We treated her with BIPM for 2 months, followed by LZD and AMK for 12 months, and the period until the next recurrence was 6 months. The third treatment was BIPM and AMK for 2 months, followed by LZD and AMK for 9 months, and the next recurrence was at 6 months. The fourth treatment consisted of alternating between the two drug combinations: IMP, AMK, and MINO, or LZD and MINO. We administered one combination for 2 weeks followed by the other combination for 2 weeks for 1 cycle of 4 weeks. We repeated this cycle over 6 months (Table 2 and Figure 1C). The fifth onset was 13 months later (Figure 1D). The same localized area in the middle lobe showed infiltration and infiltration of the lingula was unchanged. Therefore, we considered the infiltration of the middle lobe caused the symptoms including cough, fever, and fatigue. The course of the disease showed repeated infections, which we considered to be a limitation of medication. In addition, the CT findings at the initial onset showed extensive infiltration in the middle lobe indicating *N. mexicana* might have spread to the entire middle lobe. Therefore, the fifth treatment plan was a combination of medication to minimize bacterial spread and surgery, middle lobe resection, to reduce the possibility of dissemination from the margins. After the resection, we continued medication as a precaution. The fifth treatment was medically the same as the fourth treatment. The fifth treatment alternated between a combination of IMP, AMK, and MINO for 2 weeks followed by LZD and MINO for 2 weeks for a total of 4 weeks per cycle, which was repeated over 3.5 months before surgery. After surgery, we continued the same cycle for 2.5 months, for a total treatment period of 6 months pre- and post-surgery. After 2 months of medication, we confirmed no *N. mexicana* infection by bronchoscopy. Then, middle lobe resection was performed (Figure 1E). Pathological analysis showed that inflammatory cells and exudate with calcification were present in the dilated bronchial lumen, with no obvious organisms present, and no malignant findings. Bacteriological analysis of the surgical resection specimens revealed no *N. mexicana* by tissue culture. Currently, there is no sign of recurrence 30 months after the fifth treatment. Because pulmonary nocardiosis tends to form a brain abscess, we performed brain CT; however, no abscess was observed. In addition, there were no neurological findings throughout the disease course.

DISCUSSION

We report a case of pulmonary nocardiosis caused by *N. mexicana*. This patient suffered four recurrences of disease after four different treatments. The fifth treatment was a combination of medication and surgery.

To date, there have been few reports of nocardiosis caused by *N. mexicana*, including mycetoma, pulmonary infections, cerebral infections, and cutaneous infections.[3–6] The antimicrobial susceptibility patterns of *N. mexicana* are poorly understood and according to these reports, *N. mexicana* appears to be resistant to multiple antibiotics.[3–6] There has been one report regarding pulmonary nocardiosis caused by *N. mexicana* other than our case. In this report,[6] a 57-year-old man who suffered a cutaneous wound, fever, weakness,

cough, and chest pain was diagnosed with pulmonary and cutaneous nocardiosis caused by *N. mexicana*. He was treated with LZD and AMK for 6 months and his respiratory symptoms and foot wound improved after a few weeks. The antibiotic sensitivity test showed the isolate was susceptible to ciprofloxacin, clarithromycin, ceftriaxone, and LZD and resistant to TMP/SMX and MINO. In this case, treatment was performed according to antimicrobial susceptibility testing for a sufficient period. This reduced the treatment period and increased the remission period. But the recurrence of disease four times in 6 years was a burden on the patient's quality of life.

We considered a combination of medication and surgery to treat this patient. Regarding the validity of lobectomy, first, there is no established treatment for refractory pulmonary nocardiosis caused by *N. mexicana*. Second, in this case, the lesion was localized to the middle lobe, drug-resistant, caused strong side effects (nausea, vomiting, anorexia, decreased blood counts), and recurred repeatedly without effective drug treatment. The patient's respiratory function was not likely to be affected after middle lobe resection. Based on the above, we concluded that surgical resection was indicated for this patient as well as treatment for middle lobe syndrome such as non-tuberculous mycobacterial disease.[7–9] There have been no reports regarding the appropriate duration of medication pre- and post-surgery; therefore, we provided 6 months of treatment, which is generally sufficient for cases of immunocompetent moderate pulmonary nocardiosis.

Several limitations of this case should be acknowledged. First, why she was infected with *N. mexicana* is unclear because she was not immunocompromised. However, she was an ex-smoker with 20 pack years. Another factor might be that her CT showed bronchiectasis. The damage or distortion of lung structures might be a risk factor. Second, the most effective antibiotics and duration of treatment for *N. mexicana* have not been determined and therefore disease can reoccur. To overcome these limitations, more cases should be studied.

In summary, we experienced pulmonary nocardiosis caused by *N. mexicana*, which recurred four times. A combination of medication and surgery was useful for managing disease in a case of localized pulmonary nocardiosis caused by *N. mexicana*.

AUTHOR CONTRIBUTIONS

Miwako Kogure wrote and edited the manuscript. Kuninobu Kanai and Yoshimitsu Hirai reviewed the manuscript. All authors approved the final version of the manuscript for publication and agreed to accept responsibility for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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