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CASE REPORT

Post-neurosurgical Nocardia meningoventriculitis: a case report and review of the literature

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SUMMARY

The genus *Nocardia* consists of a group of gram-positive environmental bacteria. They typically cause lung and brain infections in immunocompromised patients, even though one out of three infected patients have a normally functioning immune system. Being a ubiquitous microorganism, in some cases *Nocardia* has been associated with nosocomial acquired infections and surgical procedures. A review of the literature in this field follows the case report. A 47-year-old woman underwent an endoscopic third ventriculostomy and a left retro-sigmoid craniotomy for a schwannoma removal. Meningeal symptoms began a week later, in association with C reactive protein rise and leukocytosis. Cerebrospinal fluid (CSF) examination was clear with hypoglycorrhachia, hyperprotidorrachia and polymorphonuclear cells. Cultural exam was negative. At the brain magnetic resonance imaging (MRI) purulent material was described in the occipital ventricular horns. Empirical broad spectrum antibiotic therapy was given for 31 days until the brain MRI showed a resolution of the infection. Ten days later, the patient was admitted to the hospital because of new meningeal symptoms. Cerebrospinal fluid culture and Polymerase-chain reaction (PCR) Multiplex for the most important meningitis viruses and bacteria tested negative. A broad-spectrum antibiotic therapy was started with no benefit; thus, a broad-spectrum antifungal therapy was added with little success on clinical status. Meanwhile, a 16s and 18s rRNA PCR was executed on a previous Cerebrospinal fluid with negative results, excluding bacterial and fungal infections. For this reason, all the therapies were stopped. After a few days, high fever and meningeal signs reappeared. The brain MRI showed a meningoventriculitis. An Ommaya catheter with reservoir was inserted and the drawn CSF resulted in the growth of *Nocardia farcinica*. Antibiogram-based antibiotic therapy was started with intravenous imipenem and trimethoprim-sulfamethoxazole, showing clinical benefit. The patient was sent home with oral linezolid and amoxicillin/clavulanate for a total of 12 months of therapy. *Nocardia* rarely causes post-neurosurgical complication in a nosocomial setting. This case shows the difficulty in detecting Nocardia and the importance of the correct microbiological sample and antibiogram-based antibiotic therapy to achieve successful treatment.

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INTRODUCTION

The genus *Nocardia* (Order *Actinomycetales)* consists of a group of environmental bacteria that currently includes 118 recognized species with valid names (https://lpsn.dsmz.de/genus/nocardia). Species belonging to the genus *Nocardia* can be found in soil, decomposing vegetation, and other organic matter as well as in fresh and salt water. *Nocardia* spp. can grow on most non-selective culture media under aerobic conditions, requiring at least 48 hours (more commonly 3-5 days). At microscopic examination they appear as very long, obviously branching, thin, and finely beaded gram-positive rods (*Figure 1*). Antimicrobial susceptibility varies depending on different species, with *Nocardia farcinica* being especially virulent and resistant to several antibiotics (Wilson, 2012).

From a clinical point of view, *Nocardia* is an opportunistic pathogen affecting people with deficient T-cell response (e.g., people with HIV infection, hematological malignancies and organ transplant recipients) (Deem, Doughty *et al*., 1983). Even though Nocardiosis typically occurs in immunocompromised hosts, up to one-third of patients are immunocompetent (Beaman, Burnside *et al*., 1976).

Key words:
Hospital acquired infections, clinical microbiology, nocardiosis, CNS infections, bacterial ventriculitis, bacterial meningitis.

