Case report

# Disseminated Nocardiosis with Intracranial Mycotic Aneurysm in A Patient with Autoimmune Hepatitis: A Case Report and Review of The Literature

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## Abstract

We are reporting a case of disseminated *Nocardia otitidiscaviarum* infection, manifesting as a ruptured intracranial aneurysm in an immunocompromised patient. The patient succumbed despite treatment with trimethoprim-sulfamethoxazole, amikacin, and levofloxacin along with surgical repairment. Nocardiosis should be one of the differential diagnoses for intracranial mycotic aneurysm among immunocompromised patients.

**Running title:** *Nocardia* intracranial aneurysm

**Keywords:** Nocardiosis, *Nocardia otitidiscaviarum*, Intracranial mycotic aneurysm

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## Introduction

Nocardiosis is considered an opportunistic infection affecting immunocompromised patients. Intracranial mycotic aneurysm is a rare manifestation of central nervous system nocardiosis. To date, there are only 5 reported cases of intracranial mycotic aneurysms caused by nocardial infection. We are report a case of disseminated *Nocardia otitidiscaviarum* infection, a species that was rarely described as a significant pathogen in the medical literature, manifesting as a ruptured intracranial mycotic aneurysm in an immunocompromised patient.

## Case report

A 51-year-old Thai man with autoimmune hepatitis and chronic hepatitis B virus infection presented to our hospital with altered consciousness for 7 hours. Prior to this presentation, he had been suffering from fever and productive cough for 12 days. His medications included tenofovir disoproxil fumarate 300 mg daily, prednisolone 30 mg daily, and azathioprine 50 mg daily, which had been prescribed for 7 weeks to treat chronic hepatitis B and autoimmune hepatitis before this presentation. Initial examination showed a temperature of 36.9°C, heart rate of 76 beats/minute, respiratory rate of 24 breaths/minute, and blood pressure of 186/112 mmHg. Chest auscultation revealed bronchial breath sound and coarse crepitation at the left upper lung area. Neurological examination revealed decreased level of consciousness with eyes opening, incomprehensible sounds, and response to pain. Motor power was at least grade 3 for all extremities. Papilledema was notable on ophthalmoscopy. Chest X-ray showed consolidations at both lungs predominant at left upper lung (Figure 1A). Emergency computed tomography (CT) scan of the brain showed acute hematoma in the bilateral frontal lobes with intraventricular hemorrhage and subacute infarction in the bilateral frontal lobes, genu of corpus callosum and left thalamus (Figure 1B). To search for the source of bleeding, CT angiogram of the brain was subsequently performed and revealed a 3.1 x 2.2 mm saccular aneurysm originating from the A2 segment of left anterior cerebral artery, suggesting a ruptured aneurysm (Figure 1C).

Bifrontal craniectomy was performed. The operative findings revealed subdural frank pus, more prominent in the left subdural space and a necrotic aneurysm with thrombus occlusion in the left anterior cerebral artery. Clipping the aneurysm with pus drainage was done. A pus Gram's stain showed branching filamentous, beaded gram-positive bacilli (Figure 1D) which were acid-fast on the modified Kinyoun stain. The sputum Gram's and modified Kinyoun stain showed the similar results. The treatment was started with intravenous (IV) trimethoprim-sulfamethoxazole (TMP-SMX) at the total daily dose of 15 mg/kg of TMP, 15 mg/kg/day of IV amikacin, and 750 mg/day of IV levofloxacin. *Nocardia otitidiscaviarum* was identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) in an isolated colony from the pus bacterial culture. The antimicrobial susceptibility test by broth microdilution method revealed susceptibility to TMP-SMX (MIC 0.5 μg/mL), amikacin (MIC 2 μg/mL), ciprofloxacin (MIC 1 μg/mL), moxifloxacin (MIC 1 μg/mL), doxycycline (MIC 1 μg/mL), and linezolid (MIC 2 μg/mL). The isolate was resistant to amoxicillin-clavulanate (MIC 32 μg/mL), ceftriaxone (MIC 64 μg/mL), and imipenem (MIC 16 μg/mL). The final diagnosis of disseminated nocardiosis was made. Despite surgical and antimicrobial therapy, his level of consciousness did not improve. On day 5 of hospitalization, the patient developed status epilepticus and passed away 2 days later.

