INTERNAL MEDICINE

□ CASE REPORT □

Meningitis and Ventriculitis due to *Nocardia araoensis* Infection

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Abstract

A 73-year-old man was admitted to our hospital with disturbance of consciousness, fever and headache. Cerebrospinal fluid (CSF) analysis revealed pleocytosis with neutrophil predominance, increased protein and low glucose. CSF and blood cultures yielded negative results. Antibiotics and antituberculous drugs were started for meningitis. An antimycotic was also added. The patient died from transtentorial hernia 99 days after admission. Autopsy revealed meningitis, ventriculitis and brain abscess, and *Nocardia araoensis* was detected in pus from the left lateral ventricle. This appears to represent the first report of *N. araoensis* meningitis complicated by ventriculitis and brain abscess.

Key words: *Nocardia* meningitis, *Nocardia araoensis*, *Nocardia* ventriculitis, 16S rRNA gene sequence

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Introduction

Nocardia species are rarely found as an etiological organism for meningitis. Generally, these bacteria are known to cause pulmonary, cutaneous, central nervous or systemic nocardiosis. In terms of central nervous infection due to *Nocardia*, brain abscess is a major clinical manifestation, but meningitis has rarely been reported (1).

N. araoensis was first isolated in Arao, Japan in 1997, and is most closely related to *N. beijingenesis*, according to 16S rRNA gene sequence analysis (2). *N. araoensis* infections have been reported in a few cases of pulmonary and skin disease (2, 3). To the best of our knowledge, no cases of meningitis due to *N. araoensis* have been reported previously. Herein we describe the case of a 73-year-old man with meningitis due to *N. araoensis* complicated by ventriculitis and brain abscess that was diagnosed on autopsy.

Case Report

A 73-year-old man with disturbance of consciousness, headache and high fever was admitted to the cardiology department of our hospital, and was transferred to the neurological department on day 4. Significant past medical history included an episode of pneumonia 4 months prior and meningitis 2 months prior to this admission. Pneumonia resolved with 7 days of levofloxacin (LVFX), and meropenem (MPEM) was administered for meningitis for 14 days. In both instances, no etiology was detected. The patient was addicted to alcohol, consuming approximately 150 mL of ethanol each day. Physical examination on admission revealed high fever of 38.5℃ and arrhythmia. Neurological examination identified nuchal rigidity and mild disorientation, but no paresis or numbness. The patient was severely emaciated (height, 163 cm; weight, 43 kg). Although activities of daily life had been sufficient for independence before admission, he was unable to walk without assistance due to severe emaciation; a wheelchair was required for mobility.

Peripheral blood analysis on day 4 revealed mild pancytopenia (white blood cell count, 6,200/μL; neutrophil count, 5,208/μL; lymphocyte count, 682/μL; hemoglobin, 10.2 g/dL; platelets, 88,000/μL); and CRP, 1.44 mg/dL, representing a mild increase. The CD4 T-cell count was 23/μL, but

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Table 1. Timeline of CSF Analyses.

	1st analysis (day 4)	2nd analysis (day 10)	3rd analysis (day 18)	4th analysis (day 29)	5th analysis (day 50)	6th analysis (day 80)
CSF cell count (/μL)	1244	802	128	40	1311	268
(poly:mono, %)	(90 : 10)	(90 : 10)	(83 : 17)	(65 : 35)	(85 : 15)	(86 : 14)
CSF glucose (mg/dL)	47	34	38	41	44	34
Simultaneous blood glucose (mg/dL)	141	not done	not done	101	not done	104
CSF protein (mg/dL)	273	196	117	152	753	715

Moderately decreased glucose levels and neutrophil-dominant pleocytosis are seen in all CSF analyses throughout the clinical course.

