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Review

Nocardia elegans infection: a case report and literature review

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SUMMARY

A case of disseminated nocardiosis caused by *Nocardia elegans* in a 72-year-old man with rheumatoid arthritis, treated with tacrolimus and prednisolone, is reported herein. The patient had impaired vision and was diagnosed with endophthalmitis and an abdominal skin abscess. He was started on trimethoprim–sulfamethoxazole treatment, followed by cefepime. The patient was then switched to a combination of imipenem–cilastatin and minocycline. Although the patient survived as a result of surgery and prolonged antibiotic treatment, he eventually lost vision after the infection became resistant to antibiotic treatment. Molecular analysis of samples from the abscess and vitreous fluid confirmed the extremely rare pathogen *N. elegans*, which accounts for only 0.3–0.6% of infections caused by *Nocardia* species. This organism is almost always associated with pulmonary infection, and disseminated infections are rare. As with previously reported norcardial infections, the current case was treated successfully with trimethoprim–sulfamethoxazole, carbapenems, and aminoglycosides. However, the clinical characteristics of this organism remain unclear. Further studies are therefore required to develop more effective treatment protocols for disseminated nocardiosis caused by this problematic pathogen.

1. Introduction

Nocardia species are Gram-positive aerobic actinomycetes that are ubiquitous in soil and water. They can cause local (pulmonary nocardiosis) or disseminated (systemic/disseminated nocardiosis) infection in humans, and readily cause infection in immunocompromised patients with autoimmune disease or those undergoing treatment with steroids or immunosuppressive agents. Recent reports suggest that the incidence of nocardiosis is increasing,[1–4] and that it is a life-threatening infectious disease. The number of *Nocardia* species described has been expanding rapidly; there are currently more than 100 species. Although there are differences in the distribution of *Nocardia* species worldwide, *N. asteroides*, *N. farcinica*, *N. nova*, *N. transvalensis*, *N. brasiliensis*, *N. abscessus*, and *N. cyriacigeorgica* are the most common.[1–3,5] In addition, each *Nocardia* species displays a different clinical spectrum.

In contrast, *Nocardia elegans* accounts for less than 1% of infections caused by *Nocardia* species. Since the first case of *N. elegans* infection was reported by Yassin and Brenner in 2005,[6] only a few other cases have been reported. Although almost all of these previous cases in humans have been associated with pulmonary infections, a case of disseminated nocardiosis caused by *N. elegans* in a patient undergoing immunosuppressive therapy is presented herein. The clinical significance of *Nocardia* species remains unclear because of the variety of organisms causing infection. Therefore, a new case of disseminated nocardiosis is presented and previous cases of *N. elegans* infection are reviewed.

2. Case report

A 72-year-old man undergoing tacrolimus (1.5 μg/day) and prednisolone (10 mg/day) treatment for rheumatoid arthritis was admitted to the hospital suffering from pneumonia. A chest X-ray showed consolidation in the upper lobe of the right lung, and a 2-week course of ceftriaxone was started upon admission without sputum culture. A computed tomography (CT) scan of the chest obtained approximately 3 weeks post-admission revealed gradual improvement of the infection. However, 1 week post-discharge, the patient was again admitted to the hospital with a 2-day history of recurrent episodes of eye pain and impaired vision. He was diagnosed with endophthalmitis. Blood tests indicated an elevated white blood cell count (12.9×10^9/l), high levels of C-reactive

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protein (5.5 mg/ml), and kidney malfunction (serum creatinine 0.02 mg/ml). Chest CT again showed consolidation in the upper lobe of the right lung, and cefepime (2 g/day) was administered for 5 days. In addition, voriconazole (200 mg/2 days) and fluconazole (100 mg/day) were administered for 3 and 5 days, respectively, because high β-D-glucan levels (32.6 pg/ml) indicated a fungal infection. As the causative agent of the endophthalmitis appeared to be resistant to antibiotic treatment, a vitrectomy was performed; however, neither the eye pain nor the impaired vision improved.

