IDCases 13 (2018) e00422

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case study

Nocardia paucivorans brain abscess. Clinical and microbiological characteristics

Luis Aliaga[a,b,*], Georgette Fatoul[b], Emilio Guirao-Arrabal[b], Alejandro Peña[c], Javier Rodríguez-Granger[d], Fernando Cobo[d]

[a] Department of Medicine, University of Granada, Avda. de la Ilustración, 80, 18016, Granada, Spain
[b] Department of Internal Medicine. Hospital Campus de la Salud, Avda. de la Ilustración, 80, 18016, Granada, Spain
[c] Department of Microbiology, Hospital Campus de la Salud, Avda. de la Ilustración, 80, 18016, Granada, Spain
[d] Department of Microbiology, Hospital Virgen de las Nieves, Avda. de las Fuerzas Armadas, s/n, 18014, Granada, Spain

ARTICLE INFO

Article history:
Received 16 April 2018
Received in revised form 2 July 2018
Accepted 2 July 2018

Keywords:
Nocardia
Nocardiosis
Nocardia paucivorans
Nocardia brain abscess
Nocardia infections

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.

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 [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 [1]. The identification of clinical isolates to the species level is crucial to characterize associated disease manifestations, predict antimicrobial susceptibiltiy and identify differences in epidemiology.

In 2000, Yassin et al. [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 [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 ocular myasthenia gravis two years before and received medication with pyridostigmine, 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 multiloculated 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.

* Corresponding author at: Department of Medicine, University of Granada, Avda. de la Ilustración, 80, 18016, Granada, Spain.
E-mail address: laliaga@ugr.es (L. Aliaga).

https://doi.org/10.1016/j.idcr.2018.e00422

Table 1
Characteristics of the 17 patients with *Nocardia paucivorans* brain abscess.

Case nº., [Reference]	Age (yr)/ Sex	Concomitant illnesses or condition	Location of infection	Symptom(s) and sign(s)	Brain imaging findings[a]	Source of Identification of Nocardia	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	NR	NR	Brain biopsy	NR	NR
3 [6]	63/ M	Hypertension	Bain abscess	Apathy	Right frontal lobe multi-loculated ring-enhancing lesion with vasogenic edema and mass effect	Purulent material from brain lesion	Craniotomy 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	NR	Brain abscess	NR	NR	NR	NR	NR
6 [7]	41/ M	Hodgkin's disease	Brain abscess	NR	NR	NR	NR	NR
7 [7]	58/F	Corticosteroid therapy	Brain abscess	NR	NR	NR	NR	NR
8 [7]	54/ M	None	Endocarditis, brain abscess, hand lesion	NR	NR	Blood, hand lesion	NR	NR
9 [7]	66/ M	Immunosuppressed	Brain abscess	NR	NR	Brain tissue	NR	NR
10 [7]	57/ M	NR	Brain abscess, pneumonia	NR	NR	Lung, brain lesion	NR	NR
11 [7]	67/ M	Diabetes mellitus	Brain abscess	NR	NR	NR	NR	NR
12 [8,9]	50/ M	Cigarette smoker	Brain abscesses, pneumonia, mediastinal lymph nodes, iliopsoas 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, lenalidomide and dexamethasone therapy	Brain abscesses, pneumonia	Seizures	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 (11 w)	Development of ventriculitis while on antibiotic treatment. Ventriculoperitoneal shunting required. Asymptomatic 8 mo after stopping antibiotics.
15 [12]	80/F	None	Brain, lung	Right hemiparesis, memory impairment	Multiple ring-enhancing brain lesions	NR	Surgery. Cef + TMP-SMX (35 d); TMP-SMX (9 mo)	Cured at 1 yr of follow-up
16 [12]	59/ M	None	Brain, lung	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.

Abbreviations: Amk = amikacin; Amp= Ampicillin; BAL = bronchoalveolar lavage; Cef = ceftriaxone; 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 repored; 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.

The patient was initially treated with ceftriaxone (2 g IV q12 h) and TMP-SMX intravenously (15 mg/kg/day of TMP in four divided doses). Because the patient developed unremitting vomiting, TMP-SMX was changed to linezolid (600 mg IV q12 h) and after completion of 6 weeks, the patient continued taking levofloxacin (500 mg po/day) for 10 months. At six months of treatment, the patient recovered strenght in the right extremities and he was able to walk by himself. A MRI showed disappearance of the brain abscess.

