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Case Report

A rare case of ruptured anterior cerebral artery infected aneurysm with angioinvasion secondary to disseminated *Nocardia otitidiscaviarum*: A case report and literature review

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ABSTRACT

Background: The cases of ruptured infected aneurysms secondary to disseminated nocardiosis are exceptionally rare. Therefore, there is no guideline for investigation or optimal treatment.

Case Description: A 51-year-old man with immunocompromised status was first presented with pneumonia and cerebral infarction, where the infected aneurysm was ruptured thereafter. Intraoperative findings revealed left anterior cerebral artery thrombosis and occlusion with evidence of angioinvasion along with pus discharge which was later identified with *Nocardia otitidiscaviarum*. Our case was the first to report on the angioinvasive nature of cerebral nocardiosis, which occurs concurrently with a ruptured infected aneurysm and an unusual presentation that made the diagnosis and treatment challenging.

Conclusion: Cerebral nocardiosis may cause ruptured infected aneurysms in patients with risk factors, especially for immunocompromised hosts. Furthermore, *Nocardia* can present with severe cerebral manifestation due to angioinvasion causing cerebral infarction accompanied by a ruptured infected aneurysm.

Keywords: Anterior cerebral artery aneurysm, Case report, Cerebral nocardiosis, Infected aneurysm, *Nocardia*

INTRODUCTION

Infected intracranial aneurysms are rare, describing 2–6% of all intracranial aneurysms[9,15] where the most common pathogens are bacteria. Nevertheless, the ruptured cerebral-infected aneurysm secondary to *Nocardia* infection is extremely rare, with only four cases described in the literature.[5,10-12] An infected intracranial aneurysm caused by the bacteria usually involves the distal vasculature due to lodged emboli, in contrast to the fungi (mycotic aneurysm) that would commonly destroy proximal vessels wall and manifest as cerebral infarction due to its angioinvasive nature. The mortality rate could increase to 90% in the case of intracranial vessel destruction.[4] *Nocardia* is categorized as bacteria but can act like fungi due to its clinical resemblance.[1,13] However, there was no previous report of cerebral nocardiosis with angioinvasion. Here, we describe this unusual presentation of cerebral nocardiosis where the

patient was first presented with cerebral infarction due to angioinvasion and later accompanied by a ruptured infected aneurysm.

CASE DESCRIPTION

The patient, a 51-year-old man with a history of autoimmune hepatitis, was prescribed prednisolone (30 mg/day) and had been used for 1 month together with tenofovir (300 mg/day) and azathioprine (50 mg/day). The patient was admitted to our institution after subacute fever and dyspnea for 10 days. Physical examination and the investigations showed sepsis due to pneumonia where the pathogen was not yet revealed from the culture study. The patient has been prescribed piperacillin (16 g/day) and tazobactam (2 g/day) for empirical therapy. Other infection sources were ruled out, including unremarkable results of echocardiography. After 2 days of admission, the patient developed drowsiness where physical examination revealed 13 on Glasgow Coma Scaling. Brain computed tomography (CT) showed cerebral infarction in bilateral anterior cerebral artery (ACA) territory, which is more prominent on the right side, and intracerebral hemorrhage in the right frontal region without evidence of subarachnoid hemorrhage [Figures 1a and b]. The impression was cerebral infarction with hemorrhagic transformation. CT angiography was performed on the same day to investigate the cause of the stroke, which showed an abnormal outpouching lesion at the left distal A2 segment of ACA [Figures 1c and d]. The aneurysm was wide-necked and located at a distal location; the infected aneurysm was suspected. However, the aneurysm was treated conservatively.

The following day, the patient's status deteriorated to 5 on Glasgow Coma Scaling. The patient was intubated and underwent another CT brain. CT brain showed expanded hematoma at the right frontal lobe with intraventricular hemorrhage, and left ACA territory infarction was more apparent [Figure 1e]. Rupture of the infected left ACA aneurysm was suspected, and the decision to perform emergency bifrontal decompressive craniectomy for aneurysm obliteration and to correct an increased intracranial pressure was made.

