Case study

*Nocardia paucivorans* brain abscess. Clinical and microbiological characteristics

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**Abstract**

*Nocardia paucivorans* brain abscesses are unusual in humans. Sixteen cases of this infection have been reported in the world medical literature. There is precise clinical information available from nine patients. All of these patients recovered or were cured from their brain disease with long-term antimicrobial treatment. Surgical drainage was performed in four patients.

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**Introduction**

*Nocardia* species are ubiquitous in nature and mainly cause pulmonary disease in humans; but it can also infect the central nervous system and the skin \cite{1,2}.

Traditional phenotypic laboratory methods for identification of *Nocardia* species are limited in their ability to differentiate these organisms. Instead, various molecular techniques have been developed which allow accurate species determination \cite{1}. The identification of clinical isolates to the species level is crucial to characterize associated disease manifestations, predict antimicrobial susceptibility and identify differences in epidemiology.

In 2000, Yassin et al. \cite{3} described a new species of the genus *Nocardia* based on chemotaxonomic and molecular analysis of an isolate from the respiratory secretions of a patient with chronic lung disease, which was called *Nocardia paucivorans*. We have recently studied a patient with a brain abscess caused by *N. paucivorans*. The literature has provided limited guidance regarding the care of patients with this condition \cite{4–12}. Thus, a review of this topic seems timely.

**Case report**

A 61-year-old man was admitted to the hospital because of a 2-week history of progressive right hemiplegia and frontal headache. He had been diagnosed of oculomotor paralysis of his left eye and was treated with amoxicillin-clavulanate (750 mg/250 mg orally every 8 hours) and prednisone (10 mg/day). At presentation, physical examination revealed right hemiplegia and his temperature was 36.5°C. Laboratory investigations were unremarkable.

A CT scan of the head showed a left frontal lesion suggestive of metastasis. A CT scan of the chest, abdomen and pelvis did not show abnormalities. A cerebral magnetic resonance imaging (MRI) disclosed a multilobulated necrotic cystic ring-enhancing lesion in the left frontal area, with surrounding edema. Diffusion-weighted imaging showed restriction of the diffusion. Stereotactic aspiration of the left frontal lesion was performed, obtaining twelve mL of purulent fluid. A Gram-stained smear of the fluid showed branching, filamentous Gram-positive bacilli, which were further identified, after growth in culture, as *N. paucivorans* by means of 16S rRNA sequence analysis. Susceptibility was determined by E-test method. The organism was susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), amikacin, amoxicillin-clavulanate, cefotaxime, ceftriaxone, levofloxacin, linezolid and tigecycline; and was resistant to imipenem, clarithromycin, and clindamycin. Tests for human immunodeficiency virus (HIV) types 1 and 2 antibody and p24 antigen were negative.

