Case Report

True mycotic aneurysm in a patient with gonadotropinoma after trans-sphenoidal surgery

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Abstract

Background: Immunosuppressive therapy, prolonged antibiotic use, and intrathecal injections are known risk factors for the development of invasive aspergillosis. Central nervous system (CNS) aspergillosis can manifest in many forms, including mycotic aneurysm formation. The majority of the mycotic aneurysms presents with subarachnoid hemorrhage after rupture and are associated with high mortality. Only 3 cases of true mycotic aneurysms have been reported following trans-sphenoidal surgery.

Case Description: A 38-year-old man was admitted with nonfunctioning pituitary adenoma for which he underwent trans-sphenoidal surgery. Three weeks later, he presented with cerebrospinal fluid (CSF) rhinorrhea and meningitis. He was treated with intrathecal and intravenous antibiotics, stress dose of glucocorticoids, and lumbar drain. The defect in the sphenoid bone was closed endoscopically. After 3 weeks of therapy, he suddenly became unresponsive, and computed tomography of the head showed subarachnoid hemorrhage. He succumbed to illness on the next day, and a limited autopsy of the brain was performed. The autopsy revealed extensive subarachnoid hemorrhage and aneurysmal dilatation, thrombosis of the basilar artery (BA), multiple hemorrhagic infarcts in the midbrain, and pons. Histopathology of the BA revealed the loss of internal elastic lamina and septate hyphae with an acute angle branching on Grocott's methenamine silver stain, conforming to the morphology of *Aspergillus*.

Conclusion: The possibility of intracranial fungal infection should be strongly considered in any patient receiving intrathecal antibiotics who fails to improve in 1–2 weeks, and frequent CSF culture for fungi should be performed to confirm the diagnosis. Since CSF culture has poor sensitivity in the diagnosis of fungal infections of CNS; empirical institution of antifungal therapy may be considered in this scenario.

Key Words: Aspergillosis, basilar artery, mycotic aneurysm, pituitary adenoma, subarachnoid hemorrhage, trans-sphenoidal surgery

INTRODUCTION

Aspergillosis of central nervous system (CNS) is an uncommon entity; however, the number of reported cases has increased in the past few years, possibly due to the widespread use of antibiotics, corticosteroids, and other immunosuppressants.[8] Cerebral aneurysms caused by aspergillosis are very rare and until date, 40 odd cases have been described in the English literature.

CLINICAL PRESENTATION

A 38-year-old male presented with an episode of giddiness and uneasiness that lasted for 2 days. There was no history of dyspnea or palpitation. He did not have any comorbid illness. Clinical examination revealed bitemporal hemianopia and biochemical evaluation showed hyponatremia, hypocortisolism, and hypothyroidism, with elevated follicle-stimulating hormone, luteinizing hormone, and testosterone [Supplementary file, Table 1]. Magnetic resonance imaging (MRI) brain revealed a sellar-supra-sellar mass [Figure 1]. After hormone supplementation and correction of electrolytes, he underwent gross total excision of the tumor through endonasal trans-sphenoidal route. During the perioperative period, he was given hydrocortisone infusion at 4 mg/h and during the immediate postoperative period, he was given hydrocortisone 50 mg intravenously 8th hourly. The intraoperative and immediate postoperative period was uneventful, and he was discharged on glucocorticoid (oral hydrocortisone 10 mg/m²/day) and thyroxine replacement. Histopathology and immunohistochemistry showed a gonadotropin secreting pituitary adenoma. The dura and bone was free of tumor, and the sphenoid sinus mucosa was normal.