Operation

The procedure was to obliterate the aneurysm with clot evacuation. The patient was set in a supine position, and a bicoronal incision was made. After bifrontal craniotomy, durotomy was performed first on the right side, where brain swelling was prominent, and the clot was partially evacuated. Before interhemispheric dissection, the pus was noticed in the right side subdural space [Figures 2a and b] and collected for culture study. We performed interhemispheric dissection to the exposed A3 segment of ACA and planned for A3 side-to-side bypass in case aneurysm clipping was

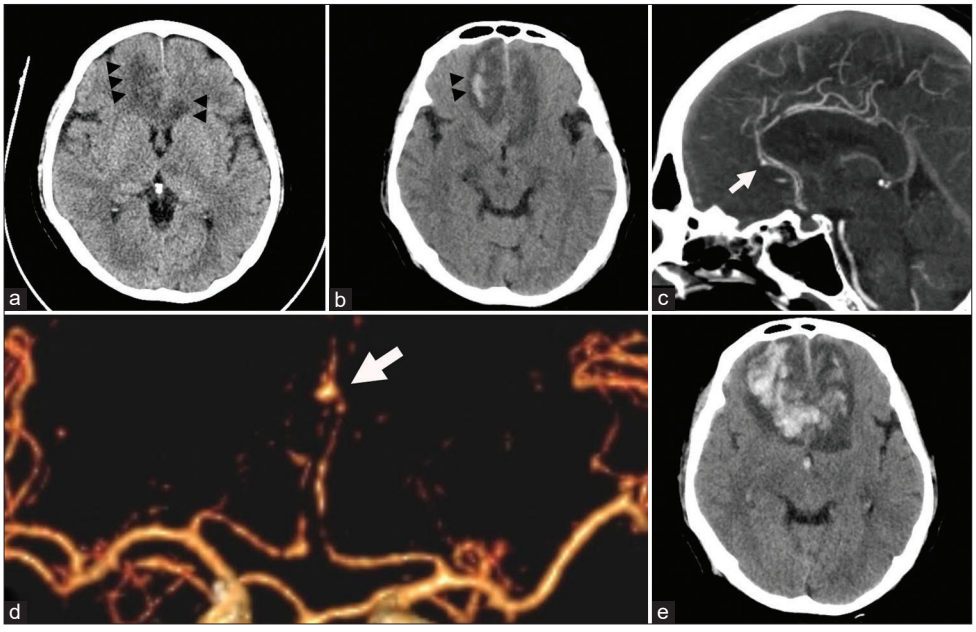

Figure 1: Preoperative computed tomography (CT) scan of the brain. (a) Cerebral infarction was noted at bilateral anterior cerebral artery (ACA) territory which is more prominent on the right side (arrowheads). (b) Small intracerebral hemorrhage was noted in the right frontal region (arrowheads). CT angiography (CTA) (c) showing distal A2 segment aneurysm (white arrow). (d) Three-dimensional CTA showing left distal A2 segment aneurysm (white arrow). (e) Repeated CT scan of the brain showing expanded hematoma at the bilateral frontal region with intraventricular hemorrhage.