negative results were obtained for human immunodeficiency virus (HIV) antibody and polymerase chain reaction for HIV. Serum testing for β-D-glucan, *Aspergillus* antigen and cryptococcal antigen were all negative. Tests to detect soluble interleukin 2 receptor, myeloperoxidase anti-neutrophil cytoplasmic antibody, proteinase 3 anti-neutrophil cytoplasmic antibody, and antinuclear antibody markers for collagen disease were also all negative. The first cerebrospinal fluid (CSF) analysis, on day 4, revealed: cell count, 1,244/μL (polymorphonuclear cells, 90%; monomorphonuclear cells, 10%); protein, 273 mg/dL; and glucose, 47 mg/dL (simultaneous blood glucose, 135 mg/dL) (Table 1 and Fig. 1). Gram staining and smear for acid-fast bacilli yielded negative results. Adenosine deaminase and cryptoccocal antigen were likewise negative. Although CSF cultures were incubated for 2 weeks for bacteria and 8 weeks for mycobacteria, both appeared to yield negative results. At the same time, two sets of blood cultures were ordered and incubated for 4 weeks, and were still negative. Computed tomography (CT) of the head on admission showed a low-density area in the left uncal region and parietal cortex (figure not shown).

On magnetic resonance imaging (MRI) performed on day 14, diffusion-weighted imaging (DWI) revealed a high-intensity spot in the posterior horn of the left lateral ventricle of the brain (Fig. 2A), implying ventriculitis. However, this region appeared iso-intense on apparent diffusion coefficient (ADC) mapping (Fig. 2B). DWI also showed a high-intensity lesion with ADC iso-intensity in the left parietal cortex, judged as representing some kind of inactive lesion (figure not shown). On fluid-attenuated inversion recovery (FLAIR) imaging, a high-intensity lesion was detected in the white matter adjacent to the posterior horn of the left lateral ventricle (Fig. 2C). The parietal cortex lesion was also signal hyperintense on FLAIR (figure not shown). Pneumonia was not detected on chest roentgenography or CT (figure not shown).

On day 4, bacterial meningitis was suspected and treatment with vancomycin (VCM), ceftriaxone (CTRX) and piperacillin (PIPC) was initiated (Fig. 1). Rifampicin (RFP), isoniazid (INH) and ethambutol (EB) were concomitantly administered for possible tuberculous meningitis. On day 10, a second analysis of CSF revealed non-significant changes compared with the first analysis: cell count, 802/μL (polymorphonuclear cells, 90%; monomorphonuclear cells, 10%); protein, 196 mg/dL; and glucose, 34 mg/dL (simultaneous blood glucose, not determined) (Table 1). High fever had not resolved (Fig. 1). Because fungal meningitis was not able to be ruled out, liposomal amphotericin-B (L-AMB) was started. The regimen of VCM, CTRX, and PIPC regimen was switched to panipenem/betamipron (PAMP/BP) and minocycline (MINO). RFP, INH and EB were terminated due to low adenosine deaminase levels in the first CSF analysis. Although negative results were obtained for the CSF culture for fungi, fever resolved several days after beginning L-AMB (Fig. 1) and findings from the third CSF analysis on day 18 had improved: cell count, 128/μL (polymorphonuclear cells, 83%; monomorphonuclear cells, 17%); protein, 117 mg/dL; and glucose, 38 mg/dL (simultaneous blood glucose, not determined) (Table 1, Fig. 1). Due to bone marrow suppression, L-AMB (100 mg once a day) was terminated on day 21.

Findings from the fourth CSF analysis, on day 29, showed further improvement: cell count, 40/μL (polymorphonuclear cells, 65%; monomorphonuclear cells, 17%); protein, 152 mg/dL; and glucose, 41 mg/dL (simultaneous blood glucose, 101 mg/dL) (Table 1 and Fig. 1).

These improvements in CSF findings suggested that an undetected fungi was the causative microorganism and that L-AMB had been effective. Fever of 37-38℃ reappeared around day 35 (Fig. 1), and oral fluconazole (FCZ) was