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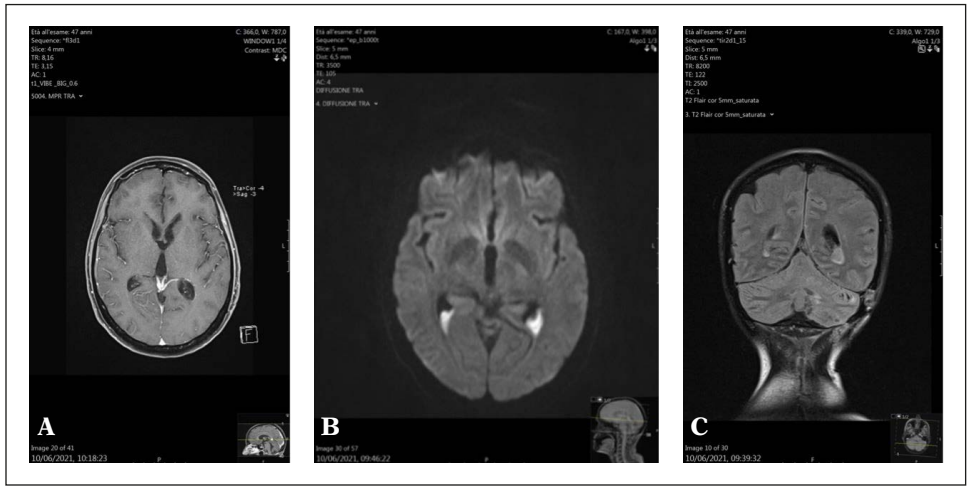

Figure 1 - *Meningoventriculitis with vertebral involvement.*
Picture A and B show the semifluid leak with diffusion restriction and signal reduction in the ventricular occipital horns on the axial plane. Picture C shows the ventricular diffusion restriction on the coronal plane. (3 months after craniotomy).

Pulmonary nocardiosis represents the most frequently diagnosed form. However, extra-pulmonary nocardiosis is common, mainly involving the central nervous system (CNS) (Beaman and Beaman, 1994). Cerebral nocardiosis typically manifests with single or multiple brain abscesses. Symptoms range from headache, nausea, and vomiting to seizures, meningeal symptoms, and alteration in consciousness (Brown-Elliott, Brown *et al.*, 2006).
We hereby report a case of meningoventriculitis due to *Nocardia farcinica* in a middle-aged immunocompetent woman after post-neurosurgical surgery.

CASE REPORT

A 47-year-old female was admitted to the Department of Infectious Diseases of our Institution (A. Manzoni Hospital of Lecco, Italy) because of high fever with chills and neck stiffness. The patient suffered from depression, and iron-deficient anemia was diagnosed on admission. Her recent history began when she started suffering from impaired hearing in the left ear and left face hypoesthesia, which led to the discovery of a brain mass in the left pontocerebellar brain region associated with hydrocephalus. Therefore, she underwent neurosurgery (in another institution) to reduce the intracranial pressure with an endoscopic third ventriculostomy. Subsequently, a left retro-sigmoid craniotomy was executed to partially remove the mass that was later identified at histological examination as a Schwannoma.
A week after surgery, high fever, neck stiffness and photophobia began, in association with C-reactive protein (CRP) rise and leukocytosis. Blood cultures and urine cultures were negative. Cerebrospinal fluid (CSF) was clear, with 480 cells/mm^3 (mostly polymorphonuclear cells), glucose was 17 mg/dL (blood glucose 80 mg/dL), proteins were 88 mg/dL and cultural examination was negative. At the brain magnetic resonance imaging (MRI) purulent material was observed in the occipital ventricular horns. Empirical antibiotic therapy for meningitis was started according to the infectious diseases consultant, at first with ceftriaxone, later with cefepime and vancomycin, then with meropenem and vancomycin, followed by meropenem and linezolid and lastly linezolid and cefepime, eventually with defervescence and clinical improvement. All changes were made empirically by an infectious diseases consultant from another center, considering the absence of microbiological isolates. The patient was thus discharged to a physical rehabilitation center, where she completed 31 days of antibiotic course before undergoing a follow-up brain MRI, which showed complete resolution of the infection.
Ten days later the patient was admitted to our Institution because of a recrudescence of fever and neck stiffness. Neurological examination revealed neck stiffness, bilateral nystagmus, left hemifacial paralysis and hypoesthesia, VI left cranial nerve paralysis with diplopia. The remaining physical examination was normal. A new brain MRI was acquired, showing ventriculitis, with enhancement in the posterior occipital ventricular horns.
Laboratory findings again showed a C-reactive protein rise and leukocytosis. Cerebrospinal fluid was partially clear and colorless, with glucose 15 mg/dL (blood glucose 120 mg/dL), proteins 219 mg/dL and cell count of 1612 cells/mm^3 (mostly polymorphonuclear cells). Cerebrospinal fluid culture was negative, as well as the multiplex polymerase chain reaction (PCR) carried out by the FilmArray instrument (bioMérieux, France) tested falsely positive for CMV (plasmatic CMV and CMV specific PCR will later result negative). The FilmArray PCR for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus* spp., *Enterovirus*, *Herpes simplex* virus (HSV)-1, HSV-2, *Human herpesvirus* (HHV-6), *Varicella-Zoster* virus tested negative.