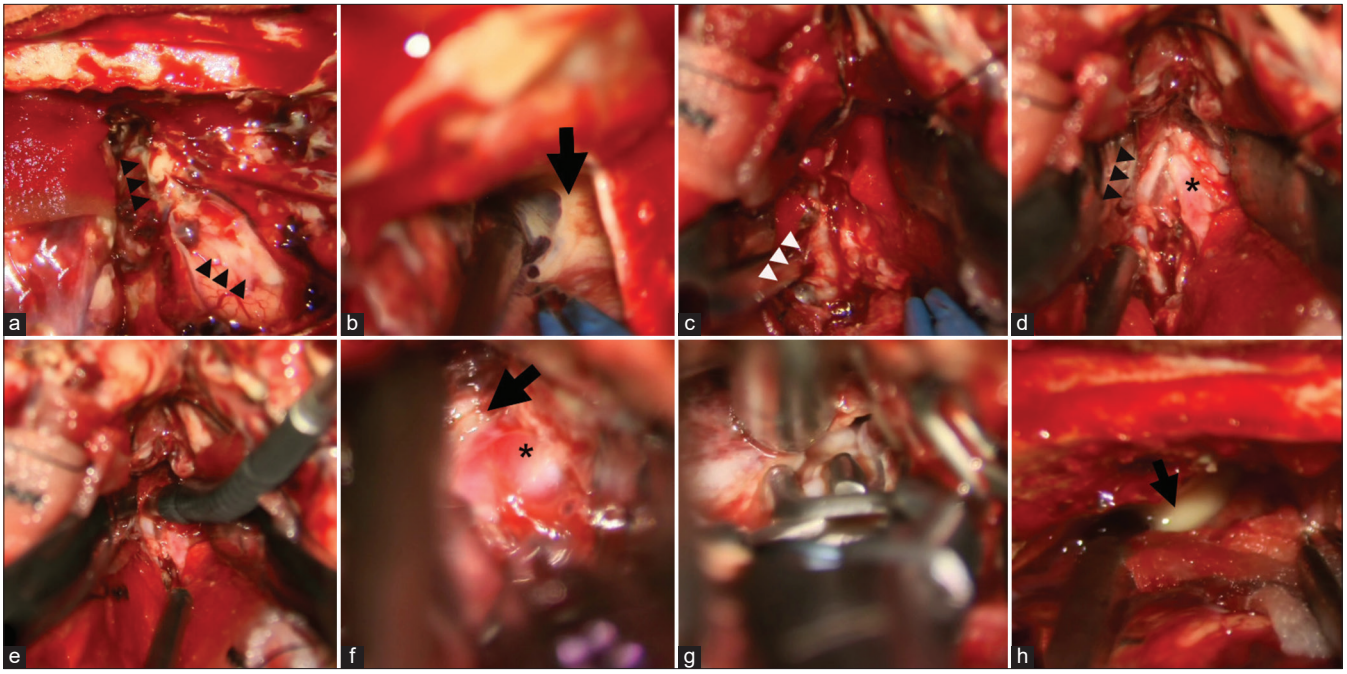

Figure 2: Intraoperative findings. (a) Pus and infected slough were noted along the bilateral frontal cortex, which is prominent on the right side (arrowheads). (b) Pus was identified in the right subdural space consistent with subdural empyema (arrow). After interhemispheric dissection, (c) thrombosis the in left distal ACA was noted at A2 to A3 segment (white arrowheads). (d) The left ACA was whitish in color and covered with slough (black arrowheads) in contrast to the right ACA (asterisk). (e) Flow was not detected in left distal ACA using intraoperative micro-Doppler ultrasound since it was thrombosed. (f) Aneurysm was identified at the left A2 segment (asterisk) with pus along proximal ACA wall (arrow). (g) Clips were applied at both proximal and distal to the aneurysm in an attempt to trap the aneurysm. (h) Pus was also noted in the left subdural space and Sylvian cistern (arrow).

not amenable. However, an unusual irregularity with whitish tissue representing vessel wall destruction of the left A3 was observed. No flow was detected by intraoperative Doppler ultrasound, which led to the diagnosis of the left ACA thrombosis secondary to severe infection [Figures 2c-e]. The microsurgical dissection was continued until the aneurysm neck and proximal ACA were encountered [Figure 2f]. During dissection, premature rupture of an aneurysm was encountered due to severely fragile tissue of the parent artery and aneurysm neck. Nevertheless, the revascularization procedure was not feasible since the left A3 segment was severely infected and already thrombosed. Therefore, the decision to perform an aneurysm trapping was made by the application of clips at both proximal and distal to the aneurysm [Figure 2g]. The clot was further evacuated, where the brain was relaxed with good pulsation. We also observed the pus in the left Sylvian cistern [Figure 2h].