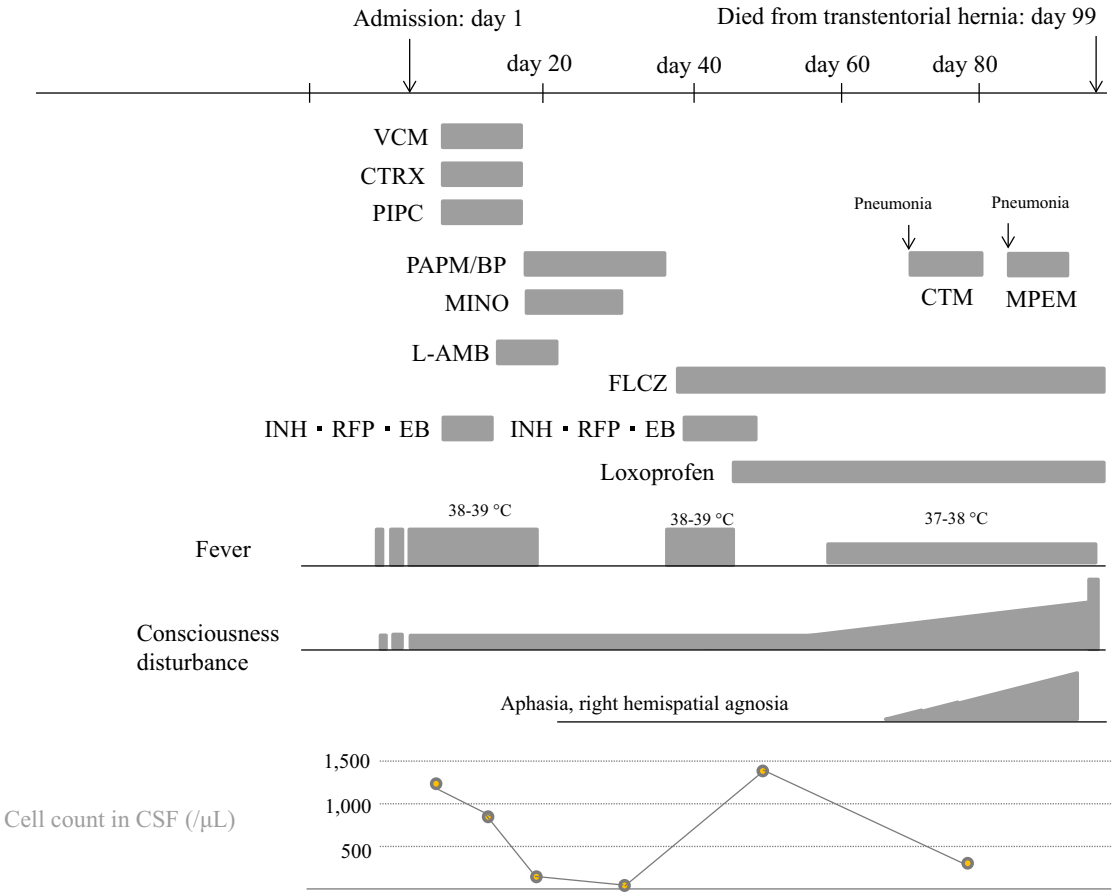

Figure 1. Timeline of the clinical course. The patient was treated for fungal meningitis. Antituberculous drugs and antibiotics were also administered, but not continuously. His condition gradually deteriorated and death from transtentorial hernia occurred on day 99. CTM: cefotiam, CTRX: ceftriaxone, EB: ethambutol, INH: isoniazid, L-AMB: liposomal amphotericin-B, MEPM: meropenem, MINO: minocycline, PAMP/BP: panipenem/betamipron, PIPC: piperacillin, RFP: rifampicin, VCM: vancomycin

started on day 36. MINO and PAPM were continued until days 28 and 35, respectively. Fever did not resolve and loxoprofen was started on day 46. Fever reduced initially, but relapsed at 37-38℃ around day 60. A fifth CSF analysis on day 50 revealed worsened findings: cell count, 1,311/μL (polymorphonuclear cells, 85%; monomorphonuclear cells, 15%); protein, 732 mg/dL; and glucose, 44 mg/dL (simultaneous blood glucose, not determined) (Table 1 and Fig. 1). DWI on days 50 and 71 revealed exacerbation of the ventriculitis (Fig. 2D and G) and partial ADC hypointensity (Fig. 2E and H). Spread of a hyperintense region was evident in the white matter adjacent to both lateral ventricles on FLAIR imaging (Fig. 2F and I). The area of high intensity may have represented brain edema due to ventriculitis. Direct paracentesis of the ventricle was considered, but the family of the patient declined to consent. Although CSF and MRI findings worsened, we persisted in suspecting fungal infection and continued with FCZ.

