Fungal Internal Carotid Artery Aneurysms: Successful Embolization of an *Aspergillus*-Associated Case and Review

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**Background.** Fungal aneurysms of the carotid artery are rare. We report here a case of *Aspergillus fumigatus* invasive sphenoidal sinusitis complicated by carotid artery aneurysms in a severely neutropenic patient who was successfully treated with a combination of antifungal therapy and embolization of all aneurysms.

**Methods and results.** Carotid aneurysms were suspected when severe epistaxis occurred during follow-up for sinusitis. MRI angiograph and cerebral angiograph revealed 5 aneurysms involving the right intracavernous carotid artery. Coil endovascular embolization was successfully used for the first time in this context, and the patient is alive 2 years later. We also reviewed the literature and identified 10 cases of fungal carotid artery aneurysms. *Aspergillus* species was the most common fungal organism. All patients were immunocompromised and had to be treated surgically.

**Conclusions.** Internal carotid arterial involvement is a rare but life-threatening complication of invasive fungal sinusitis. Fungal aneurysms should be diagnosed early, so that the embolization procedure can be performed before the occurrence of severe bleeding.

Aneurysms of the extracranial portion of the internal carotid artery are rare, accounting for only 0.1%–2% of all surgical procedures affecting the internal carotid artery and for 0.4%–1% of all arterial aneurysms [1]. Infectious aneurysms involving the internal carotid artery are even rarer, believed to represent only 2%–5% of all carotid aneurysms [2]. Most infection-associated carotid aneurysms are caused by bacterial pathogens in the context of endocarditis, contrasting with the rare occurrence of the fungal-related carotid aneurysms. Fungal aneurysms of carotid arteries are extremely rare, with <15 cases reported since 1968 [3, 4]. However, with the prolonged survival of severely immunocompromised patients, the incidence of fungal arterial infections is expected to increase, making the recognition of this devastating complication extremely important. Fungal aneurysms pose challenges for diagnosis and management, because they are rare, unpredictable, and often occur in a clinical context that is neither specific nor alarming. Treatment strategy is controversial owing to the risk of complications associated with surgery of the cavernous sinus.

We report here a case of *Aspergillus fumigatus* invasive sphenoidal sinusitis complicated by 5 internal carotid artery aneurysms in a severely neutropenic patient who was successfully treated with a combination of antifungal therapy and embolization of all aneurysms. We also review fungal aneurysms of internal carotid arteries. This report of intrasphenoid carotid fungal aneurysms associated with *Aspergillus* species is of particular interest, not because of the rarity of this condition, but rather because we describe for the first time, to our knowledge, the successful use of coil endovascular embolization of such fungal aneurysms as an alternative to invasive neurosurgical procedures, which had been used in all of the previously reported cases.
METHODS
The international medical literature was reviewed for cases of fungal carotid aneurysms. The Medline and EMBASE databases were screened for the period 1966–2006 using the keywords "carotid aneurysm," "carotid artery pseudo aneurysm," "mycotic internal carotid aneurysm," and "cerebral mycotic aneurysm;" the subset heading was "invasive fungal infection," "Aspergillus spp mycotic aneurysm," and "Candida spp mycotic aneurysm." Cases were excluded if fungal arterial aneurysm complicated the course of local surgical procedure. The case of our patient and 10 additional cases of fungal internal carotid aneurysms are presented. All cases were confirmed by culture and/or local histopathological examination.

CASE REPORT AND RESULTS
A 61-year-old man was referred to our hospital for the management of hairy cell leukemia and received 1 course of cladribine therapy. He also received valaciclovir and atovaquone as primary prophylaxis. He had a long history of leukoneutropenia before the diagnosis of leukemia. During the profound neutropenia that followed cladribine therapy (35 days), the patient presented with persistent cough; CT of the chest disclosed a mass and nodules surrounded by the halo sign (halo of ground-glass attenuation). These images were highly suggestive of invasive pulmonary aspergillosis. The patient received voriconazole and caspofungin as a combination antifungal treatment regimen. After 1 month, a left upper lobectomy was performed because of massive hemoptysis secondary to upper pulmonary artery invasion. Histological examination of the lung tissue specimen revealed fungal hyphae evocative of Aspergillus species. Culture of a sputum specimen was positive for A. fumigatus. The serum galactomannan titer was 0.75. Two months later, while receiving therapy with voriconazole only, the patient presented with headache and epistaxis. Neurological examination findings were unremarkable. Laboratory examination findings were normal, except for the presence of thrombocytopenia (platelet count, $25 \times 10^9$ platelets/L) and neutropenia (WBC count, $0.5 \times 10^9$ cells/L).