Cefepime was started, and after 48 hours linezolid was added because of persistent fever. Finally, meropenem was introduced in place of cefepime, eventually leading to clinical improvement: fever subsided, rigor nucalis partially receded. No steroids were used.

On the 8th day of antibiotic therapy, a new lumbar puncture was performed. Cerebrospinal fluid examination still showed a clear liquor, hypoglycorrhachia (liquor glucose 22 mg/dL, blood glucose 110 mg/dL), proteins 343 mg/dL, cell count 1328/mm^3. Cerebrospinal fluid culture and multiplex PCR tested negative. Galactomannan, cryptococcal antigen, and acid-fast staining were also negative. Immunophenotype tested negative for anomalies, T cells and granulocytes were prevalent.

Due to the persistence of neurological symptoms and cerebrospinal fluid alterations, with the aim of covering *Toxoplasma gondii* and fungal pathogens, trimethoprim-sulfamethoxazole (TMP-SMX) and liposomal amphotericin B (L-AMB) were started, with complete defervescence and resolution of neck stiffness.

A new lumbar puncture was performed after 1 week of treatment: hypoglycorrhachia persisted (CSF glucose 21 mg/dL, blood glucose 110 mg/dL), proteins were 243 mg/dL, cell count plummeted to 123/mm^3. CSF culture yielded a negative result. Moreover, to increase sensitivity given the concomitant antimicrobial treatment with L-AMB and TMP-SMX, the previously acquired cerebrospinal fluid was tested with a 16s and 18s rRNA PCR giving negative results; moreover, the specific PCR for *Toxoplasma gondii* also tested negative. Due to nausea and hypokalemia and the absence of positive results for *Toxoplasma* and fungal infection, both TMP-SMX and L-AMB were discontinued, leaving the patient in therapy wash-out.

The clinical condition worsened again: fever peaked at 38.5°C, neck stiffness and zygomatic pain appeared. A new brain MRI was acquired: the occipital ventricular horn alteration persisted with the addition of a bulbar enhancement, with findings suggesting meningoventriculitis (*Figure 2*). A week after the antibiotic suspension the case was discussed with fellow neurosurgeons and an endoventricular catheter with Ommaya reservoir was inserted. The catheter-drawn cerebrospinal fluid was examined: hypoglycorrhachia persisted, proteins were 242 mg/dL, and cell count was 2281/mm^3. India Ink test and multiplex PCR were negative. Following this approach, small and chalky white colonies started to grow on different enriched agar media even though only after subculturing of CSF from Thioglycollate broth. Microorganisms were Gram-positive with a branching microscopic feature typical for *Nocardia* (*Figure 2*) and were then identified as *Nocardia farcinica* using both MALDI-TOF mass spectrometry (Vitek MS, bioMérieux) and 16s rRNA PCR.

Antimicrobial susceptibility testing was performed, showing susceptibility to linezolid, meropenem, amikacin and amoxicillin/clavulanate (*Table 1*). Targeted antibiotic therapy was started with intravenous meropenem 2 g tid and linezolid 600 mg bid, both stopped after 8 days due to anemia, confusion, and elevated plasmatic concentration. Instead of meropenem and linezolid intravenous imipenem 500 mg qid and TMP-SMX 1200/240 mg tid were started, the latter switched after 5 days to amikacin due to nausea and vomiting.

The patient's clinical condition progressively improved, and she was discharged with the reintroduction of oral linezolid and amoxicillin/clavulanate for a total of 12 months of therapy.