Disturbance of consciousness slowly worsened (Fig. 1), and aphasia and left hemispatial neglect gradually appeared around day 60. MRI on day 71 showed the ventriculitis and hyperintense lesion in the white matter adjacent to both lateral ventricles on FLAIR imaging had become more severe (Fig. 2D-F). Neither swelling of the brain nor encephalocele was seen. On days 71 and 84, pneumonia complicated the hospital course, resulting in administration of CTM for 9 days and MEPM for 11 days, respectively (Fig. 1). In both episodes of pneumonia, no causative bacteria were detected. Although the sixth CSF analysis on day 80 revealed improvements in cell count (268/μL; polymorphonuclear cells, 86%; monomorphonuclear cells, 14%), no improvements were seen in protein (753 mg/dL) or glucose (34 mg/dL; simultaneous blood glucose, 104 mg/dL) (Table 1 and Fig. 1). FCZ was continued because of improvements in cell counts. The general condition of the patient did not improve and he died on day 99 due to transtentorial hernia, as confirmed on head CT (figures not shown). The transtentorial hernia was attributed to brain edema ventriculitis and meningitis. Repeated cultures of CSF and blood until death had consistently yielded negative results for bacteria, fungi and mycobacteria.

Autopsy was performed 2 hours after death. On opening the cranium, yellowish pus flowed from the left ventricle (Fig. 3A). This pus was not malodorous, and Gram staining

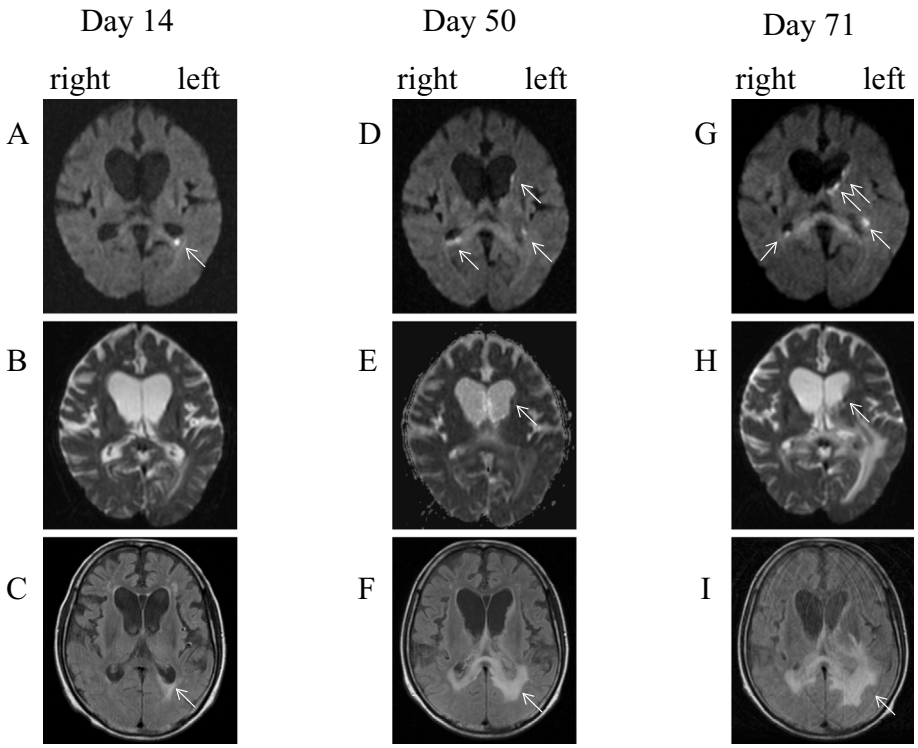

Figure 2. **MRI on days 14, 50 and 71. A) MRI on day 14 shows a DWI hyperintense spot in the posterior horn of the left lateral ventricle (arrow). B) The lesion is iso-intense on ADC. C) On FLAIR, a hyperintense lesion is apparent in the white matter adjacent to the posterior horn of the left lateral ventricle (arrow). D, G) DWI on days 50 and 71 reveals gradual deterioration of ventriculitis (arrows). E, H) ADC mapping, the area of the DWI-hyperintense lesion appears partially hypointense (arrows). F, I) Spread of the FLAIR-hyperintense lesion in the white matter adjacent to the ventricles (arrows).**

revealed a delicate, branching, filamentous organism (Fig. 3B). Although acid-fast staining was not performed, the organism was determined to be a *Nocardia* species from the colony appearance, and was identified as *N. araoensis* by 16s rRNA gene sequencing. Pus was observed throughout the basal cistern and pontomedullary cistern (Fig. 3C). In formalin-fixed sections of brain, both lateral ventricles were filled with pus (Fig. 3D) and some small abscesses that had remained undetectable on MRI were seen in the cerebral white matter (Fig. 3E). No infectious lesions were identified in other organs, including the lungs and skin. No evidence of pancytopenia, such as hematological disease or liver cirrhosis, was found. Minimal inhibitory concentration (MIC) testing showed that only doxycycline (DOXY), ciprofloxacin (CPFX) and MINO seemed ineffective (Table 2). The final diagnosis was meningitis, ventriculitis and brain abscess due to *N. araoensis*.