Three weeks later, he presented with intermittent

fever and cerebrospinal fluid (CSF) rhinorrhea of 5 days duration. On examination, he had terminal neck rigidity. CSF studies were suggestive of pyogenic meningitis, CSF culture showed *Enterobacter* species, and he was started on appropriate antibiotics. The computed tomography (CT) scan showed pneumocephalus. Endoscopic repair of the defect was done after the infection was apparently controlled, and CSF was diverted through an external lumbar drain, to aid healing. Despite the repair, CSF rhinorrhea persisted, and CT scan showed the progression of pneumocephalus. Repeat CSF culture after a week grew *Staphylococcus* and he was started on intravenous Vancomycin and Meropenem with intrathecal Vancomycin. His preoperative total leukocyte count was 8700 mm³ with neutrophils 71%, lymphocytes 22%, monocytes 5%, and eosinophils 2%. At present admission, his total leukocyte count was 15,800 with neutrophils 82%, lymphocytes 14%, and monocytes 4%. His serum albumin and globulin were 4.5 g/dl and 3.5 g/dl, respectively. Serology for HIV was negative. The serial CSF reports of the patient are given in the Supplementary file, Table 2. Throughout the course, he was on therapy with injectable hydrocortisone 50 mg every 8th hourly and thyroxine 100 μg, and required subcutaneous desmopressin intermittently for diabetes insipidus. After 3 weeks of hospital stay, he suddenly became unresponsive and CT scan showed a subarachnoid hemorrhage with intraventricular extension [Figure 2]. The patient expired a day later, despite the external ventricular drainage.

The cause of death was speculated to be due to rupture of an intracranial aneurysm. This may have been an association with pituitary macroadenoma (although it is seen often with functioning pituitary macroadenoma), or due to the weakening of vessel wall due to inflammatory

Figure 1: Coronal T1-weighted magnetic resonance image of the sella showing a pituitary macroadenoma with supra-sellar extension

Figure 2: Axial noncontrast computed tomography scan of head showing subarachnoid hemorrhage with intra-ventricular extension
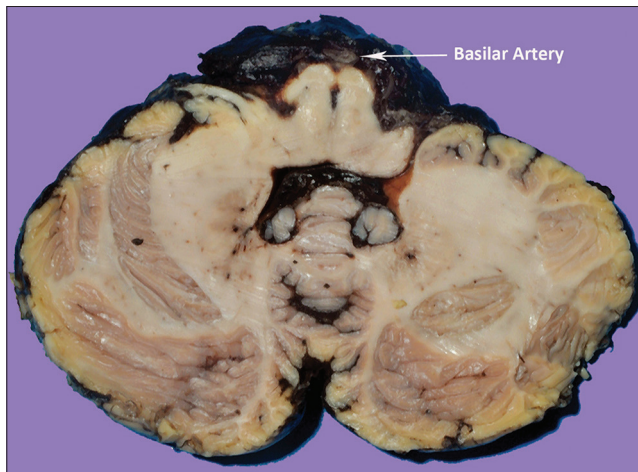
Figure 3: Cut section of brain showing extensive subarachnoid hemorrhage and ruptured basilar artery aneurysm

exudates. The third possibility could be an inadvertent intraoperative injury such as snapping of a perforator from a distal vessel, resulting in pseudoaneurysm formation. To confirm the cause of death, a limited brain autopsy was performed, which revealed extensive subarachnoid hemorrhage and aneurysmal dilatation and thrombosis of the basilar artery (BA) [Figure 3]. There were multiple hemorrhagic infarcts in the midbrain and pons. Histopathology of the BA revealed the loss of internal elastic lamina and septate hyphae with an acute angle branching on Grocott's methenamine silver stain, conforming to the morphology of *Aspergillus* [Figure 4a-d].