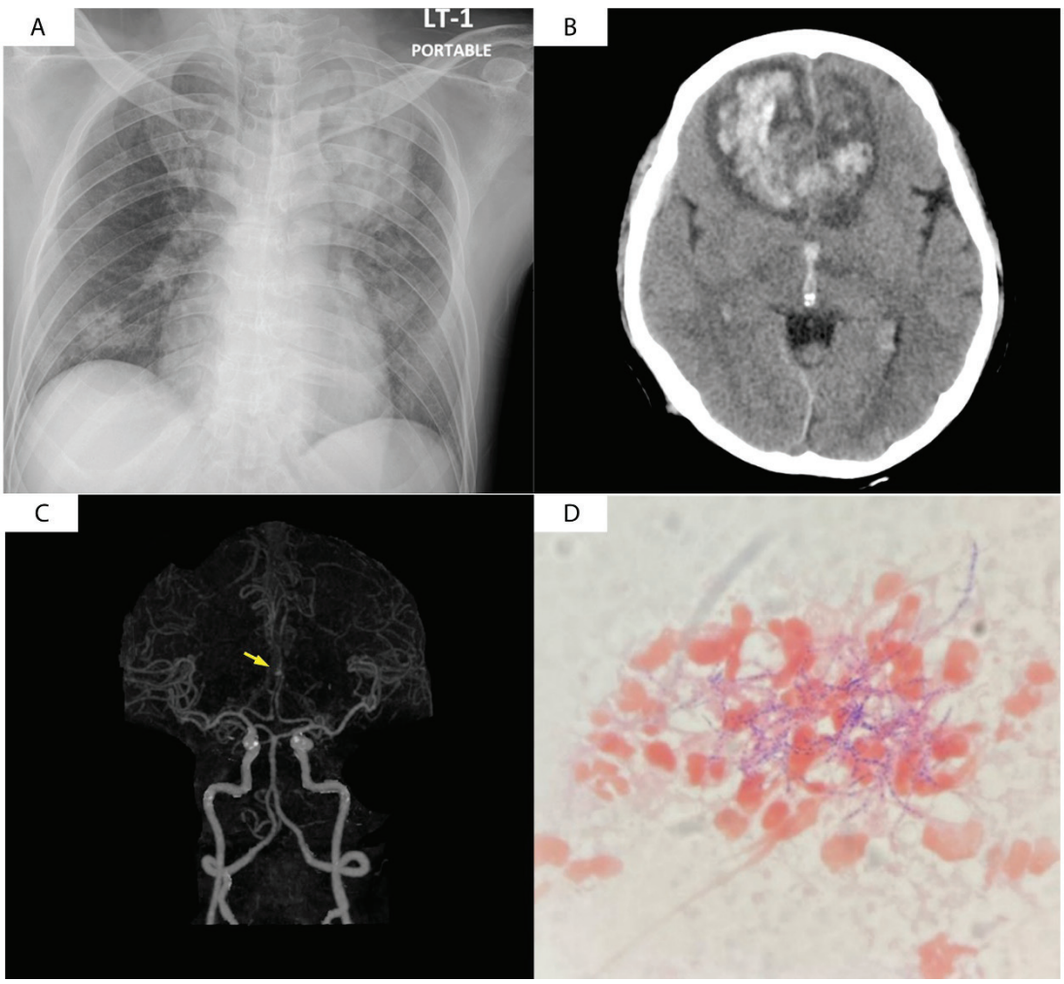


**Figure 1** (A) Chest X-ray showed consolidations at both lungs predominantly in the left upper lung. (B) Computed tomography scan of the brain showed acute hematoma in the bilateral frontal lobes with intraventricular hemorrhage and subacute infarction in the bilateral frontal lobes, genu of corpus callosum and left thalamus. (C) Computed tomography angiogram of the brain reveled a 3.1 x 2.2 mm saccular aneurysm originated from A2 segment of left anterior cerebral artery (arrow). (D) A pus sample from the brain Gram stain showed branching filamentous, beaded gram-positive bacilli.

## Discussion

*Nocardia* species are filamentous, Gram-positive, partially acid-fast, branched bacteria that are ubiquitous in the environment, particularly in the soil. *Nocardia* can be regarded as primary pathogens, without evidence of underlying illnesses or immunosuppressive therapy, although they are considered opportunistic pathogens.[1] The species *N. otitidiscaviarum* was first isolated from the mid-ear of a guinea pig and reported by Snijders in 1924. The first human infection due to *N. otitidiscaviarum* was reported in 1974 and was previously named *Nocardia caviae*. *N. otitidiscaviarum* is an infrequent cause of human nocardial infections. In some case series, it accounted for only 0.3-2.9% of all nocardial infections.[2] There have been 53 reported cases of *N. otitidiscaviarum* disease. Isolated pulmonary involvement was the most frequent presentation accounting for 35.8% of all cases, followed by isolated cutaneous infections accounting for 32.1%, while 18.9% had disseminated disease involving two or more organs. The central nervous system (CNS) was involved in 60% of those with disseminated disease. Isolated CNS infection accounted for 9.4% of cases.[5]

Certain risk factors predispose to nocardial infection. Individuals with weakened immune systems, such as patients with conditions requiring long-term or large doses of corticosteroid treatment, human immunodeficiency virus (HIV) infection, diabetes mellitus, chronic obstructive pulmonary disease, cirrhosis, malignancies, and stem cell or solid organ transplantation are at Increased risk of infection.[3] In our case, a prolonged course of corticosteroid was most likely a predisposing factor to nocardiosis.