Discussion

We encountered a case of *N. araoensis* meningitis, ventriculitis and brain abscess that was only diagnosed on autopsy. A correct diagnosis was unable to be made while the patient was still alive.

MRI on day 14 showed mild ventriculitis and a high-intensity region on FLAIR. Ventriculitis and the hyperintense lesion on FLAIR developed on later MRI. Given the temporal course of the MRI findings, meningitis was considered to be the first clinical manifestation, with ventriculitis and brain abscess arising as complications of the deteriorating condition.

The major clinical manifestation of CNS infection is brain abscess, and meningitis is extremely rare (4, 5). As Bross and Gordon reported that 43% of cases of *Nocardia* meningitis were complicated by brain abscess (4), isolated *Nocardia* meningitis appears even rarer. Despite complication of ventriculitis and brain abscess arising, the main problem in the present case was meningitis.

Diagnosis of *Nocardia* meningitis is difficult for a number of reasons. First, CSF culture is insufficient to achieve diagnosis. Bross and Gordon reported that 75% of *Nocardia* meningitis cases were diagnosed through CSF incubation (4). Soub et al. reported that 80% of meningitis cases were diagnosed using CSF cultures (6). However, these values do not provide information on the positive ratio of CSF cultures for meningitis. Some reports have shown a need for repeated CSF punctures to diagnose *Nocardia* meningitis from CSF cultures (4, 6-9). A larger volume of CSF may improve the positive rate for cultures (4). In our case, CSF was incubated 5 times with 1- to 2-mL samples, and all cul-