A month after discharge a clear and colorless CSF

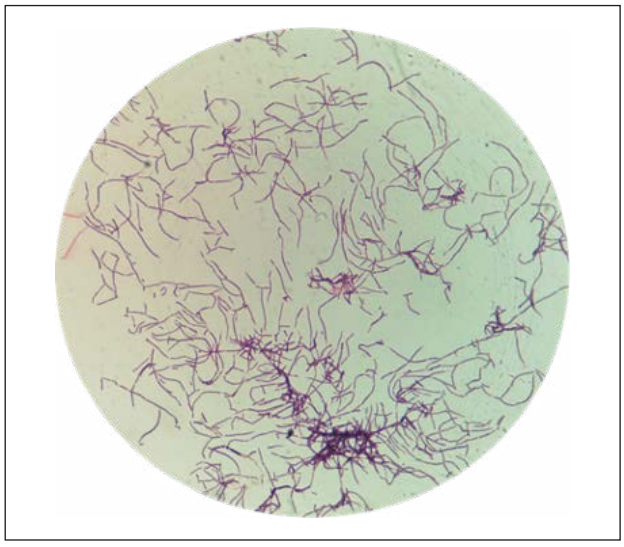

Figure 2 - *Nocardia farcinica as seen at the microscopical examination at our institution.*
It is a Gram-positive bacterium with a branched pattern of growth.

Table 1

ANTIBIOTIC	*MIC*	
LINEZOLID	2 mg/L	S
TMP/SMX	0.12 mg/L	IE
MEROPENEM	2 mg/L	S
CEFOTAXIME	32 mg/L	R
CIPROFLOXACIN	1 mg/L	R
GENTAMICIN	64 mg/L	R
AMIKACIN	1 mg/L	S
CEFTOBIPROLE	>32 mg/L	R
AMOXICILLIN/CLAVULANATE	1 mg/L	S
DAPTOMYCIN	>256 mg/L	R
TIGECYCLINE	4 mg/L	R
CEFTAROLINE	>32 mg/L	R

N. farcinica antibiogram. Antimicrobial susceptibility of Nocardia farcinica., Nocardia was tested on Mueller Hinton F incubated in CO2. MICs were interpreted according to PK-PD (Non-species related) EUCAST breakpoints.