During the treatment of endophthalmitis, swelling and warmth in the abdominal wall was diagnosed as a subcutaneous abscess. A specimen was obtained following drainage of the abscess, and bacteriological examination identified *Nocardia* species. Based on drug susceptibility analysis, trimethoprim–sulfamethoxazole (ST) treatment (10 mg/kg, as trimethoprim) was started. However, drug-induced kidney injury was detected 7 days after the onset of ST treatment, necessitating a change of therapy to a combination of imipenem–cilastatin (IPM–CS, 0.5 g every 12 h) and minomycin (MINO, 100 mg every 12 h). The abdominal abscess improved following antibiotic treatment. However, a right-side ophthalmectomy was performed 1 month after the initiation of antibiotic therapy following treatment failure of IPM–CS and MINO and worsening of the endophthalmitis.

After 6 weeks of IPM–CS administration, treatment was changed to MINO monotherapy. However, because of observed liver dysfunction during MINO administration, clarithromycin therapy (CAM, 200 mg every 12 h) was finally selected. Long-term CAM therapy has been in place for 20 months without relapse.

Gram staining of bacteria isolated from the abscess and vitreous fluid samples revealed Gram-positive rods that formed an extensively branched substrate mycelium. Kinyoun staining indicated that cells had a thin, acid-fast cell wall. Following aerobic incubation at 35 °C for 3 days on 5% sheep blood agar, white colonies with a wrinkled surface were observed. The identities of the clinical isolates were confirmed by 16S rRNA gene sequencing analysis, as described previously.[4] Susceptibility testing was performed using the broth microdilution method, according to the guidelines of the Clinical and Laboratory Standards Institute. The results of susceptibility testing carried out pre-treatment and at 1-month post-treatment are shown in Table 1. Molecular analysis confirmed that the isolates from both the abdominal wall abscess and vitreous body samples were *N. elegans*.

Table 1
Susceptibility testing of the *Nocardia elegans* strain isolated in the current case, pre- and post-therapy

Agent	MIC[a]	Interpretation[b]	MIC[c]	Interpretation[b]
AMPC/CVA	>32/16	R	>32/16	R
CTRX	<2	S	4	S
CTX	<2	S	4	S
CFPM	<1	S	2	S
IPM	<0.5	S	<0.5	S
LZD	<1	S	2	S
AMK	<0.5	S	<0.5	S
TOB	>16	R	>16	R
CFPX	4	R	>4	R
MINO	1	S	2	I
DOXY	4	I	8	R
CAM	<0.25	S	<0.25	S
ST	19/1	S	38/2	S

MIC, minimum inhibitory concentration (μg/ml); AMPC/CVA, amoxicillin clavulanate; CTRX, ceftriaxone; CTX, cefotaxime; CPFX, ciprofloxacin; CFPM, cefepime; IPM, imipenem; LZD, linezolid; AMK, amikacin; TOB, tobramycin; CFPX,; MINO, minocycline; DOXY, doxycycline; CAM, clarithromycin; ST, trimethoprim–sulfamethoxazole.
[a] Analysis of the strain isolated pre-antibiotic treatment.
[b] Interpretation according to Clinical and Laboratory Standards Institute guidelines: S, susceptible; I, intermediate; R, resistant.
[c] Analysis of the isolate following 2 months of antibiotic treatment.

3. Literature review

3.1. Methods

To identify previously reported cases of *N. elegans* infection, the PubMed database was searched using the search words "*Nocardia elegans*" and "*N. elegans*". In addition, the references cited in previously published reports were also reviewed. To compare the more common *Nocardia* species with *N. elegans*, the incidence and treatment protocols for all *Nocardia* species were also searched.

3.2. Incidence of N. elegans

Recent reports have shown that the incidence of infection caused by Nocardia species is increasing.[1–4] However, trends in the incidence of *N. elegans* infection are less clear because of the rarity of this disease. Only seven cases of nocardiosis caused by *N. elegans* have been reported to date.[2,6–11] In general, *N. elegans* is very rarely isolated and accounts for only 0.3–0.6% of infections caused by *Nocardia* species.[2,10,12] Previous reports on the epidemiology of nocardiosis have not included any cases caused by *N. elegans*.[1,3–5] Therefore, the incidence of *N. elegans* infection is presumed to be very low.