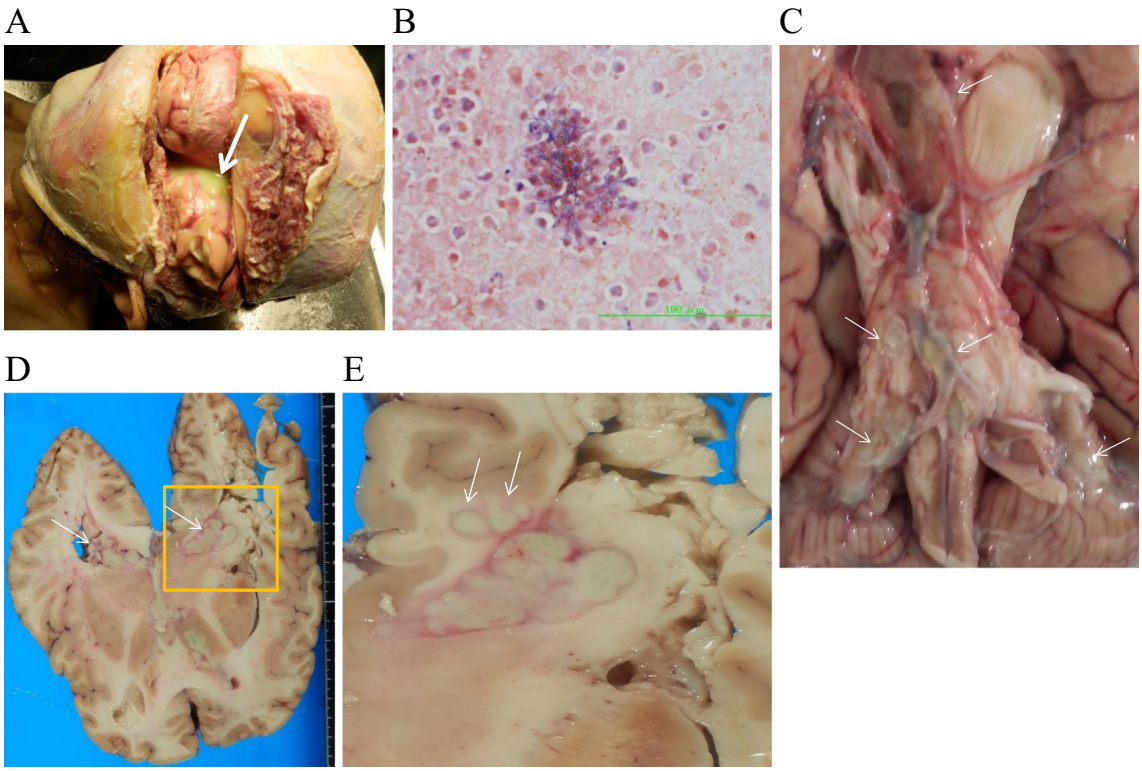

Figure 3. **Autopsy findings. A) Yellowish pus is seen flowing from a ventricle (arrow). B) Gram staining of pus from the ventricle reveals a delicate, branching, filamentous organism. C) Pus is scattered throughout the basal cistern and pontomedullary cistern (arrows). D) In formalin-fixed brain sections, both lateral ventricles are full of pus (arrows). E) Magnification of the outlined square in D shows some small abscesses in the cerebral white matter (arrows).**

tures were negative. Antibiotics may have interfered with the growth of *Nocardia*, and CSF should have been incubated with as large a volume as possible. Second, *Nocardia* species are slow-growing organism (4, 10). Bross and Gordon reported that 3-21 days are necessary to recover *Nocardia* from CSF cultures (4). Cultures for *Nocardia* require a minimum of 48-72 hours before colony formation, and incubation should then be maintained for at least 2 weeks (1), and longer if possible (10). *Nocardia* often grow on fungal and mycobacterial culture media (1, 10), and 4-6 weeks may be needed for positive results from fungal cultures (10). As a result, if fungal culture is ordered, cultures should not be discarded before that time. Blood cultures can yield positive results if incubated for 30 days (10). In the present case, CSF cultures were conducted 5 times for bacteria, once for fungi and once for mycobacteria. Only one culture for bacteria was incubated for 14 days, while the others were incubated for only 7 days. The culture for fungi was incubated for 14 days and the culture for mycobacteria was incubated for 56 days. Blood cultures were also repeated 7 times, but only one culture was incubated for 28 days, with all others discarded at 7 days. Longer incubation of CSF and blood cultures may have allowed identification of *Nocardia* in this case. If no productive result was obtained by incubation within the routine incubation period, CSF should be incubated at least for 4 weeks for slow-growing organisms like *Nocardia*. *Nocardia* can be highly elusive unless pus is obtained (10). The patient showed ventriculitis with pus on MRI, and a direct approach to the lateral ventricle to collect pus may have been useful. However, the family did not consent to that procedure in the present case.

When concomitant lesions outside the CNS exist, such as skin or pulmonary lesions, bacterial investigations of these lesions may be useful (4, 6). Our patient suffered pneumonia twice during the clinical course, but *Nocardia* was not detected from sputa cultures. No skin lesions were identified.

The biggest problem in our case was that *Nocardia* meningitis was not included among the differential diagnoses at any time during the clinical course. As noted above, *Nocardia* meningitis is difficult to diagnose, although CSF findings can provide a clue. Moderately decreased glucose levels and neutrophil-dominant pleocytosis are seen in the CSF during nocardial meningitis (4, 6). These findings continue even during antibiotic therapy (4, 6), as seen in the current case (Table 1). Moderately decreased glucose levels in CSF may be associated with the slow-growing nature of *Nocardia*. As a result, *Nocardia* meningitis should be included among the differential diagnoses when moderately low glucose levels in CSF and neutrophil-dominant pleocytosis continue. However, these CSF findings of neutrophil-dominant pleocytosis and moderately decreased glucose are not spe-

Table 2. Results of Minimal Inhibitory Concentration (MIC) Testing for Antibiotics.

antibiotics	MIC (μg/mL)
AMK	<0.5 (susceptible)
CTRX	<2 (susceptible)
CPFX	4 (resistant)
IPM	4 (susceptible)
LZD	4 (susceptible)
MINO	2 (intermediate)
ST	9.5/0.5 (susceptible)
TOB	<0.5 (susceptible)
CTX	<2 (susceptible)
CFPM	4 (susceptible)
DOXY	8 (resistant)
GM	<0.5 (susceptible)
CAM	<0.25 (susceptible)