DISCUSSION

The common fungi associated with CNS infections include yeasts (*Candida*, *Cryptococcus*), moniliaceous molds (*Aspergillus* spp. and *Fusarium* spp.), dimorphic fungi (*Blastomyces*, *Coccidioides*, and *Histoplasma*), zygomycetes (*Mucor* spp., *Rhizopus* spp.), and dematiaceous fungi (*Scedosporium* spp.).[17] Fungal infections of the CNS can be endemic mycoses or opportunistic mycoses. Fungi such as *Blastomyces*, *Coccidioides*, and *Histoplasma* are not part of the normal human microbiota and are acquired from the environment; these agents cause endemic mycoses. Other fungi such as *Candida*, *Cryptococcus*, *Aspergillus*, and *Mucor* are commensals in the human body and cause opportunistic mycoses, in an immunodeficient individual.[6] Fungi may enter into the CNS through hematogenous route, infection from adjacent structures such as paranasal sinuses and orbit or direct inoculation as a result of trauma or surgery.[12] Fungal infections of the CNS are associated with various clinical syndromes; meningitis, intracranial mass lesions, skull base syndromes, rhinocerebral form,
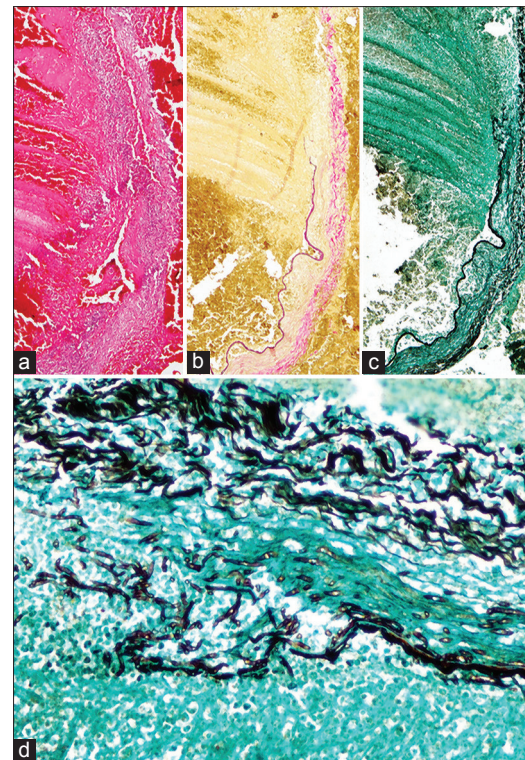

Figure 4: Low power photo micrographs taken through the wall of the basilar artery at the site of aneurysm. (a) H and E staining showing dilated and destroyed arterial wall. (b) Elastic Van Gieson staining is showing the loss of internal elastic lamina on the upper part. (c) Gomorri methenamine silver staining is showing an invasive fungal elements from outer to the inner side in the aneurysmal wall. (d) High power photo micrograph showing numerous filamentary infiltrates with an acute angle branching confirming to the morphology of *Aspergillus* species

stroke syndrome, or spinal syndrome. Meningitis and meningoencephalitis are common presenting clinical syndrome with most of the yeasts, whereas rhinocerebral form is usually caused by zygomycetes. Intracranial mass lesions can be caused by *Aspergillus*, zygomycetes, dematiaceous fungi, and *Candida*; the skull base syndromes are associated with *Aspergillus* infections.[15]

Aspergillus is a ubiquitous fungus, and more than 180 species of *Aspergillus* have been described. *Aspergillus fumigatus* is the most common pathogen responsible for invasive Aspergillosis; although *Aspergillus flavus*, *Aspergillus terreus*, *Aspergillus* niger, and *Aspergillus nidulans* can also cause invasive disease.[20] The risk factors for the development of invasive aspergillosis include prolonged severe neutropenia, hematopoietic stem cell and solid organ transplantation, advanced AIDS, and chronic granulomatous disease. Although the sinopulmonary disease is the most common form of Aspergillosis, it can virtually affect any organ.[19] CNS can be infected by *Aspergillus* as a result of hematogenous dissemination from a pulmonary focus, direct extension

from paranasal sinuses, middle ear or after head injury, brain surgery, or lumbar puncture.[5] The diagnosis of CNS aspergillosis requires a high index of suspicion because the clinical features are nonspecific and CT and MRI findings, although helpful are also nondiagnostic.[18] The CNS aspergillosis can present as meningitis, meningoencephalitis, abscess, granuloma, vasculitis, and myelitis.[14,18] Vasculitis may result in thrombosis, hemorrhage, or aneurysm formation.

