Case Report
Recurrent cerebral aneurysm formation and rupture within a short period due to invasive aspergillosis of the nasal sinus; pathological analysis of the catastrophic clinical course

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Abstract: Destructive infiltration of invasive fungal sinusitis can easily occur into the central nervous system (CNS). Cerebral aneurysms associated with fungal infection are highly vulnerable to rupture, and can frequently and rapidly take a serious clinical course. We experienced a patient who twice developed cerebral aneurysm followed by rupture due to invasive fungal sinusitis. This 77-year-old man was admitted for progressive bilateral visual disturbance, which was initially treated as idiopathic hypertrophic pachymeningitis. The patient subsequently suffered subarachnoid hemorrhage (SAH) twice in only 12 days. Both SAH originated from different newly formed cerebral aneurysms. Trapping was performed for both ruptured aneurysms. Pathological examination of the resected aneurysms indicated the presence of fungi determined to be Aspergillus. This Aspergillus infection was also discovered inside the frontal sinus by endoscopic biopsy, so a regimen of antifungal agents was instituted. Prolonged antifungal therapy caused renal impairment, which ultimately led to the patient’s death. Autopsy detected no mycotic infiltration of the major cerebral arteries, except for the 2 ruptured cerebral aneurysms. However, prolonged mycosis of the CNS, such as in the deep part in the falx cerebri and in the small veins proximal to the tentorium cerebelli, was observed, indicating that mycosis invading the cranium is refractory even to long-term administration of antifungal agents. The present case strongly suggests that urgent and proactive definitive diagnosis is essential to successfully treat invasive paranasal sinus aspergillosis. If infiltration of the CNS is suspected, early surgical resection and antifungal therapy must be initiated immediately.

Keywords: Mycotic cerebral aneurysm, fungal sinusitis, Aspergillus, subarachnoid hemorrhage

Introduction

Fungal sinusitis is generally classified into the parasitic (non-invasive) type, which is limited to localized lesions, and the invasive type, which infiltrates and destroys surrounding tissue, resulting in serious symptoms [1]. Invasive fungal sinusitis has a poor prognosis with a mortality rate of around 50% [2-6]. Invasive fungal sinusitis causing destructive infiltration of the skull can easily affect the central nervous system (CNS) located close to the nasal sinuses across the skull base bone. Invasion of fungal sinusitis into the CNS has a mortality rate of more than 80% [7, 8]. This high mortality rate is partly due to the high tendency of mycosis to cause cerebrovascular complications. The causative fungi include Aspergillus, Penicillium, Phycomycetes, Candida, Mucor, and Scedosporium. Spread of destructive mycosis directly to the intracranial arteries results in invasion of the cerebral blood vessels and is complicated by various cerebrovascular disorders [9, 10]. Therefore, initiation of antifungal therapy at the earliest opportunity is essential to prevent these serious cerebrovascular complications.
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However, early definitive diagnosis of the fungal infection is occasionally difficult. Fungal sinusitis confined to the paranasal sinus is often asymptomatic. Infiltration of the CNS often causes nonspecific early symptoms such as fever, convulsions, hemiplegia, headache, encephalopathy, impaired consciousness, and visual disturbance [11, 12]. Unfortunately, any delay in the accurate definitive diagnosis at the early stage of infection can lead to severe clinical progression.

We describe a case of invasive fungal sinusitis (aspergillosis of the nasal sinus) which caused recurrent cerebral aneurysm formation and rupture within a short time, resulting in a catastrophic clinical course. We further describe the pathological findings obtained by autopsy.

Case report

Initial presentation

A 77-year-old man with normal immune function suddenly developed reduced visual acuity of the right eye to only sensus luminis and attenuated light reflexes in both eyes, as well as right omni-directional ocular motility disorder, and was admitted to our hospital 27 days after onset of the initial symptoms. The patient had a history of mild diabetes mellitus and chronic kidney failure, and had undergone surgeries for bilateral chronic sinusitis at age 16 years and bile duct cancer at age 63 years, but he had remained in good general health without cancer relapse.

Physical examination found no fever or signs of meningeal irritation, and blood and cerebrospinal fluid tests detected no signs of infection. Ophthalmic examination, such as fluorescence fundus angiography, did not identify any abnormalities in the anterior ocular segment or fundus. Therefore, the cause of the symptoms was suspected to be located in the CNS, including the optic nerve. Magnetic resonance (MR) imaging showed non-uniform hypertrophy and abnormal diffuse enhancement in the anterior and medial region of the cranial base and dura mater in the falx cerebri (Figure 1).