The present strain of *N. araoensis* was resistant to DOXY and CPFX, with intermediate susceptibility to MINO. AMK: amikacin sulfate, CTRX: ceftriaxone, CPFX: ciprofloxacin, IMP: imipenem/cilastatin, LZD: linezolid, MINO: minocycline, ST: sulfamethoxazole/trimethoprim, TOB: tobramycin, CTX: cefotaxime, CFPM: cefepim, DOXY: doxycycline hydrochloride, GM: gentamycin, CAM: clarithromycin

cific for *Nocardia* meningitis (11), with similar findings in meningitis due to *Mycobacterium tuberculosis* (12), *Actinomyces* spp. (13, 14), *Candida* spp. (15, 16) and *Cryptococcus* spp. (17).

Nocardia species are known to represent a cause of opportunistic infections (1, 4, 6, 10), and most patients with nocardiosis have underlying diseases contributing to an immunodeficient state, such as acquired immunodeficiency syndrome, diabetes mellitus, hematological malignancies, immunosuppressive drugs or renal failure. In *Nocardia* meningitis, 75% of cases are immunocompromised due to immunosuppressive drugs, malignancy or miscellaneous conditions (4). Our case showed a low CD4 lymphocyte count (23/μL). Given these low CD4 cell counts, we performed HIV-PCR during the course and bone marrow at autopsy, but no positive findings were obtained. In a study with BALB/c mice, Rosas-Taraco et al. reported that infection by *N. brasiliensis* induced an immunosuppressive microenvironment in the chronic stage (18). Alcohol consumption can cause low CD4 cell counts via low levels of interleukin 2 (19). The *N. araoensis* infection itself coupled with heavy alcohol consumption might thus have caused the low CD4 cell counts in the present case.

The optimal duration of pharmacotherapy remains uncertain. *Nocardia* infections tend to relapse, so treatment must be continued for a long period. All immunosuppressed patients, whatever the syndrome, should receive a minimum of 12 months of therapy (10). Patients with *Nocardia* infection of the CNS need 12 months of therapy, even if immunocompetent (10). In the current case, meningitis 2 months prior to admission was probably due to *N. araoensis* infection, because the treatment duration was too short for control of *Nocardia* meningitis, at only 14 days.

CNS disease due to *Nocardia* is generally thought to occur via hematogenous dissemination from a primary site, usually in the lungs (4, 10). This primary site may not be apparent when the CNS infection is active (4), so the organism causing pneumonia 4 months prior to this admission might have been *N. araoensis*.

In the current case, *Nocardia* was isolated from pus from the left lateral ventricle, and was identified as *N. araoensis* by 16S rRNA gene sequence analysis.

Infection by *N. araoensis* seems rare; the organism has been isolated from the sputum of a patient with nontuberculous mycobacterial infection (2) and the skin of a patient with cutaneous lymph duct-type nocardiosis (3). Although *N. brasiliensis*, *N. pseudobrasiliensis*, *N. asteroides* and *N. caviae* have all been reported as etiological organisms for nocardial meningitis (4, 9), this appears to represent the first report of meningitis due to *N. araoensis*. The clinical features of *N. araoensis* meningitis are indistinguishable from those of other cases of nocardial meningitis, and patients need long-term antibiotic treatment (10).

In MIC tests for antibiotics, CPFX and DOXY appeared ineffective and MINO was intermediately effective, while other tested drugs appeared effective (Table 2).

In the present case, LVFX, MEPM, VCM, CTRX, PAMP/BP, MINO and CTM were administered during the clinical course. Among these antibiotics, the *N. araoensis* strain present in the patient was susceptible to CTRX. MEPM and PAMP/BP may have been effective because the *N. araoensis* was susceptible to IMP/CS. Considering the results of susceptibility testing, we could have saved the patient if we had been able to reach the correct diagnosis.

In conclusion, the maximum effort to reach a correct diagnosis requires: 1) inclusion of nocardial meningitis among the differential diagnoses; 2) continuation of CSF cultures for longer than several weeks; and 3) acquisition of pus samples if at all possible.

The authors state that they have no Conflict of Interest (COI).

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