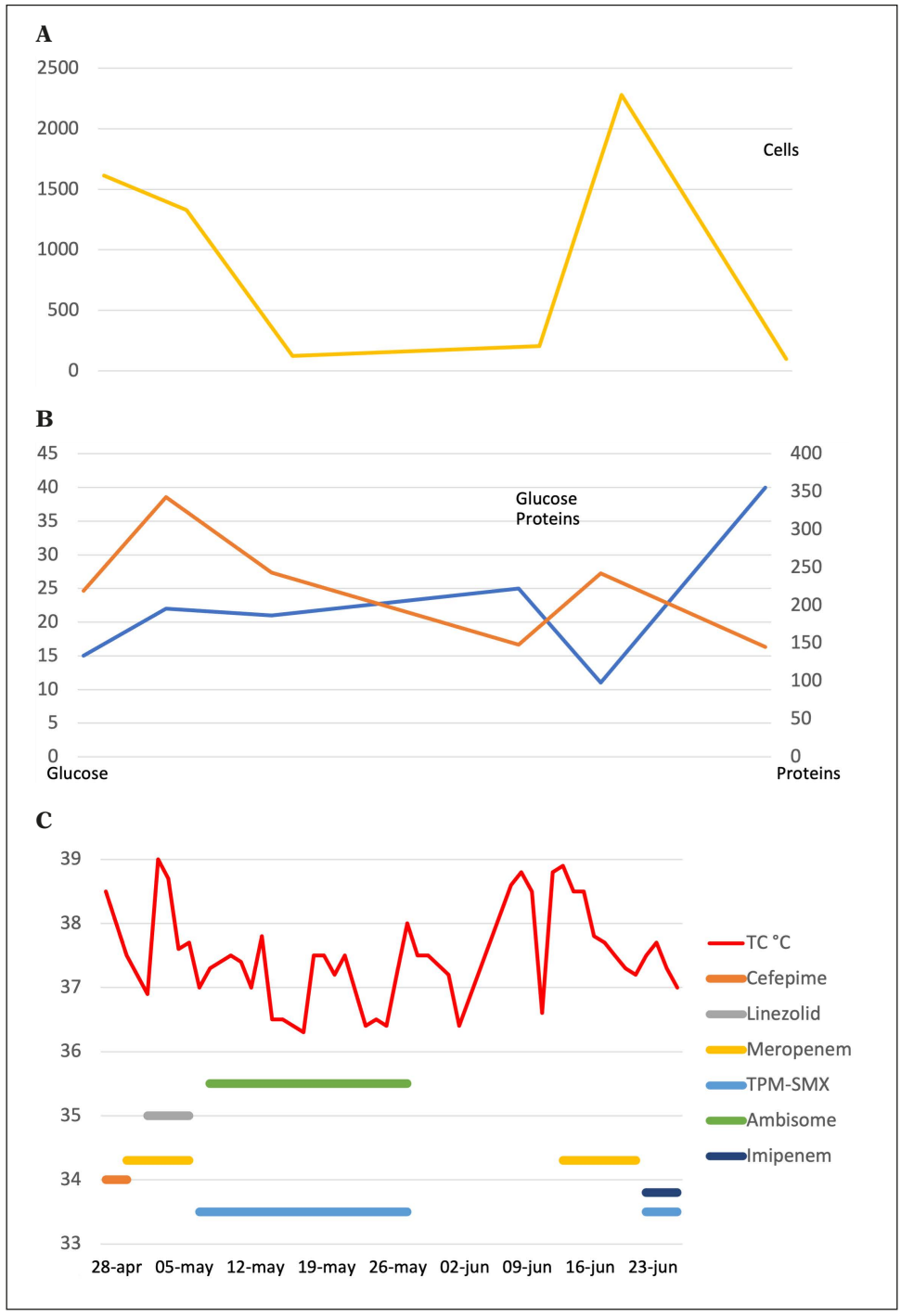

Figure 3 - *Changes in temperature and cerebrospinal fluid characteristics according to antibiotic therapy during the hospital stay at the Infectious diseases Unit of Lecco.*
Figure A shows the cell concentration in the CSF during the hospital stay.
Figure B describes the concentration of glycorrhachia and protidorrhachia in the CSF in the different lumbar punctures.
Finally, figure C depicts the fever curve in relationship to the different antibiotics used during the hospital stay.

was drawn, with liquor/plasma glucose ratio of 0.8, proteins 51 mg/dL, cell count 15 cells/mm^3 and negative culture. A month later, a new lumbar puncture was executed, showing an unchanged liquor. For this reason, the Ommaya catheter was removed.

DISCUSSION

Here we report a challenging case of *Nocardia farcinica* ventriculitis following brain surgery. This case is worth describing first due to the limited number of ventriculitis caused by *Nocardia* spp reported in the literature (Kandasamy, Iqbal *et al.*, 2008) but also due to the atypical manifestation of cerebral nocardiosis. Normally *Nocardia* causes single or multiple brain abscesses (Anagnostou, Arvanitis *et al.*, 2014), while we documented ventricular leak and meningitis with no other apparent brain localizations in an immunocompetent individual. This probably happened because *Nocardia* was inoculated directly into

the brain tissue during the neurosurgical procedure rather than developing a more typical brain metastatic infection that would have appeared as an abscess.
Nocardia species are typically inoculated through inhalation, ingestion, or direct contact (especially in cutaneous nocardiosis) (Beaman and Beaman, 1994; Lerner, 1996) Hospital-acquired cases are described in the literature (Houang, Lovett *et al*., 1980; Lovett, Houang *et al*., 1981; Sahathevan, Harvey *et al*., 1991; Kalpoe, Templeton *et al*., 2007; Beaman and Beaman, 1994). In this scenario, *Nocardia* was very likely inoculated during the aforementioned neurosurgical procedure. No cases of possible hospital-acquired nocardiosis were reported in our Institution prior to this.
Interestingly, the detection of this microorganism was possible only through culture of a CSF sample obtained by ventricular catheterization while the patient was in antibiotic wash-out. The CSF obtained via lumbar puncture always tested negative both for standard culture and with molecular diagnostics. The literature shows that very often *Nocardia* needs to be detected through isolation of the microorganism on biopsies of the suspected site (Restrepo and Clark, 2019). In this case no biopsy was executed, but *Nocardia* was found only in the CSF with a significant microbiological burden.
This case report again shows the importance of performing antimicrobial susceptibility testing for the *Nocardia* species. During hospitalization, the patient was treated with different antibiotics for too short a time that partially targeted *Nocardia farcinica* and always resulted in a partial clinical benefit. Only when treated with effective drugs with sufficient CNS penetration she did get better with disappearance of fever and rigor nucalis.
Antimicrobial susceptibility testing is strongly recommended, as there can be variable inter- and intraspecies susceptibility patterns (Restrepo and Clark, 2019).