Endoscopic examination of the sphenoid sinus revealed purulent secretions. Results of repeated serum galactomannan detection assays were negative. Histological examination of the sinus mucosa biopsy specimen revealed septate hyphae, and sinusal secretions grew A. fumigatus, although the patient was still receiving oral voriconazole therapy. Caspofungin was added to the treatment regimen. At this time, MRI of the paranasal sinuses was performed but did not show evidence of tissue invasion. One month later, the patient experienced a new episode of severe epistaxis and was readmitted to the hospital. A second MRI highlighted mucosal thickening of the sphenoid and ethmoid sinuses but disclosed no pathological image of the cavernous sinus and internal carotid artery. Ten days later, another episode of epistaxis occurred, and at this time, MRI revealed images evocative of multiple aneurysms of the cavernous segment of the internal carotid. MRI was performed using coronal and T2- and T1-weighted sequences before and after intravenous administration of gadopentetate dimeglumine. It revealed soft-tissue filling of the sphenoid sinus. A low-signal intensity pouch was detected in the superior and right lateral region of the sinus in connection with the right internal carotid artery through a thin channel (figure 1), defining an aneurysm producing the same normal signal void as that produced by the right internal carotid artery.

The patient was transferred to the interventional neuroradiology unit, where computerized arterial angiograph revealed 5 aneurysms involving the entire cavernous segment of the right internal carotid artery (figure 2). The aneurysmal dilated cavernous carotid artery was packed with detachable metallic coils, and the cervical internal carotid artery was occluded using detachable balloons. Postembolization injection of the left internal carotid artery revealed good cross-filling with reflux into the supraclinoid internal carotid artery on the right. Functionality of the Willis polygon was checked. The visualized portion of the right supraclinoid internal carotid artery was of normal size. As of November 2007, the patient had not presented with...
any recurrence of epistaxis, and repeated endoscopic sinus examinations did not reveal any bleeding or tissue debris. Voriconazole therapy was stopped after 2 years, when immune reconstitution was obtained. A chest and sinus CT performed 1 year after diagnosis revealed complete resolution of all pulmonary nodules and sinusitis.

LITERATURE REVIEW AND DISCUSSION

There are few previous reports of fungal aneurysms of the internal carotid artery. We identified 10 cases. Table 1 presents the major clinical and microbiological features of these fungal aneurysms. All but 1 patient were immunosuppressed.

Carotid artery aneurysms are uncommon but are associated with life-threatening CNS complications [14]. The most common cause of carotid aneurysms is atherosclerosis [15]. The early case reports emphasized syphils, tuberculosis, and untreated endocarditis as the most common causes [14, 16]. Other common mechanisms include direct spreading of infection from a contiguous focus. The most common bacterial microorganisms cultured from carotid infectious aneurysms are Staphylococcus aureus and Salmonella species [17]. Infectious carotid aneurysms most commonly present as a febrile, pulsatile lateral cervical mass [16]. Fungal infections are estimated to represented ~1% of all infectious aneurysms [18], but in the most recent series, they represented up to 10 (14%) of all 73 cases of carotid infectious aneurysms [19]. In this latter series, Aspergillus species represented the most common organism (6 cases), followed by zygomycetes (2 cases) and Penicillium and Candida species (1 case each). All patients had known causes of immunosuppression, except for an 11-year-old boy with Penicillium infection associated with aneurismatic rupture [10]. Immunosuppressing conditions consisted of diabetes mellitus in 2 patients and hematological malignancies in the others. In 3 patients, rupture was complicated by a lethal subarachnoidal hemorrhage, and in 1 patient, fungal aneurysm was complicated by a cerebral infarction. In our patient, sphenoidal aspergillar sinusitis led to contiguous invasion of the carotid tissue. It is highly likely that, in this context, fungal invasion of the adventitia resulted in inflammation and necrosis that thinned and weakened the wall and finally lead to aneurysm formation.