Based on these imaging findings and laboratory data, idiopathic hypertrophic pachymeningitis was suspected. Since the visual disturbance had rapidly deteriorated to total blindness in only 27 days, steroid pulse therapy was started on the day of admission. The patient received 3 courses of methylprednisolone pulse therapy (1000 mg/day, each lasting 3 days), as well as a post-treatment regimen of 1 mg/kg/day prednisolone. However, the patient's visual acuity temporarily improved to just sensus luminis and imaging findings found no changes in the dural hypertrophy and abnormal diffuse enhancement in the anterior and medial region of the cranial base and dura mater. At 58 days after onset of the initial symptoms (day 32 of hospitalization), the patient suddenly showed impaired consciousness (Glasgow Coma Scale

Figure 1. Gadolinium-enhanced T1-weighted magnetic resonance images on admission showing non-uniform hypertrophy and abnormal diffuse enhancement in the anterior and medial base of the skull and dura mater in the falx cerebri (arrows).
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score of E1V1M5), right conjugate deviation of the eyes, and hemiparesis of the left upper and lower limbs.

First ruptured aneurysm

Computed tomography (CT) showed a massive hematoma in the right temporal lobe and diffuse subarachnoid hemorrhage (SAH) (Figure 2C). Digital subtraction angiography (DSA) revealed an intracranial aneurysm in the right internal carotid artery (ICA). The aneurysm was 10 mm in diameter and irregularly shaped. This fusiform-shaped aneurysm had an unusual appearance as a protrusion of the entire ICA rather than occurring at a vascular bifurcation (Figure 2D). This aneurysm had not been detected by MR angiography on the day of admission (Figure 2A) or MR imaging performed 12 days before the occurrence of SAH (Figure 2B). Therefore, we concluded that the aneurysm had developed rapidly over a period of 12 days. To prevent re-rupture of the aneurysm, trapping of the right ICA was performed, since neck clipping was deemed unfeasible due to the shape of the aneurysm (Figure 2E). To maintain the distal flow of the ICA, superficial temporal artery-middle cerebral artery (MCA) bypass was also performed. A clip was applied to the terminal portion of the right ICA distal to the aneurysm, and the ICA was ligated at the extracranial portion to the aneurysm. These procedures succeeded in trapping the aneurysm (Figure 2F). However, the patient’s severely impaired consciousness persisted after surgery.
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Twelve days later (day 44 of hospitalization), CT showed that another SAH had suddenly occurred (Figure 3A). Coronal CT also revealed thinning of the skull base bone (Figure 3B). Three-dimensional CT angiography subsequently demonstrated a cerebral aneurysm in the right posterior cerebral artery (PCA) (Figure 3C). This aneurysm had not been detected by DSA performed 4 days previously (Figure 3D), so presumably formed rapidly over a period of 4 days. This aneurysm appeared as a fusiform-shaped growth in the P1-P2 portion of the right PCA. Neck clipping was again considered unfeasible, and trapping of the right PCA was performed (Figure 3E, 3F). The surgery succeeded in trapping the aneurysm. However, the patient continued to have seriously impaired consciousness.

The cerebral aneurysm trapped by this surgery was subsequently resected and sent for pathological examination (Figure 4A). The findings included structural collapse in the aneurysm wall (Figure 4B, 4C), and a rupture in the internal elastic membrane in part of the artery wall near the aneurysm (Figure 4D). Grocott staining revealed abundant fungi in the artery wall (Figure 4E, 4F). These hyphae-forming fungi were thought to be Aspergillus based on positive blood testing for the specific antigen for Aspergillus. Therefore, this aneurysm was considered to have been caused by fungal infection (Aspergillus infection).
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Figure 4. Pathological findings of the aneurysm in the posterior cerebral artery resected after trapping. (A) Macroscopic image of the cerebral aneurysm of the right posterior cerebral artery and cerebral artery near the aneurysm. Scale bar = 1 cm. (B and C) Elastica van Gieson staining showing structural collapse in the aneurysm wall. Scale bars = 5 mm. (D) Elastica van Gieson staining showing a rupture in the internal elastic membrane in part of the artery wall near the aneurysm. Scale bar = 500 μm. (E and F) Grocott staining revealing abundant fungi in the ruptured internal elastic membrane in part of the artery wall near the aneurysm. Scale bars = 500 μm (E), 200 μm (F).