Literature review

Post-neurosurgical meningitis (PNM) typically occurs after craniectomy, craniotomy or following the insertion of internal or external ventricular and lumbar catheters (Hussein, Bitterman *et al*., 2017). There is no defined epidemiological data, and according to different case series meningitis follows craniotomy in 0.18% to 8.6% of treated patients (McClelland and Hall, 2007; Chen, Zhang *et al*., 2014; Lin, Chen *et al*., 2014).
The majority of post-neurosurgical meningitis is caused by gram-positive microorganisms, mainly cutaneous flora like coagulase-negative *staphylococci* (CoNS), *Staphylococcus aureus,* and *Propionibacterium acnes*. Gram-negative bacilli are less common, (Hussein, Bitterman *et al*., 2017), even though *Acinetobacter baumannii* is emerging as a post-neurosurgical meningitis pathogen in some neurosurgical units (Metan, Alp *et al*., 2007; Chen, Zhang *et al*., 2014).
To date, no case series about post-neurosurgical meningoventricular nocardiosis have been published and very little literature exists in this specific field.
In the 2017 "Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis," *Nocardia* is not mentioned as a possible ventriculitis and meningitis pathogen and thus no insights on its management are present (Tunkel, Hasbun *et al*., 2017).
A *Nocardia nova* brain abscess case following a craniotomy with temporal lobe resection in a brain with small cell lung cancer (SCLC) metastases has been described (Abel, Hasan *et a*l., 2016). In other surgical fields post-operative Nocardiosis has been described. A peritonsillary abscess caused by a *Nocardia asteroides* that was probably introduced iatrogenically during a tonsillar incision is reported (Adair, Amber *et al*., 1987) along with a post-sternotomy *Nocardia asteroides* wound infection. (Yew, Wong *et al*., 1991). In both these scenarios the microorganism contaminated the surgical devices used during the procedure. Because *Nocardia* is a ubiquitous microorganism, outbreaks due to contamination of the hospital environment in transplant units have been reported (Lovett, Houang *et al*., 1981; Sahathevan, Harvey *et al*., 1991). In these particular cases, an infected patient contaminated the unit and the medical devices with *Nocardia*, resulting in other infections and in the organism's detection even in the air and dust of the hospital unit.
Physicians very often deal with patients who have meningeal symptoms and inflammatory CSF but no positive cultures, and who still respond to empiric antibiotical treatment (Tattevin, Tchamgoué *et al*., 2019). We may speculate that inadequate CSF sampling could be a factor impacting microbiological diagnostic yield.
Moreover, it is possible that a conflict of interests exists in the report of *Nocardia* post-neurosurgical meningitis. For a neurosurgical unit to have a post-operatory Nocardiosis case or outbreak would mean having a non-sterile surgical field, thus hurting a particular unit's medical credibility.
To sum up, even though Nocardiosis is a rare condition, in view of the diagnostic difficulty and the long and complicated antibiotical treatment of this pathogen, more case series and experience in a post-operatory setting are needed to better understand how to manage this clinical scenario.

CONCLUSIONS

Nocardia spp. should be taken into consideration as a possible agent of post-neurosurgical infectious complications, especially when first- and second-line empirical treatments for hospital-acquired meningitis

fail. Moreover, every effort should be made to obtain diagnostic samples directly from infected tissues. In this case, only the liquor drawn directly from the brain ventriculi showed the presence of *Nocardia farcinica*. Lastly, specific *Nocardia* species have different antibiotic susceptibilities; therefore, performing a susceptibility test is crucial to ensure the highest probability of clinical success.

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