Postoperative course

On the day of an operation, the previously sent sputum culture study revealed *Nocardia otitidiscaviarum,* where the Gram stain showed only mixed organisms. The Gram stain and modified acid-fast stain of subdural pus and thrombus in an aneurysm also showed Gram positive with branching filament, which put suspicion on the *Nocardia* spp. [Figures 3a and b]. The aerobic bacterial cultures from pus, thrombus, and aneurysm wall grew chalky white colonies on chocolate media (Oxoid Limited, France), and macroscopic growth on the Lowenstein-Jensen medium was also noted [Figures 3c and d]. The isolate was further identified by 16s ribosomal RNA sequencing (BIONEER Corp., Korea) of the first 500 base pairs as *N. otitidiscaviarum*. All of the other cultural studies, including fungus, were negative. The antibiotics were then changed to imipenem (2 g/day) and trimethoprim-sulfamethoxazole (TMP-SMX) (15 mg/kg/day). Two days later, the antibiotics susceptibility test using the broth microdilution method revealed the susceptibility of the organism to TMP-SMX (MIC 0.5 ug/mL), amikacin (MIC 2 ug/mL), and moxifloxacin (MIC 1 ug/mL), and resistance to imipenem (MIC >16 ug/mL). Hence, the treatment regimen was switched to TMP-SMX (15 mg/kg/day), amikacin (1 g/day), and moxifloxacin (400 mg/day).

The postoperative CT brain showed multiple infarctions at bilateral subcortical white matter and internal capsule, including the brainstem, which corresponded to an invasion of the bilateral internal carotid artery and basilar artery [Figures 4a-c]. Regarding the patient's comatose status, the dilated right pupils were noted, which was explained by the

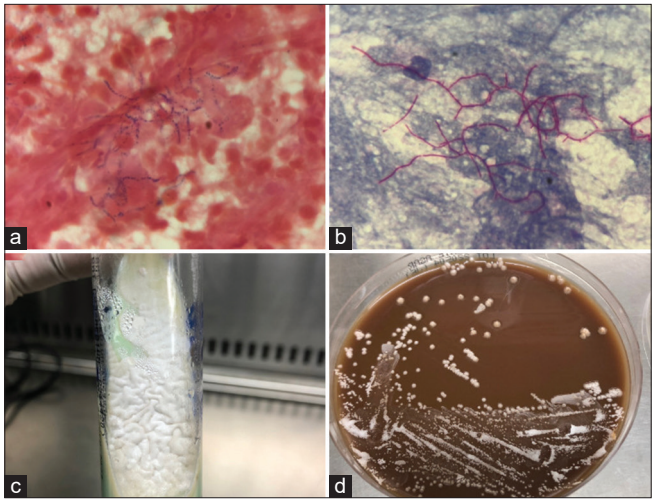

Figure 3: Microscopic findings from brain pus and thrombus in an. (a) Gram stain showing Gram-positive branching filament with prominent polymorphonuclear leukocytes in the background (×1000). (b) Modified acid-fast staining of the same specimen showing a positive result (×1000). Macroscopic growth of the *Nocardia* from brain pus and thrombus in an aneurysm. (c) Chalky white colonies were identified in the Lowenstein-Jensen medium. (d) Colonies' growth was evident in chocolate media after 3 days.