Figure 5. Brain computed tomography (CT) scans and magnetic resonance (MR) image on admission, retrospective interpretation. A: CT scan showing calcified lesion (arrow) in the nasal frontal sinus. B: Bone window CT scan showing destruction of the orbital medial wall (arrow) of the right eye. C: T2-weighted MR image showing a hypointense lesion (arrow) in the frontal sinus.

Treatment of fungal infection

Retrospective inspection of the imaging studies found that T2-weighted MR imaging on admission had shown a hypointense lesion in the frontal sinus (Figure 5C). CT on admission had also revealed high density accumulation corresponding to fungus ball in the frontal sinus.
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and destruction of the orbital medial wall of the right eye (Figure 5A, 5B). This lesion was initially less suspected to be the cause of the rapidly progressive bilateral visual disturbance, since the high density areas on CT and hypointense lesion on T2-weighted MR imaging of the frontal sinus were located far from the dura mater surrounding the optic nerve. Endoscopic resection of this calcified granuloma in the frontal sinus on day 46 of hospitalization revealed filamentous fungal growth that was suspected to be Aspergillus infection, demonstrating that mycosis of the paranasal sinuses was the underlying disease (Figure 6). Based on the imaging finding of thinning of the skull base and other imaging findings, paranasal sinus aspergillosis was considered to have spread inside the cranium after infiltrating and destroying the skull base bone, triggering mycosis of the CNS.

Based on these imaging and pathological findings, a regimen of antifungal agents was administered (firstly, liposomal amphotericin B 300 mg and micafungin 300 mg per day from days 34 to 80 of hospitalization, and secondly, voriconazole 480 mg and micafungin 300 mg per day from days 81 to 84 of hospitalization). CT angiography was performed several times after starting the antifungal therapy, but no newly formed aneurysms were observed. However, laboratory data evaluating the progression of fungal infection, for instance Aspergillus antigen and β-D glucan, did not show any improvement, so the antifungal therapy had to be prolonged. After 7 weeks of antifungal therapy, the patient developed renal impairment that caused his general condition to deteriorate, eventually resulting in death 110 days after the initial symptoms (84 days after admission). The

Figure 6. Pathological findings of the fungal ball in the frontal sinus resected by endoscopy. (A) Hematoxylin and eosin staining of the fungal ball in the frontal sinus. Scale bar = 5 mm. (B and C) Grocott staining showing black-stained fungi with Y-shaped branches, diagnosed as Aspergillus. Scale bars = 1 mm (B), 40 μm (C).
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Autopsy analysis

A pathological autopsy was performed with the consent of his family. The dura mater in the anterior and middle skull base was opaque and hypertrophic, and the bone on the right base of the sella had been destroyed as a result of fibrosis associated with the mycosis (Figure 8A, 8B). Abundant fibrosis and inflammatory cell infiltration were observed beneath the membrane in the paranasal sinuses outside the skull, and phagocytosed fungi were found in areas of infiltration of multinucleated giant cells (Figure 8C-F). Numerous fungi were also observed in the dura mater of skull base, together with inflammatory cell infiltration and fibrosis (Figure 9). These findings demonstrated that the invasive fungal sinusitis had spread osteoclastically inside the cranium.

A series of specimens was prepared from the major intracranial arteries, including the basilar artery (BA), ICA, and MCA, but no fungal infection or inflammation was identified outside the areas of aneurysm formation (Figure 10). These findings suggest that the antifungal agents had succeeded in preventing the formation of further aneurysms and vascular damage subsequent to the 2 ruptured aneurysms which had occurred before the start of antifungal therapy. However, the falx cerebri located far from the skull base revealed fungal proliferation accompanied by map-like necrosis, conglomerated multinucleated giant cells, and inflammatory cell infiltration (Figure 11A-C). Moreover, fungal proliferation was detected in the walls of small veins near the superior cerebellar artery located far from the sites of the 2 ruptured aneurysms (Figure 11D, 11E), demonstrating that mycosis of the CNS was prolonged despite long-term administration of antifungal agents.