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| Case n. | Age (yr) | Sex | Concomitant illnesses or condition | Location of infection | Symptom(s) and sign(s) | Brain imaging findings | Source of identification of N. paucivorans | Treatment | Outcome |
|---------|----------|-----|-----------------------------------|----------------------|------------------------|------------------------|---------------------------------|------------|---------|
| 1 [4]   | 63       | M   | Low CD4+ T-cell count, HIV negative, cerebellar abscess removed 6 mo before | Cerebellar mass, meningitis | Headache, singultus | Cerebellar mass with surrounding edema | CSF | Cef + Amp (3 d); Amk + Mer (6 w); Levo + Mino (12 mo) | Neurological symptoms improved. No change in MRI findings |
| 2 [5]   | 40       | F   | NR | Brain abscesses | Brain abscess | Right frontal lobe multi-loculated ring-enhancing lesion with vasogenic edema and mass effect | Brain biopsy | NR | NR |
| 3 [6]   | 63       | M   | Hypertension | Brain abscesses | Apathy | Purulent material from brain lesion | Cranietomy and pus removed. | TMP-SMX (4 mo) | Complete resolution of brain CT scan after 4 mo of antibiotics |
| 4 [7]   | 53       | M   | Cigarette smoker, hepatitis C virus infection | Pneumonia, brain abscess, arm lesion | Cough, sputum, nausea, cachexia, ataxia, tender skin lesion | Multiple ring-enhancing brain lesions with surrounding edema | BAL fluid, skin lesion | TMP-SMX (12 mo) | Clinical and radiological resolution. No relapse after 12 mo of stopping antibiotics |
| 5 [7]   | 55       | M   | Hodgkin's disease | Brain abscess | NR | NR | NR | NR | NR |
| 6 [7]   | 41       | M   | Corticosteroid therapy | Brain abscess | NR | NR | NR | NR | NR |
| 7 [7]   | 58       | F   | Endocarditis | Brain abscess, hand lesion | Brain abscess | Blood, hand lesion | NR | NR | NR |
| 8 [7]   | 54       | M   | Immunosuppressed | Brain abscess, pneumonia | Brain abscess | Lung, brain lesion | NR | NR | NR |
| 9 [7]   | 66       | M   | Diabetes mellitus | Brain abscess, pneumonia | Brain abscess | Brain tissue | NR | NR | NR |
| 10 [7]  | 57       | M   | Multiple myeloma, levaldilomide and dexamethasone therapy | Brain abscesses, pneumonia | Brain abscesses, pneumonia | Seizures | Brain biopsy | TMP-SMX + Mer (3 w); Cip (12 mo) | Complete resolution of brain lesions on CT scan. No relapse of seizure. |
| 11 [10] | 70       | M   | Multiple myeloma | Brain abscesses, pneumonia | Brain abscesses, pneumonia | Seizures | Brain biopsy | TMP-SMX + Mer (3 w); Cip (12 mo) | Complete resolution of brain lesions on CT scan. No relapse of seizure. |
| 12 [8,9]| 50       | M   | Cigarette smoker | Brain abscesses, pneumonia, mediastial lymph nodes, iliposas muscle | Headache, vomiting, cough, confusion, nuchal rigidity, slight upper monoparesia, cachexia | Multiple ring-enhancing brain lesions | Subcarinal lymph node | TMP-SMX + Imi (2 w); TMP-SMX + Imi + Line + dexamethasone (3 w); TMP-SMX + Moxi (4 mo); Moxi (7 mo) | Resolution of brain and pulmonary lesions. Complete neurological recovery. |
| 13 [10] | 70       | M   | Multiple myeloma, levaldilomide and dexamethasone therapy | Brain abscesses, pneumonia | Brain abscesses, pneumonia | Six ring-enhancing brain lesions with surrounding edema | Brain biopsy | TMP-SMX + Mer (3 w); Cip (12 mo) | Complete resolution of brain lesions on CT scan. No relapse of seizure. |
| 14 [11] | 54       | M   | Right pneumonia two mo before | Cerebellar abscess | NR | Ring-enhancing cerebellar lesion and hydrocephalus | Cerebellar biopsy | Abscess drainage and EVD, Cef + Met (2 w); Line + Mer (1 w); Line + Imi (7 w); Cef + Met + Mer (2 w); Van + Rif + Mer (2 w); Van + Rif + Cef + TMP-SMX (2 w); Cef + TMP-SMX + Line (2 mo); Cef + TMP-SMX + Rif (5 w); TMP-SMX + Line (4 w); TMP-SMX + Line + Rif (5 w); TMP-SMX + Line (11 w) Surgery. Cef + TMP-SMX (35 d); TMP-SMX (9 mo) | Development of ventriculitis while on antibiotic treatment. Ventriculoperitoneal shunting required. Asymptomatic 8 mo after stopping antibiotics. Cured at 1 yr of follow-up |
| 15 [12] | 80       | F   | None | Brain, lung | Right hemiparesis, memory impairment Headache, confusion | Multiple ring-enhancing brain lesions | NR | EVD. Mer + TMP-SMX (2 mo); TMP-SMX (12 mo) | Recovered with neurologic sequelae at 1 yr of follow-up |
| 16 [12] | 50       | M   | None | Brain, lung | Right hemiparesis, memory impairment Headache, confusion | Multiple ring-enhancing brain lesions and hydrocephalus | NR | EVD. Mer + TMP-SMX (2 mo); TMP-SMX (12 mo) | Recovered with neurologic sequelae at 1 yr of follow-up |
| 17 [PR] | 63       | M   | Ocular myasthenia gravis, corticosteroids therapy | Brain abscess | Headache, right hemiplegia | Left frontal lobe multiloculated ring-enhancing lesion | Stereotactic abscess aspiration | Abscess aspiration, TMP-SMX + Cef + Met (3 d); TMP-SMX + Cef (2 w); Line + Cef (6 w); Levo (10 mo) | Recovered, with minimal sequelae. |
Discussion

Standard phenotype-based identification methods for *Nocardi a* species are slow and often imprecise. Therefore, various nucleic acid amplification tools targeting conserved gene regions have been used to provide rapid and accurate species determination. Of these tools, 16S rRNA gene sequence analysis is the most frequently used and has become “the gold standard” method for definitive species identification [1]. We performed 5’ end 16S rRNA gene PCR targeting the first 500-bp of the gene. There is consensus that this region contains sufficient sequence variability for species identification [1].

*N. paucivorans* has seldom been isolated from humans. In Queensland, an Australian state with a population of 3.66 million people, all nocardia isolated were identified to the species level between 1985 and 2004. Only 33 patient strains were characterized as *N. paucivorans* among approximately 1800 isolates of *Nocardia* species [7]. Using the MEDLINE database back to the year 2000, we found six cases of brain abscess caused by *N. paucivorans* in the world medical literature [4–12]. The clinical features of the sixteen patients and the one described herein are summarized in Table 1. The average age of the patients was 59 years (range 40–80 years) and 81% were male. There are brain imaging findings available from nine patients. Single ring-enhancing lesions were observed in four patients and multiple lesions in five patients. The infection was primary in the Central Nervous System (CNS) in ten patients. Six cases also had pneumonia in addition to CNS disease. The organism was identified from samples of the CNS in eight patients and from samples outside the CNS in three cases. No information is available on the remaining six patients.