3.3. Clinical spectrum of N. elegans

A literature review indicated that the most common sites/types of nocardial infection are pulmonary (39%), systemic/disseminated (32%), extrapulmonary (12%), and central nervous system (9%).[13] Interestingly, *N. elegans* is almost always associated with pulmonary infection, with only one case without pulmonary involvement (purulent arthritis) reported to date. However, rare cases of severe disseminated infection do occur (Table 2). The first report of disseminated infection caused by *N. elegans* was published in 2014,[11] and the current case appears to be only the second reported case.

Nocardiosis infection appears to occur in patients with underlying disease or who are undergoing treatment with an immunosuppressive agent. In the current case, the patient had rheumatoid arthritis and was being treated with steroid and immunosuppressive therapies. Although previous reports on *N. elegans* infection provide little information on underlying conditions, half of the cases had connective tissue disease.

3.4. Identification of N. elegans

As traditional identification methods are not particularly useful for *Nocardia* species because of limited biochemical and physiological differences between organisms, molecular techniques are more frequently used.[5] In particular, 16S rRNA gene identification has greatly expanded the number of recorded *Nocardia* species and is used widely for the identification of *N.elegans*.[1,2,4,6,9,11,12] In addition, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is reported to have potential for the identification of *N.elegans*.[8,14]

3.5. Antimicrobial susceptibility and antimicrobial treatment of N. elegans

Because *Nocardia* species differ in clinical spectrum and susceptibility to antibiotics, it is important to identify *Nocardia* isolates precisely, beyond the genus level. Increasing resistance of *Nocardia* species to ST has been problematic, with resistance rates

Table 2
Clinical characteristics and outcomes of *Nocardia elegans* infections in the current case and in seven previously published cases

No. [Ref.]	Age, years	Sex	Site[a]	Type	Treatment[b]	Outcome
1[6]	-	-	P	Local	-	-
2[2]	46	F	P	Local	-	-
3[7]	26	M	P	Local	MEPM + TOB	-
4[8]	73	M	P	Local	IPM + AMK	Improved
5[9]	66	F	J	Local	-	-
6[10]	51	M	P	Local	ST	Improved
7[11]	69	M	P + B	Disseminated	ST + CAM	Improved
Case	73	M	P + E + S	Disseminated	ST → IPM + MINO → CAM	Improved with ophthalmectomy

F, female; M, male; '-', unknown.
[a] P, pulmonary; J, joint; B, brain; E, eye; S, skin.
[b] MEPM, meropenem; TOB, tobramycin; IPM, imipenem–cilastatin; AMK, amikacin; ST, trimethoprim–sulfamethoxazole; CAM, clarithromycin; MINO, minocycline.

reported to be as high as 42%.[3] Other than ST, IPM–CS, the third-generation cephalosporin amikacin (AMK), and MINO are key antibiotics used for the treatment of nocardiosis. A previous study indicated that IPM–CS, AMK, linezolid (LZD), and daptomycin had the lowest minimum inhibitory concentration (MIC_{90}) values for the unusual *Nocardia* species.[12]

The antibiotic susceptibility of *N. elegans* in previous reports has mainly been determined using the broth microdilution method, as recommended by the Clinical and Laboratory Standards Institute (document M24-A). Some reports regarding the antibiotic susceptibility of *N. elegans* show in vivo susceptibility to ST, IPM–CS, CAM, MINO, and LZD.[2,6–9] Although previous studies have provided little information on the response to antimicrobial treatment, ST, carbapenems, aminoglycosides, and CAM have been used to successfully treat nocardial infections (Table 2). Importantly, resistance to ST was only seen in one case.[8] These antimicrobial agents were also selected based on susceptibility analysis in the present case; however, drug toxicity and resistance during therapy meant that treatment was ceased. In addition, decreasing susceptibility to other antimicrobial agents was observed during treatment. Therefore, further reports on appropriate antimicrobial treatment are needed.

4. Summary

The clinical characteristics, diagnostic methods, antimicrobial susceptibility, and optimal treatment protocols for *N. elegans* remain unclear because of the small number of reported cases. Further studies are therefore required to develop more effective treatment protocols for disseminated nocardiosis caused by this problematic pathogen.

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