Mycotic aneurysms account for 0.7–5.4% of all intracranial aneurysms and is most commonly caused by bacteria; fungi are a rare cause of mycotic aneurysm.[1] Aneurysms caused by bacteria tend to be multiple, spherical, and typically arise from the peripheral cortical arteries, especially middle and anterior cerebral arteries. They are commonly caused by *Staphylococcus* and *Streptococcus*. In contrast, aneurysms caused by fungi are usually single, fusiform, and involve internal carotid, or BA.[11] Mycotic aneurysms can result from infective emboli, occlusion of the vasa vasorum, invasion of the arterial wall from within, extension from an infection of neighboring structures, or vascular injury due to immune complexes.[2] *Aspergillus* species accounts for approximately 65% of mycotic aneurysms caused by fungi, while the rest by *Candida* and *Mucorale* (zygomycetes, *Penicillium*).[3] *Aspergillus* is an angioinvasive fungus and this is due to its ability to produce the enzyme elastase, which destroys elastin present in blood vessels. Aneurysm formation is due to the proliferation of fungi within the internal elastic lamina, dissecting it away from media, aided by hydrostatic pulsation, and thrust against the infected arterial wall.[4,16] The other mechanism postulated is the weakening of vessel wall due to bathing of vessels in the inflammatory exudates collected in basal cisterns.

Postoperative mycotic aneurysms of the CNS are rare.[4] Only 3 cases of true mycotic aneurysms have been reported following pituitary surgery [Table 1]. One patient had aneurysm of basilar artery, one had aneurysm of internal carotid artery while the third patient had aneurysms of both basilar and internal carotid artery. All three patients succumbed to the disease, and diagnosis could be made only at autopsy. Our patient presented with meningitis 3 weeks after surgery and died 24 h after the onset of subarachnoid hemorrhage. The probable cause of death was infarction of vital structures in the brain stem.

Komatsu *et al.* have described the two processes of mycotic aneurysm formation; those secondary to meningitis and those secondary to sepsis. The former tend to affect the larger vessels and are a result of fungal invasion of vessels from outside, whereas the latter tend to involve peripheral vessels and are a result of the invasion of vessel wall from within.[9] The aneurysm formation in our patient probably occurred due to the direct invasion of arterial wall by fungal hyphae from outer to inner side, leading to *de-novo* mycotic aneurysm formation and subsequent rupture due to weakening of vessel wall [Figure 4a-d]. Infection of a preexisting aneurysm or the development following surgical trauma are unlikely as preoperative MR-angiography was normal, and the aneurysm was quite away from the surgical field. Serial angiograms performed in a previous case have shown that only a few days are required for a fungal aneurysm to develop.[23]

There are various possible portals through which the fungi would have entered into CNS. Hematogenous dissemination was unlikely as the histopathology showed that vessel was invaded from outside. The direct entry through the operative route was also unlikely, as the sphenoid mucosa showed no evidence of fungus; however, the possibility of subsequent lodgment and focal arachnoiditis due to the persistent CSF leak could not be excluded. Our patient received the intrathecal antibiotics, and this could have given the fungus access to CNS. Fungal meningitis has been reported after epidural steroids for pain.[7] Alternatively, the prolonged placement of lumbar drain could be another portal of entry leading to the deposition of fungus and exudates in the dependent part of the brain. Another possibility is that of a fungus getting in along with the air that was sucked in the cranial cavity due to the negative pressure secondary to CSF drainage. Our patient received a supraphysiological dose of glucocorticoids, which led to immunosuppression and prolonged use of antibiotics might have caused the selective growth of fungi and subsequent development of invasive aspergillosis. The absence of recurrent skin, ear, and sinopulmonary infections since childhood, negative HIV serology, and normal serum globulin is strongly against the possibility of congenital or noniatrogenic immunodeficiency; however, we do not have a CD4 count to exclude primary CD4 deficiency.