Discussion

In recent years, *Aspergillus* has been the fungus most often associated with invasive fungal sinusitis, and approximately 9% of cases of
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invasive *Aspergillus* result in infiltration of the CNS [1, 12, 13]. *Aspergillus* is also the fungus most often responsible for the formation of cerebral aneurysms. Cerebral aneurysms associated with mycosis are highly likely to rupture over the short term, resulting in SAH [9, 14, 15]. SAH associated with mycotic cerebral aneurysm rupture frequently and rapidly results in a serious clinical course [10, 13, 16, 17].

The present patient suffered the rupture of 2 different cerebral aneurysms over a period of several days, with the second aneurysm forming and rupturing in just 4 days. Such an extremely rapid course is in stark contrast to the formation and rupture of typical cerebral aneurysms, reflecting the highly vascular invasive nature of mycosis. After *Aspergillus* was detected in the frontal sinus and the cerebral aneurysm, administration of antifungal agents achieved temporary improvement in the patient’s symptoms, but his impaired consciousness was prolonged by the second SAH, leading to deterioration in his general condition that resulted in death (Figure 7). Previous studies reported that ruptured mycotic cerebral aneurysm caused by invasive aspergillosis has a very poor prognosis, with a high mortality rate [9, 13, 16].

*Aspergillus* has a morphology that is suited to cerebrovascular infiltration and contains elastase and other catabolic enzymes with high potential to invade blood vessels and to penetrate and easily cause rupture of aneurysms [10]. Once inside the arterial wall, *Aspergillus* forms a mycelial mass that can rupture the arterial wall structure [9], which often results in the formation of fusiform-shaped aneurysms that protrude from the entire artery [18]. As in

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**Figure 8.** Pathological findings at autopsy 1. A and B: Macroscopic images of the skull base showing that the dura mater in the anterior and middle skull base was opaque and hypertrophic (arrows), and the bone of the right base of the sella had been destroyed as a result of fibrosis associated with the fungal infection (arrows). C: Hematoxylin and eosin staining of the intracranial and extracranial sagittal sections including the sella turcica showing abundant fibrosis and inflammatory cell infiltration (arrows) in both areas. Scale bar = 5 mm. D and E: Hematoxylin and eosin staining of the membrane in the paranasal sinuses outside the skull showing fibrosis and inflammatory cell infiltration (multinucleated giant cells) beneath the epithelia in the paranasal sinuses. Scale bars = 1 mm. F: Grocott staining showing phagocytosed fungi (arrows) in areas of infiltration of multinucleated giant cells. Scale bar = 200 μm.
the present case, mycotic cerebral aneurysm is often large and isolated, and frequently occurs in major cerebral arteries at the skull base, namely the ICA, BA, and PCA [9, 14]. Neck clipping is thus often unfeasible, so the vessel supplying blood to the aneurysm must be trapped, resulting in the poor prognosis associated with mycotic cerebral aneurysm.

In the present study, the autopsy examination detected no mycotic infiltrate in the major cerebral arteries other than at the locations of the 2 ruptured aneurysms, suggesting that the antifungal therapy had prevented further spread of the mycosis into the vasculature. However, despite approximately 7 weeks of antifungal therapy, the fungal infiltration had penetrated deep within the falx cerebri and in the small veins near the tentorium cerebelli, which are far from the suspected route of intracranial infiltration through the skull base. The present findings show that, once the skull is invaded, the fungus spreads extensively through the dura mater, suggesting that the course of this condition is typically refractory even to prolonged administration of antifungal agents. Furthermore, the present findings strongly suggest that the earliest possible diagnosis and therapeutic intervention are essential in patients with invasive fungal sinusitis.

Once the mycosis has entered the paranasal sinuses, definitive diagnosis followed by immediate initiation of therapy is the best course of action. Mycosis is often diagnosed through symptoms such as headache and chronic cough, but mycosis limited to the paranasal sinuses is often difficult to diagnose precisely due to the absence of any specific symptoms. Characteristic imaging findings include high
density regions within the paranasal sinuses that appear calcified on CT, and hypointensity on T2-weighted MR imaging. The high density regions that appear calcified on CT are attributed to the presence of concentrated proteinaceous fluid, iron, manganese, and other heavy metals, as well as calcium that are produced by the metabolism in the fungus. The hypointensity seen on T2-weighted MR imaging has been identified as iron and manganese agglomerated within the fungus [19, 20]. Patients with a history of immune failure and abnormal glucose tolerance are at high risk of fungal sinusitis [10, 12], so the imaging findings of such individuals should be carefully scrutinized.