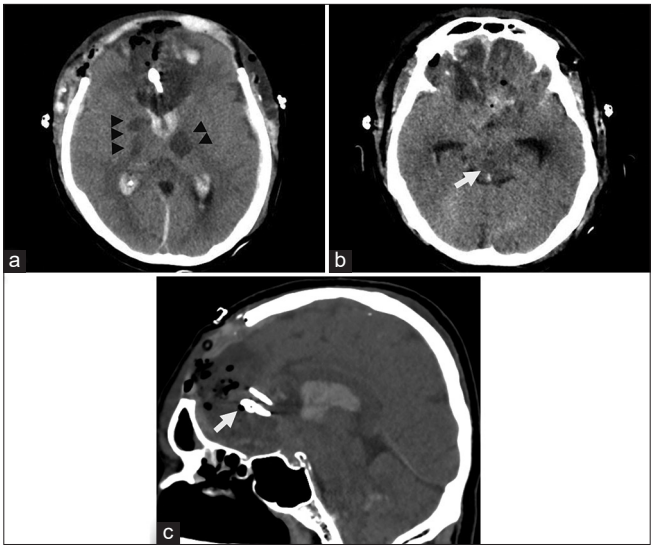

Figure 4: Postoperative CT scan of the brain. (a) New infarction was evident at the right internal capsule and right thalamus, including the left thalamus (arrowheads). (b) Infarction was also noted at the right midbrain (white arrow). (c) Sagittal view showing the applied clips at proximal and distal to an aneurysm (arrow).

right midbrain infarction. Unfortunately, the patient was eventually deceased 3 days later as a consequence of septic shock, where the disseminated infection was unable to control.

DISCUSSION

Nocardia is soil-borne and aerobic Gram-positive bacteria with branching filaments that can cause opportunistic infection, particularly in immunocompromised hosts. Nocardiosis is most frequently affected in the lungs because inhalation is the primary route of bacterial exposure followed by cerebral infection.[17] Cerebral nocardiosis was reported from 25 to 44% in patients with a pulmonary infection where brain abscess is the most common manifestation.[3] However, infected aneurysms secondary to disseminated nocardiosis are even rarer, with only four cases had been described, as shown in Table 1. Our case is the fifth ruptured infected aneurysm caused by cerebral nocardiosis reported in the literature. Furthermore, to the best of our knowledge, this case is the first to describe the angioinvasive character of *Nocardia*, which leads to cerebral infarction. Diagnosis of primary or disseminated nocardiosis is challenging due to the lack of specific signs and symptoms, which can be initially diagnosed as a bacterial or fungal infection because of its clinical similarity.[1,13] Moreover, due to its slow growth on routine culture, which may require a minimum of 48–72 h or weeks before the colonies will be apparent,[14] the appropriate antibiotics regimen might be delayed. Therefore, in patients presenting with pneumonia or disseminated cerebral infection, the high index of suspicion for nocardiosis is crucial, especially in immunocompromised hosts. Prompt diagnosis and treatment are essential to prevent unfavorable outcomes; patients with suspected *Nocardia* infection should then be treated empirically with antimicrobial with good penetration to the lungs and blood–brain barrier, which includes TMP-SMX as the antimicrobials of choice as well as alternative agents, for example, amikacin, a carbapenem (imipenem and meropenem), cephalosporin (ceftriaxone and cefotaxime), minocycline, fluoroquinolones (moxifloxacin and levofloxacin), linezolid, tigecycline, and amoxicillin-clavulanic acid.[17] Nevertheless, antimicrobial susceptibility tests are essential since they may differ among *Nocardia* species.[16,17] In addition, some authors suggested that brain imaging should be considered in all patients with pulmonary nocardiosis.[2] Regarding the tools for species identification, 16S ribosomal RNA gene PCR is recommended as a feasible method since the test is rapid, inexpensive, and reliable.[7,8]

N. otitidiscaviarum is an infrequent cause of human infections, mainly producing mild cutaneous and lymphocutaneous infections and less virulence than other *Nocardia* species, which are revealed for only 2% of all *Nocardia* cases.[2,3,6] However, our patient showed severe manifestations caused by this rare species. Moreover, *N. otitidiscaviarum* has a high resistance rate to multiple antimicrobials, including TMP-SMX, ceftriaxone, and imipenem.[2]

The mycotic aneurysm secondary to fungal infection, the aspergillosis in particular, usually involves the proximal

Table 1: Summary of the published case report of infected aneurysm caused by cerebral nocardiosis since 2000.