Table 1: Summary of the cases of true mycotic aneurysms caused by *Aspergillus* after trans-sphenoidal surgery

Author, year, reference	Age, gender	Primary disease	How diagnosed and site of an aneurysm	Management	Outcome
Visudhiphan *et al.* (1973)[22]	13/male	Craniopharyngioma	Autopsy, BA	Amphotericin-B for 5 weeks	Death after 6 weeks of surgery
Mielke *et al.* (1981)[13]	58/female	Somatotropinoma	Autopsy, BA, and ICA	No antifungals	Death after 10 months of surgery
Komatsu *et al.* (1991)[9]	61/female	Rathke's cleft cyst	Autopsy, ICA	No antifungals	Death after 5th weeks of surgery
Radotra *et al.* (Present case)	38/male	Gonadotropinoma	Autopsy, ICA	No antifungals	Death after 7 weeks of surgery

BA: Basilar artery, ICA: Intracranial internal carotid artery

Aspergillus species may be found as a commensal in paranasal sinuses.[21] *Aspergillus* species are known to induce allergic reactions in susceptible individuation without causing infection. This commonly occurs after the repeated inhalation of spores of *Aspergillus* species, which induce a Type I (immunoglobulin E mediated) hypersensitivity reaction; however, Type III (immune complex mediated) and Type IV (cell-mediated) reactions have also been implicated. It has been shown that 28% of patients with asthma demonstrate hypersensitivity to *Aspergillus* antigens.[10]

High index of the suspicion based on clinical, radiological, and fungal culture is essential to make a diagnosis of CNS aspergillosis, and brain biopsy is required for the definitive diagnosis, which is not feasible in most of the cases.[18] In our patient, there was no scope to diagnose the fungal disease by neuroimaging. Unfortunately, histopathology of vital structures was not possible and ultimately it could be diagnosed only at autopsy.

CONCLUSION

The possibility of intracranial fungal infection should be strongly considered in any patient receiving intrathecal antibiotics who fails to improve in 1–2 weeks, and frequent CSF culture for fungi should be performed to confirm the diagnosis. Since CSF culture has poor sensitivity in the diagnosis of the fungal infections of CNS, the empirical institution of antifungal therapy may be considered in this scenario.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Ducruet AF, Hickman ZL, Zacharia BE, Narula R, Grobelny BT, Gorski J, *et al.* Intracranial infectious aneurysms: A comprehensive review. Neurosurg Rev 2010;33:37-46.
2. Horten BC, Abbott GF, Porro RS. Fungal aneurysms of intracranial vessels. Arch Neurol 1976;33:577-9.
3. Hot A, Mazighi M, Lecuit M, Poirée S, Viard JP, Loulergue P, *et al.* Fungal internal carotid artery aneurysms: Successful embolization of an *Aspergillus*-associated case and review. Clin Infect Dis 2007;45:e156-61.
4. Hurst RW, Judkins A, Bolger W, Chu A, Loevner LA. Mycotic aneurysm and cerebral infarction resulting from fungal sinusitis: Imaging and pathologic correlation. AJNR Am J Neuroradiol 2001;22:858-63.
5. Iihara K, Makita Y, Nabeshima S, Tei T, Keyaki A, Nioka H. Aspergillosis of the central nervous system causing subarachnoid hemorrhage from mycotic aneurysm of the basilar artery – Case report. Neurol Med Chir (Tokyo) 1990;30:618-23.
6. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Diagnosis and treatment of fungal infections. In: Harrison's Principles of Internal Medicine. 19th ed., Vol. I. New York: McGraw-Hill; 2015. p. 1239.
7. Kleinfeld K, Jones P, Riebau D, Beck A, Paueksakon P, Abel T, *et al.* Vascular complications of fungal meningitis attributed to injections of contaminated methylprednisolone acetate. JAMA Neurol 2013;70:1173-6.
8. Kleinschmidt-DeMasters BK. Central nervous system aspergillosis: A 20-year retrospective series. Hum Pathol 2002;33:116-24.
9. Komatsu Y, Narushima K, Kobayashi E, Tomono Y, Nose T. *Aspergillus* mycotic aneurysm – Case report. Neurol Med Chir (Tokyo) 1991;31:346-50.
10. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: A clinical review. Eur Respir Rev 2011;20:156-74.
11. Masago A, Fukuoka H, Yoshida T, Majima K, Tada T, Nagai H. Intracranial mycotic aneurysm caused by *Aspergillus* – Case report. Neurol Med Chir (Tokyo) 1992;32:904-7.
12. McCarthy M, Rosengart A, Schuetz AN, Kontoyiannis DP, Walsh TJ. Mold infections of the central nervous system. N Engl J Med 2014;371:150-60.
13. Mielke B, Weir B, Oldring D, von Westarp C. Fungal aneurysm: Case report and review of the literature. Neurosurgery 1981;9:578-82.
14. Mukoyama M, Gimple K, Poser CM. Aspergillosis of the central nervous system. Report of a brain abscess due to *A. fumigatus* and review of the literature. Neurology 1969;19:967-74.
15. Murthy JM. Fungal infections of the central nervous system: The clinical syndromes. Neurol India 2007;55:221-5.
16. Okada Y, Shima T, Nishida M, Yamane K, Yoshida A. Subarachnoid hemorrhage caused by *Aspergillus* aneurysm as a complication of transcranial biopsy of an orbital apex lesion – Case report. Neurol Med Chir (Tokyo) 1998;38:432-7.
17. Redmond A, Dancer C, Woods ML. Fungal infections of the central nervous system: A review of fungal pathogens and treatment. Neurol India 2007;55:251-9.
18. Ruhnke M, Kofla G, Otto K, Schwartz S. CNS aspergillosis: Recognition, diagnosis and management. CNS Drugs 2007;21:659-76.
19. Segal BH, Walsh TJ. Current approaches to diagnosis and treatment of invasive aspergillosis. Am J Respir Crit Care Med 2006;173:707-17.
20. Sugui JA, Kwon-Chung KJ, Juvvadi PR, Latgé JP, Steinbach WJ. *Aspergillus fumigatus* and related species. Cold Spring Harb Perspect Med 2014;5:a019786.
21. Vennewald I, Henker M, Klemm E, Seebacher C. Fungal colonization of the paranasal sinuses. Mycoses 1999;42 Suppl 2:33-6.
22. Visudhiphan P, Bunyaratavej S, Khantanaphar S. Cerebral aspergillosis. Report of three cases. J Neurosurg 1973;38:472-6.
23. Walsh TJ, Mendelsohn G. Invasive aspergillosis complicating Cushing's syndrome. Arch Intern Med 1981;141:1227-8.