The most common predisposing factors for nocardiosis are corticosteroid use, organ transplantation, malignancy and HIV infection [1,2]. In this series, two patients had neoplasia, two patients received corticosteroids and two had unspecified immunosuppression. Six patients had no predisposing conditions. In contrast with previous studies [2], no patient was seropositive for HIV infection nor had been an organ transplant recipient.

Clinical manifestations of eight patients are available. The most frequent symptoms at presentation were headache and altered mental status (in four patients each). Focal neurological deficits were observed in five patients. Two patients had hemiplegia, one patient had a slight right-sided pronator drift and one had ataxia. One individual presented with seizures. Nuchal rigidity was noted in one instance. Fever was not registered in any case. The duration of symptoms was documented in six patients, and had an average duration of 12.8 days (from immediate onset to one month).

Of the nine patients for whom details about treatment are reported, eight received treatment with regimens including TMP-SMX, in combination with other antimicrobials in six patients. Therapeutic regimens lasted between 4 and 14 months. Four patients were treated only with antibiotics with resolution of the cerebral lesion. Surgery was undertaken in four patients (abscess removal in three patients; and aspiration in one patient). Complete clinical resolution was achieved in five patients. Four patients recovered from neurological clinical symptoms but with sequelae. Despite the high mortality rate reported in patients with cerebral nocardiosis, ranging from 31% to 55% [1,12], no patient died in our review.

Optimal treatment regimens for *Nocardia* infections have not been established by controlled clinical trials [1]. Thus, treatment is based on case series and expert opinion. TMP-SMX is the mainstay of treatment of *Nocardia*, and it is the drug of choice for cerebral nocardiosis due to its good penetration in the CNS [1,2,12]. As empiric treatment, Rafiei et al. [12] recommended intravenous TMP-SMX plus meropenem for brain nocardiosis. Some authorities also advise a combination of drugs, including carbapenem derivatives, as induction therapy [2]. However, antimicrobial susceptibility testing is a useful guide to therapy in the setting of the newly described *Nocardia* species, when combination therapy is warranted, and in patients with TMP-SMX intolerance [1,13].

The Clinical and Laboratory Standards Institute has approved a broth microdilution method for antimicrobial testing of the aerobic actinomycetes and it is the reference method for *Nocardia* spp. [14]. Broth microdilution method, nonetheless, is somewhat impractical to many microbiology laboratories owing to cost, availability of supplies, and expertise needed to perform and interpret the results [15]. Other methods for *Nocardia* susceptibility testing include the E test and the BACTEC radiometric methods, which have been shown to correlate well with broth microdilution and are simpler to use in the routine clinical laboratory [15].

Antimicrobial susceptibility data available from *N. paucivorans* are scarce. Schlaberg et al. [13] have recently tested 11 strains of *N. paucivorans*. Nonsusceptible (resistant or intermediate) were 90% for amoxicillin-clavulanic acid, 18% for clarithromycin, and 9% for ciprofloxacin and minocycline, respectively. All isolates tested were susceptible to TMP-SMX, amikacin, imipenem, ceftriaxone, tobramycin and moxifloxacin. In our review, there are available data on susceptibility testing from patient number 1, 2, 12, 13, 15, 16, and 17 (see Table 1). One patient showed intermediate resistance to amoxicillin-clavulanate (patient 16), three patients tested showed resistance to clarithromycin (patients 15, 16 and 17), and our patient showed resistance to imipenem.

In recent years, linezolid has been included as an alternative to TMP-SMX, although adverse side effects should be considered for long-term therapy [2]. Interestingly, all *Nocardia* strains tested for linezolid are uniformly susceptible up to now [1,2,13]. There are no formal guidelines to define treatment duration; however, 12 months is commonly recommended by experts [1,2,12].

In conclusion, brain abscess caused by *N. paucivorans* is an infrequent disease in humans that may have a favourable prognosis with long-term antimicrobial treatment.

Conflict of interest

None.

Funding source

None.

Abbreviations: Amik = amikacin; Amp = Ampicillin; BAL = bronchoalveolar lavage; Cef = ceftriazone; CSF = cerebrospinal fluid; Cip = ciprofloxacin; d = days; EVD = external ventricular drain; Imi = imipenem; Levo = levofloxacin; Line = linezolid; Mer = meropenem; Met = metronidazole; Mino = minocycline; mo = months; Moxi = moxifloxacin; NR = not reported; PR = present report; Rif = rifampin; TMP-SMX = trimethoprim-sulfamethoxazole; Van = vancomycin; w = weeks.

a Brain imaging includes findings of brain CT scan and/or brain Magnetic Resonance Imaging.
Ethical approval

Not required.

Author statement

The author agrees with the recommendations and rules of the Journal (IDCases). On the other hand, all authors have contributed to the writing paper, have read it and agree with the content.

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