Discussion

Standard phenotype-based identification methods for *Nocardia* 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 fequently 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 sixteen 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 antibacterials 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*. Nonsusceptibility (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, amickacin, 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.

Ethical approval

Not required.

Author statement

The author agree 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.

References

[1] Sorrell T.C., Mitchell DH, Iredell JR, Chen SC-A. *Nocardia* species. 8th ed. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas and Bennett's principles and practice of infectious diseases, Vol 2. Philadelphia: Elsevier; 2015. p. 2853–63 e2.

[2] Minero MV, Marín M, Cercenado E, Rabadán PM, Bouza E, Muñoz P. Nocardiosis at the turn of the century. Medicine (Baltimore) 2009;88:250–61.

[3] Yassin AF, Rainey FA, Burghardt J, Brzezinka H, Mauch M, Schaal KP, et al. *Nocardia paucivorans* sp. nov. Int J Syst Evol Microbiol 2000;50:803–9.

[4] Eisenblätter M, Disko U, Stoltenburg-Didinger G, Scherübl H, Schaal KP, Roth A. Isolation of *Nocardia paucivorans* from the cerebrospinal fund of a patient with relapse of cerebral nocardiosis. J Clin Microbiol 2002;40:3532–4.

[5] Wellinghausen N, Pietzcker T, Kern WV, Essig A, Marre R. Expanded spectrum of *Nocardia* species causing clinical nocardiosis detected by molecular methods. Int J Med Microbiol 2002;292:277–82.

[6] Khan S-NH, Sanche SE, Robinson CA, Pirouzmand F. *N. paucivorans* infection presenting as a brain abscess. Can J Neurol Sci 2006;33:426–7.

[7] Gray TJ, Serisier DJ, Gilpin CM, Coulter C, Bowler SJ, McCormack JG. *Nocardia paucivorans*- a cause of disseminated Nocardiosis. J Infect 2007;54:e95–8.

[8] Hammoud M, Kraft C, Pulst-Korenberg J, Chenoweth C, Gregg KS. Disseminated *Nocardia paucivorans* infection in an immunocompetent host. Infection 2014;42:917–20.

[9] Delavari N, Than KD, Chen KS, McKeever PE, Wang AC, Pandy AS. Resolution of innumerable cerebral *Nocardia paucivorans* abscesses after medical management. J Clin Neurosci 2016;27:175–7.

[10] Monticelli J, Luzzati R, Maurel C, Rosin C, Valentinotti R, Farina C. Brain abscesses caused by *Nocardia paucivorans* in a multiple mieloma patient treated with Lenalidomide and Dexamethasone: a case report and review of literature. Mediterr J Hematol Infect Dis 2015;7:e2015011, doi:http://dx.doi.org/10.4084/MJHID.2015.011.

[11] Schiaroli E, Pasticci MB, De Carolis E, Mello E, Pallotto C, Leli C, et al. Diagnosis of *Nocardia paucivorans* central nervous system infection by DNA sequencing from paraffin-embedded tissue. Infez Med 2016;24:147–52.

[12] Rafiei N, Peri AM, Righi E, Harris P, Paterson DL. Central nervous system nocardiosis in Queensland. A report of 20 cases and review of the literature. Medicine (Baltimore) 2016;95:e5255, doi:http://dx.doi.org/10.1097/MD.0000000000005255.

[13] Schlaberg R, Fisher MA, Hanson KE. Susceptibility profiles of *Nocardia isolates* based on current taxonomy. Antimicrob Agents Chemother 2014;58:795–800.

[14] Woods GL, Brown-Elliot BA, Conville PS, Desmond EP, Hall GS, Lin G, 2nd ed Susceptibility testing of *Mycobacteria*, Nocardiae, and other aerobic *Actinomycetes;* approved standard, vol 31. Wayne PA: Clinical and Laboratory Standards Institute; 2011 CLSI document M24-A2.

[15] Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. Mayo Clin Proc 2012;87:290–308.