Supplementary Table 1: Preoperative hormonal profile of the patient

Hormone	Patient's value	Reference range
Serum cortisol	98.6 nmol/L	171-536 nmol/L
Free T4	0.34 ng/dl	0.8-1.8 ng/dl
Free T3	1.37 pg/ml	3-7 pg/ml
TSH	26.1 μIU/ml	0.5-4.8 μIU/ml
LH	9.95 μIU/ml	1.7-8.6 μIU/ml
FSH	12.71 μIU/ml	1.5-12.4 μIU/ml
Serum testosterone	44.4 nmol/L	9.9-27.8 nmol/L

TSH: Thyroid stimulating hormone, LH: Luteinizing hormone, FSH: Follicle stimulating hormone

Supplementary Table 2: Serial CSF analysis of the patient

CSF (site)	Day	CSF - Glucose (corresponding blood glucose) in mg/dl	CSF - Protein in mg/dl	CSF - Total count (polymorphs) (%)	Culture	Sensitivity
Nasal	1	48	92	220 (60)	Gram-positive Cocci	-
Lumbar	2	7	147		*Enterobacter*	Ceftazidime
Lumbar	16	32	139	200 (60)	Coagulase negative *Staphylococcus aureus*	Vancomycin, linezolid, and Netilmicin
Lumbar	22	12	40	4000 (95)	Not done	Not done
Lumbar	25	48 (200)	148	2600 (90)	Sterile	
Ventricular	27	11 (160)	18	140	Not done	Not done
Lumbar	35	65	52	1200	Not done	Not done
Lumbar	39	64	145	1400 (90)	Not done	Not done

CSF: Cerebrospinal fluid