Asymptomatic cerebral abscesses after pleuropulmonary *Nocardia farcinica* infection

S. Zayet[1], **S. Lang**[1], **Y. Ben Abdallah**[2], **T. Klopfenstein**[1] and **V. Gendrin**[1]

1) *Infectious Diseases Department and* 2) *Pneumology Department, Nord Franche-Comté Hospital, Trévenans, France*

Abstract

We report the case of a 68-year-old man with long-term receipt of steroid therapy who was diagnosed with cerebral abscesses and pulmonary nocardiosis. This patient displayed only respiratory symptoms. Confirmation of *Nocardia farcinica* species was achieved by specific PCR sequencing of the 16S ribosome RNA in bronchoalveolar lavage cultures. Cerebral magnetic resonance imaging revealed abscesses. Antibiotic therapy with trimethoprim/sulfamethoxazole was prescribed given the results of susceptibility tests and was maintained for 12 months, with no evidence of relapse afterwards.

Keywords: Abscesses, disseminated, *Nocardia farcinica*, nocardiosis, Trimethoprim-sulfamethoxazole

Original Submission: 23 October 2020; **Revised Submission:** 29 October 2020; **Accepted:** 31 October 2020

Article published online: 7 November 2020

Corresponding author: S. Zayet, Infectious Diseases Department, Nord Franche-Comté Hospital, 100 route de Moval, 90400 Trévenans, France.

E-mail: souhail.zayet@gmail.com

Introduction

Nocardia is an aerobic filamentous environmental Gram-positive bacterium belonging to the order *Actinomycetes*. Typically *Nocardia* is considered as an opportunistic pathogen that primarily affects immunosuppressed patients. It is potentially associated with disseminated infections such as respiratory tract infections (most common), central nervous system (CNS) infections or cutaneous infections. The *Nocardia farcinica* species is particularly associated with CNS involvement.

We report the case of an immunocompromised patient manifesting pleuropulmonary nocardiosis (*N. farcinica* infection) with asymptomatic cerebral abscesses discovered by systematic brain magnetic resonance imaging (MRI).

Case report

A 68-year-old man with a history of multinodular goiter with Graves orbitopathy treated with steroids sought care for respiratory symptoms, including dyspnoea and cough. His family members reported a thoracic trauma that occurred 2 months earlier and resulted in multiple rib fractures. At admission, the patient was afebrile and had unilateral crackling sounds on pulmonary auscultation. Physical examination revealed a blood pressure of 120/70 mm Hg with a regular heartbeat (100 beats/min) and normal saturation O_2 (95%). Neurologic examination was normal; there was no history of seizure or cranial nerve palsy. Laboratory findings revealed lymphopenia of 800 cells/mm^3 (normal range, 4000–10 000/mm^3) and elevated C-reactive protein of 110 mg/L (normal range, <5 mg/L). Chest radiograph reveled a round parenchymal opacity on the right upper lobe. Supportive treatment was initiated (analgesics, antitussives with empirical antimicrobial drugs (amoxicillin/clavulanate 3 g by intravenous (iv) infusion per day).

On day 3 after admission, the patient developed severe acute respiratory distress. Chest computed tomography (CT) showed a pulmonary opacity on the right upper lobe containing multiple excavations with bilateral (but predominantly right-sided) pleural effusions and a nondisplaced rib fracture (Fig. 1(A)). The patient was transferred to the intensive care unit and mechanically ventilated. The right pleural effusion was drained with a closed intercostal 16F chest tube. The fluid was purulent and abundant (about 1100 mL). Laboratory tests performed on the fluid revealed white cell count of 2200/μL (84% neutrophils), lactate dehydrogenase >700 IU/L and glucose concentration 7.4 mmol/L. After incubation of the pleural effusion sample at a temperature of 37°C, numerous pale yellow, dry and rough colonies grew, wrinkled and encrusted in the agar. No growth was noted after incubation at 45°C. Gram staining of these colonies showed crooked, branching Gram-positive filaments (Fig. 1(B)). The modified acid-fast stain was positive, suggesting nocardial infection. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Microflex; Bruker Daltonics, Bremen, Germany) was carried out; results identified *N. farcinica*. PCR amplification

https://doi.org/10.1016/j.nmni.2020.100808

of the 16S ribosomal RNA gene was then performed using primers A2 (5′-AGAGTTTGATCATGGCTCAG-3′) and S15 (5′-GGGCGCTGTGTACAAGGCC-3′). The sequences were compared with sequences published in the GenBank database using the BLAST algorithm; the closest sequence based on patristic distance was *N. farcinica*. Only *N. farcinica* had homology throughout the entire sequence. The gene is exclusive to *Nocardia* spp., with no similar orthologs in any other bacteria according to a BLAST analysis. The same colonies of *Nocardia* were found in the bronchoalveolar lavage cultures.