In the present case, the imaging studies on admission showed both of these findings, high density on CT and hypointensity on T2-weighted MR imaging in the frontal sinus. Thus, fungal sinusitis of the frontal sinus was suspected. However, fungal CNS invasion was less obviously the cause of the rapidly progressive bilateral visual disturbance since the high density on CT and hypointensity on T2-weighted MR imaging were far from the dura mater surrounding the optic nerve. Consequently, idiopathic pachymeningitis was firstly diagnosed as the cause of the visual disturbance, which led to delay in the initiation of therapy. The possibility of CNS invasion of fungal sinusitis is important to consider regardless of the location of the high density on CT and hypointensity on T2-weighted MR imaging.

Diagnosis of mycosis limited to the paranasal sinuses is difficult, but should be established at the earliest possible opportunity after infiltra-
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Clinical symptoms of CNS mycosis do not always manifest as typical signs of infection such as fever and headache, and often tend to be nonspecific, such as impaired consciousness, cranial nerve symptoms, hemiplegia, encephalopathy, and convulsions [1, 11, 12]. Specifically, the onset of orbital apex syndrome in the form of visual disturbance and ocular motility disorder is frequently associated with intracranial mycosis [12], so these clinical signs indicate the possibility of CNS infiltration and the patient should be referred for investigation. Distinctive imaging findings can also prove useful in diagnosing fungal sinusitis. Cranial CT findings of destruction of bone of the skull base are an important indicator that the fungus has spread directly inside the skull [10], and infection that has spread to the dura mater often appears as diffuse hypertrophy [20, 21]. These particular findings were also present in our case. Autoimmune inflammatory diseases such as idiopathic hypertrophic pachymeningitis have similar appearances on imaging [12] that require further differential diagnosis. Steroid therapy to treat such conditions can exacerbate the mycosis, so steroids should only be administered after fungal infection has been definitively excluded [22]. In the present case, the use of steroids may have adversely impacted the mycosis.

Mycosis confined to the paranasal sinuses or infiltrated into the CNS requires biopsy of the paranasal sinuses via craniotomy or endoscopy and consideration of surgical resection of the lesion or diagnostic therapy with antifungal

Figure 11. Pathological findings at autopsy 4. (A) Hematoxylin and eosin staining of the coronal section of the superior sagittal sinus and other regions of the falx cerebri showing map-like necroses and severe inflammatory cell infiltration. Scale bar = 5 mm. (B) Enlarged view of (A) showing conglomerated multinucleated giant cells. Scale bar = 100 μm. (C) Grocott staining showing invasive fungal proliferation (arrows). Scale bar = 100 μm. (D) Hematoxylin and eosin staining of the walls of small veins near the superior cerebellar artery located far from the sites of the 2 ruptured aneurysms showing invasive fungal proliferation. Scale bar = 800 μm. (E) Grocott staining of the walls of small veins near the superior cerebellar artery located far from the sites of the 2 ruptured aneurysms showing invasive fungal proliferation. Scale bar = 100 μm.
agents. Endoscopic dissection enables radical treatment of the mycosis localized in the paranasal sinuses [23], so proactive endoscopic treatment intended to achieve definitive diagnosis should be seriously considered, especially in high-risk patients. Our present patient with initial complaints of visual disturbance presented with calcified high density lesions on CT and hypointense lesion on T2-weighted MR imaging, so earlier endoscopic dissection may have enabled definitive diagnosis and appropriate treatment.

Conclusion

Our patient presented with invasive aspergillosis of the nasal sinus manifesting as visual disturbance which caused subsequent repeated mycotic cerebral aneurysm formation and rupture, ultimately led to the patient’s death. Autopsy findings revealed prolonged mycosis of the CNS despite long-term administration of antifungal agents. If CNS infiltration is suspected, early surgical resection and antifungal therapy must be initiated immediately. Specific radiological findings, such as high density on CT and hypointensity on T2-weighted MR imaging, could be indicators of fungal sinusitis.

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Disclosure of conflict of interest

None.

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