Author/year	Age/ sex	Underlying conditions and risk factors	Aneurysm location	Presentation	Species	Operation	Treatment regimen	Outcomes
Farran *et al*., 2016[10]	60/M	Immunocompetent	ICA	Brain abscess with unruptured aneurysm	*Nocardia abscessus*	Abscess drainage and aneurysm resection	6 weeks of Ceftriaxone and TMP-SMX	Survived
Chansirikarnjana *et al*., 2019[5]	69/M	Multiple myeloma with chemotherapy	MCA	SAH	*Nocardia farcinica*	Aneurysm clipping	28 days of ceftriaxone and TMP-SMX then oral moxifloxacin for 12 months	Survived
Goto *et al*., 2020[11]	22/F	Still's disease with chronic steroid use	MCA	SAH	N/A	Aneurysm trapping	3 months of imipenem/ cilastatin and amikacin then TMP-SMX was continued to 6 months	Improved
McCormack *et al*., 2022[12]	Middle aged/M	Post kidney transplant	PCA	Acute SDH with IVH	*Nocardia otitidiscaviarum*	Sacrifice through coiling	N/A	Died
Present case	51/M	Autoimmune hepatitis with immunosuppressant and steroid use	ACA	ICH with cerebral infarction	*Nocardia otitidiscaviarum*	Aneurysm trapping	TMP-SMX, amikacin, moxifloxacin	Died

M: Male, ICA: Internal carotid artery, SAH: Subarachnoid hemorrhage, MCA: Middle cerebral artery, TMP-SMX: Trimethoprim-sulfamethoxazole, N/A: Not available, F: Female, PCA: Posterior cerebral artery, SDH: Subdural hematoma, IVH: Intraventricular hemorrhage, ACA: Anterior cerebral artery, ICH: Intracerebral hemorrhage

cerebral vasculature with angioinvasive nature where the vessels are destroyed and can be manifested as cerebral infarction.[9] This character differs from bacterial infection, which mainly involves distal vessels without angioinvasion. The clinical presentation of our case is noteworthy since *Nocardia* which is categorized as bacteria acted like fungi and was potentially aggressive, causing rapid clinical deterioration as a consequence of a ruptured aneurysm concurrently with cerebral infarction.

Concerning the outcome of reported cases of *Nocardia* intracranial infected aneurysms, a good clinical outcome was achieved in two cases where one case had an unruptured aneurysm[10] and another had a ruptured aneurysm of the M2-3 segment with good preoperative grade.[5] The remaining three cases include one with clinically improved and two patients who died. The causes of the poor outcome were poor preoperative grade,[11] intracranial bleeding due to intrathecal tissue plasminogen activator administration,[12] and uncontrolled infection, as in our case. The clinical outcomes might be predicted by various factors regardless of the surgical strategies.

Surgical management for the infected aneurysms has been well described, including clipping, excision, trapping with or without revascularization, and endovascular coiling embolization. The infected aneurysm is usually friable, making simple clipping not feasible.[17] Furthermore, revascularization can be complex due to infected or destroyed vessels wall, which could lead to thrombosis of the anastomosis. In our case, bypass surgery was not an option since the left ACA was destructed by the infection and already occluded; the decision to trap the aneurysm was performed instead. Our report highlights the angioinvasive nature of cerebral nocardiosis with this rare species and its unusual presentation. Therefore, early pathogen identification is crucial, along with prompt diagnosis and adequate treatment, especially in immunocompromised patients.

CONCLUSION

Cerebral nocardiosis may cause ruptured infected aneurysms in patients with risk factors, especially for immunocompromised hosts. Furthermore, *Nocardia* can present with severe manifestation due to angioinvasion causing cerebral infarction concurrently with the ruptured infected aneurysm. Therefore, a high index of suspicion with careful evaluation is crucial for prompt diagnosis and adequate treatment despite its rarity.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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