Determination of the minimum inhibitory concentrations of cefotaxime, ceftazidime, imipenem, gentamicin, tobramycin, clarithromycin, ciprofloxacin and trimethoprim/sulfamethoxazole (TMP/SMX) was performed using Etest (bioMérieux, Marcy l'Etoile, France). This *N. farcinica* strain was resistant *in vitro* to cefotaxime, ceftazidime, gentamicin, tobramycin, clarithromycin and ciprofloxacin and was susceptible to imipenem, amikacin and TMP/SMX. Antimicrobial drugs were switched to imipenem/cilastatin (3 g by iv infusion per day) and TMP/SMX (30 mg/kg iv infusion per day). The evolution was favourable; the patient was extubated, and the chest tube was removed when imaging confirmed durable resolution of pleural effusion and reduction of parenchymal consolidation. Cerebral MRI showed a single round well-circumscribed lesion on the right frontal lobe, with low T1 and high T2 signal, heterogenous with peripheral enhancement, with a distinctive high signal in diffusion sequences. These results were in favour of a brain abscess (Fig. 1(C)). Disseminated (pulmonary and cerebral) nocardiosis was diagnosed from the results of 16S ribosomal RNA sequencing, microbiologic testing and imaging. The patient was discharged after 6 weeks of treatment with iv antimicrobial drugs. Treatment with TMP/SMX (640/3200 mg in two dived doses orally) was maintained for 12 months after discovering brain involvement. The patient underwent subsequent brain imaging, which returned to normal, without any relapse during 2 years' follow-up.

Discussion

Nocardiosis is an opportunistic infection responsible for localized or disseminated diseases. In France, its incidence is 0.31 cases per 100 000 habitants [1]. Pulmonary nocardiosis is a well-described infectious disease in immunosuppressed patients, but it also occurs in immunocompetent patients in nearly 30% of cases [2]. In some studies, authors have suggested that there are no differences in onset or clinical presentation between immunocompetent patients and immunosuppressed patients. In our case, we noted two predisposing factors that could explain the *Nocardia* infection: thoracic trauma is a potential gateway for the bacterium [3] and long-term steroid therapy is usually considered a risk factor of *Nocardia* spp. infection [1,2,4]. No specific telluric exposure was found in our case. Nocardiosis usually presents as a self-limited respiratory tract infection. However, in some patients *Nocardia* spreads from lungs to other organs with a particular affinity for the brain, especially *N. farcinica*.

N. farcinica is one of the most frequent *Nocardia* species isolated from human specimens in France. The proportion of *N. farcinica* has increased significantly over time, from 13% in 2010 to 27.6% in 2014 [5]. In this first epidemiologic study of *Nocardia* isolated from human samples in France, *N. farcinica* was the most frequently isolated species in blood cultures and brain abscesses (21/39, 54% and 19/43, 44.2% respectively). The particularity of this species is its predilection for the CNS. Several cases have been reported in medical literature [3,6–8].

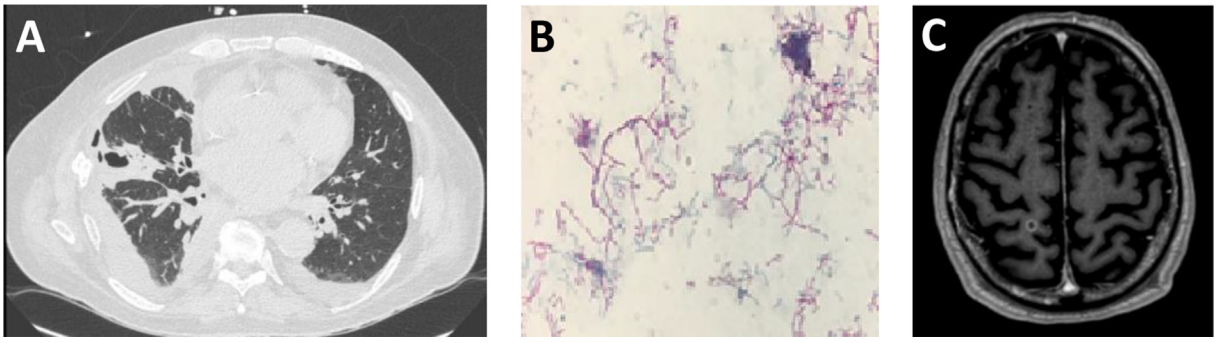

FIG. 1. (A) Chest computed tomographic scan revealing large pulmonary opacity on right upper lobe containing multiple excavations, linear atelectasis with bronchogram on right middle lobe lateral segment, predominantly right-sided pleural effusion and nondisplaced rib fracture (K6). (B) Gram staining of bacterial cultures shows Gram-positive filaments, suggesting *Nocardia* spp. infection. (C) Cerebral magnetic resonance imaging, axial view, showing well-circumscribed round lesion in right central paramedian sulcus with low T1 signal and peripheral enhancement and two small lesions in right frontal lobe.