Intracranial mycotic aneurysms represent 0.5-6.5% of all intracranial aneurysms in a systematic review. Patients with intracranial mycotic aneurysms often present with neurological signs and symptoms secondary to bleeding or rupture of the aneurysms such as acute onset of altered consciousness,[4,6] similar to our patient. Intracranial mycotic aneurysm from nocardial infection is a rare manifestation, while the most common manifestation of CNS involvement is brain abscess. There have been 5 reported cases of *Nocardia* spp. causing mycotic aneurysms in intracranial arteries.[5-9] Two of these 5 patients had a history of SLE treated with corticosteroid, one had a history of autoimmune hepatitis receiving corticosteroid, one had a history of multiple myeloma receiving corticosteroid and bortezomib, while another one had no evidence of immunosuppression. Three of them presented with disseminated disease and the others presented with isolated CNS infection. Two patients had an aneurysm at the anterior cerebral artery and *N. otitidiscaviarum* is the identified pathogen, similar to our patient. Most of them responded to surgical management combined with TMP-SMX-based antimicrobial therapy. The characteristics of these five cases are summarized in Table 1.

The diagnosis of nocardiosis is based on the identification of *Nocardia* spp. from the infected sites. Gram's and modified Kinyoun staining are commonly used for initial identification. Molecular methods for identifying *Nocardia* spp. including 16s ribosomal RNA sequencing and MALDI-TOF are fast, sensitive, and highly reliable. The species identification is important due to the species-specific differences in antimicrobial susceptibility patterns. Most *N. otitidiscaviarum* isolates are reported to be resistant to beta-lactams while usually being susceptible to amikacin, fluoroquinolones and TMP-SMX. Hence, TMP-SMX remains the standard agent for treatment.[10] For a definitive treatment of pulmonary and CNS nocardiosis, antimicrobial regimens should consist of agents with good penetration into the lung tissue and blood-brain barrier. These include TMP-SMX, ceftriaxone, meropenem, and fluoroquinolones. Overall mortality of *N. otitidiscaviarum* disease was 26.4%. Patients with disseminated disease had mortality rate of 30% while mortality of those with CNS disease reached 54.5%.[5] Even though our patient was started on the proper antimicrobial agents along with the surgical intervention, the outcome was still fatal.

In conclusion, intracranial mycotic aneurysm is an uncommon presentation of CNS involvement of nocardiosis and can have a severe outcome. Patients with intracranial mycotic aneurysms often present with neurological signs and symptoms secondary to bleeding or rupture of the aneurysms. Early diagnosis and species identification as well as antimicrobial susceptibility testing are needed for optimizing antimicrobial therapy. Physicians should have a high index of suspicion for this uncommon infection in patients presenting with such neurological manifestations while receiving long-term corticosteroids.

**Table 1** The characteristics of previously reported cases of Nocardia causing aneurysms in intracranial arteries

| Age | Sex | Comorbidity | Immunosuppressive drugs | Clinical presentation | Procedure | Site of aneurysm | Species | Antibiotic regimen | Outcome | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| 60 | Male | None | None | Headaches, fatigue, memory loss, and behavioral abnormalities for 3 weeks | Drainage of abscess with resection of the infected aneurysm | Internal carotid artery | *Nocardia abscessus* | Ceftriaxone and TMP-SMX for 6 weeks | Recovered | Farran et al.[6] |
| 69 | Male | Multiple myeloma | Bortezomib Lenalidomide Dexamethasone | Thoracic empyema and alteration of consciousness with right-sided motor weakness | Emergency clipping of the aneurysm | Left middle cerebral artery | *Nocardia farcinica* | TMP-SMX and Ceftriaxone followed by TMP-SMX and Moxifloxacin for a total of 12 months | Recovered | Chansirikarnjana et al.[7] |
| 28 | Female | SLE | Prednisolone | Headache, irritability, and nuchal rigidity | Surgical excision of aneurysm | Right middle cerebral artery | *Nocardia asteroides* | TMP-SMX for 3 weeks Cefotaxime and Amikacin for 2 weeks and Doxycycline 4 weeks | Recovered | Hadley et al.[8] |
| 51 | Male | Autoimmune hepatitis | Prednisolone | Subacute fever and dyspnea for 10 days | Aneurysm trapping | Anterior cerebral artery | *Nocardia otitidiscaviarum* | TMP-SMX and Amikacin and Moxifloxacin | Died | Duangprasert G et al.[9] |
| 29 | Female | SLE | Prednisolone | Necrotizing pneumonia with lung abscess, and alteration of consciousness | Life-saving decompressive craniectomy and EVD insertion | Right anterior cerebral artery | *Nocardia otitidiscaviarum* | TMP-SMX and high- dose Meropenem and Amikacin for 8 weeks followed by TMP-SMX and Moxifloxacin for 10 months | Recovered | Parengal et al.[5] |
| 51 | Male | Autoimmune hepatitis | Prednisolone | Alteration of consciousness | Bifrontal craniectomy with clipping aneurysm | Left anterior cerebral artery | *Nocardia otitidiscaviarum* | TMP-SMX and Levofloxacin and Amikacin | Died | Our case |

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