In our case, neurologic examination was normal; cerebral abscesses were discovered on systematic imaging. MRI of the brain should be considered an important examination in *Nocardia* spp. infection, especially in *N. farcinica*. In a review of literature, only 2 of 54 patients considered to have CNS nocardiosis presented without any neurologic abnormalities [4]. 18-Fluorodeoxyglucose positron emission tomography and computed tomography (^{18}F-FDG PET/CT) can also be performed to distinguish rare infection as nocardiosis from malignancy and to assess the extent of the infection [9,10]. ^{18}F-FDG PET/CT is useful in identifying an elevated ^{18}F-FDG uptake locus in pulmonary or brain nodule and in performing biopsy using CT-guided puncture of the lesion site in easily accessible nodules (especially in cases of pleural location) [10].

Moreover, *N. farcinica* has specific drug susceptibility patterns. In French data, *N. farcinica* was frequently not susceptible to cefotaxime (80% of the isolates), meropenem (73% of isolates) and aminoglycosides (more than 90%) [5], but it was frequently susceptible to amoxicillin/clavulanic acid or imipenem, with 20% and 23% of nonsusceptible isolates, respectively. For carbapenem antibiotics, *N. farcinica* isolates were more frequently resistant to meropenem than to imipenem. Third-generation cephalosporins and meropenem should be avoided until obtaining the antimicrobial susceptibility testing result.

TMP/SMX is the standard treatment for *N. farcinica* infections, especially in CNS nocardiosis, thanks to its good penetration into the CNS. Recommended are 5 to 10 mg/kg per day of trimethoprim and 25 to 50 mg/kg per day of sulfamethoxazole (provided as divided doses), resulting in sulfonamide serum concentrations between 100 and 150 µg/mL [11]. *N. farcinica* is occasionally resistant to TMP/SMX [11]. Usually TMP/SMX is initially combined with imipenem or amikacin for the treatment CNS or disseminated nocardiosis [12]. A prolonged duration of therapy (6 months to 1 year) is recommended for CNS and/or disseminated nocardiosis, depending on CNS involvement, and seems to influence the outcome of the disease.

Conclusion

This case is a reminder that brain nocardiosis needs to be suspected, especially in infection with *N. farcinica,* and that systematic brain imaging is necessary. Early identification of the specific species is paramount in order to initiate long-term antibiotic therapy, acknowledging the inherent resistance of *N. farcinica* to third-generation cephalosporins and its susceptibility to TMP/SMX and imipenem.

Conflict of interest

None declared.

References

[1] Le Coustumier EM, Denes E, Martin C, Weinbreck P. Nocardiosis: a retrospective case series of 19 patients. Rev Med Int 2017;38:81–9.
[2] Fujita T, Ikari J, Watanabe A, Tatsumi K. Clinical characteristics of pulmonary nocardiosis in immunocompetent patients. J Infect Chemother 2016;22:738–43.
[3] Wang A, Xu Q, Wang Y, Liao H. Orbital and intracranial *Nocardia farcinica* infection caused by trauma to the orbit: a case report. BMC Infect Dis 2019;19:953.
[4] Anagnostou T, Arvanitis M, Kourkoumpetis TK, Desalermos A, Carneiro HA, Mylonakis E. Nocardiosis of the central nervous system: experience from a general hospital and review of 84 cases from the literature. Medicine (Baltimore) 2014;93:19–32.
[5] Lebeaux D, Bergeron E, Berthet J, Djadi-Prat J, Mouniée D, Boiron P, et al. Antibiotic susceptibility testing and species identification of *Nocardia* isolates: a retrospective analysis of data from a French expert laboratory, 2010–2015. Clin Microbiol Infect 2019;25:489–95.
[6] Moniuszko-Malinowska A, Czupryna P, Swiecicka I, Grześ H, Siemieniako A, Grygorczuk S, et al. *Nocardia farcinica* as a cause of chronic meningitis—case report. BMC Infect Dis 2020;20:56.
[7] Galacho-Harriero A, Delgado-López PD, Ortega-Lafont MP, Martín-Alonso J, Castilla-Díez JM, Sánchez-Borge B. *Nocardia farcinica* brain abscess: report of 3 cases. World Neurosurg 2017;106:1053.e15–24.
[8] Izawa D, Sakano K, Okumura H, Kuwata T, Tsuji N. Two cases of *Nocardia farcinica* brain abscess. No Shinkei Geka 2011;39:1167–72.
[9] Playe M, Einfalt M, Toch SR, Froissart A, Bodardel G. ^{18}F-FDG imaging of a case of disseminated nocardiosis. Clin Nucl Med 2020;45:55–6.
[10] Zhao K, Dong MJ, Sheng ZK, Liu KF, Yang SY, Liu ZF, et al. Elevated uptake of ^{18}F-FDG in PET/CT imaging of a nocardial pleural nodule. Clin Imaging 2012;36:383–5.
[11] Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc 2012;87:403–7.
[12] Eschapasse E, Hussenet C, Bergeron A, Lebeaux D. Respiratory infections caused by slow-growing bacteria: *Nocardia, Actinomyces, Rhodococcus*. Rev Mal Respir 2017;34:661–71.