Aspergillus species are able to directly invade the wall of blood vessels [19]. Fungal aneurysms are usually fusiform and tend to involve proximal segments of the intracranial vessels. Five cases of fungal carotid aneurysms were located in the extracranial portion of the internal carotid artery [5–9, 20]. Clinical presentation is heterogeneous; severe epistaxis, as seen in our patient, was also observed in the patient described by Hurst et al. [9]. Severe epistaxis may indicate aneurismatic rupture or cavernous fistula. Other clinical signs are related to cerebral infarction caused by vessel invasion and extension of hyphae into the lumen, with local thrombosis or embolization of hyphal masses.

Our literature review of internal carotid artery fungal aneurysms revealed a dramatically high mortality rate of 80% (8 of 10 patients died). Antifungal treatments alone do not appear to be curative and may not prevent arterial wall rupture. Most of the patients described in the literature received amphotericin B as antifungal treatment. Our case was the first in the era of new antifungal treatment for which a combination therapy with voriconazole and caspofungin was used. This decision was made on the basis of currently available experimental and clinical information and, notably, data recently obtained involving solid-organ transplant recipients that demonstrate the potential value of this combination [21–23]. Despite this treatment, multiple carotid artery aneurysms developed; our observation argues for the necessity of repeated and careful carotid imaging in patients with nasal bleeding during the course of sphenoid
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Study</th>
<th>Year</th>
<th>Underlying disease</th>
<th>Fungus</th>
<th>Clinical presentation</th>
<th>Site of aneurysm</th>
<th>Antifungal therapy</th>
<th>Interventional procedure</th>
<th>Outcome</th>
<th>Postmortem findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>Present case</td>
<td>2007</td>
<td>Hairy cell leukemia</td>
<td>Aspergillus fumigatus</td>
<td>Headache, epistaxis cough, low grade fever</td>
<td>Right extra cranial internal carotid</td>
<td>Voriconazole, caspofungin</td>
<td>Endovascular embolization</td>
<td>Survived</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>M</td>
<td>[5] 1997 Acute lymphoid leukemia</td>
<td>A. fumigatus</td>
<td>Hard swelling in the neck, dyspnea, brain abscesses, right vocal cord paralysis</td>
<td>Right common CA</td>
<td>AmB</td>
<td>Surgical procedure</td>
<td>Survived</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>M</td>
<td>[6] 1998 Chronic cutaneous candidiasis</td>
<td>Candida albicans</td>
<td>Stupor, left hemiparesis, right middle cerebral artery infarction</td>
<td>Intracranial CA, C-2 segment extracranial CA</td>
<td>Oral flucytosine, nystatine, AmB intravenously</td>
<td>None</td>
<td>None</td>
<td>Died</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>F</td>
<td>[7] 1991 Trans-sphenoidal surgery for Rathke cleft cyst</td>
<td>A. fumigatus</td>
<td>Subarachnoid hemorrhage</td>
<td>C1-segment of the right internal CA</td>
<td>AmB</td>
<td>None</td>
<td>Died</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>F</td>
<td>[3] 1968 Acute leukemia</td>
<td>Aspergillus species</td>
<td>...</td>
<td>Right internal CA</td>
<td>None</td>
<td>None</td>
<td>Died</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>M</td>
<td>[8] 1989 Chronic lymphoid leukemia</td>
<td>A. fumigatus</td>
<td>Facial pain, deterioration in left visual acuity, left total ophthalmoplegia, subarachnoid hemorrhage</td>
<td>Siphon of the left internal CA</td>
<td>AmB and 5FC</td>
<td>None</td>
<td>Died</td>
<td>Subarachnoidal hemorrhage due to the rupture of an aneurysm of the basilar artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>73</td>
<td>M</td>
<td>[9] 2001 Idiopathic thrombocytopenic purpura, steroids; chronic lymphoid leukemia</td>
<td>A. fumigatus</td>
<td>Epistaxis, decreased visual acuity, cranial nerves III, IV, and V paralysis</td>
<td>Right cavernous CA</td>
<td>AmB</td>
<td>Endovascular embolization</td>
<td>Died</td>
<td>Pus in the lateral sinus wall, aneurysm rupture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>M</td>
<td>[10] 1970 Maxillary tooth extraction</td>
<td>Penicillium species</td>
<td>Pain, jaw osteitis</td>
<td>Intracranial CA</td>
<td>AmB</td>
<td>None</td>
<td>Died</td>
<td>Penicillium on the CA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>76</td>
<td>M</td>
<td>[12] 1988 Diabetes mellitus</td>
<td>Mucorale</td>
<td>Neck pain</td>
<td>Right intracavernous CA</td>
<td>AmB</td>
<td>None</td>
<td>Died</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>M</td>
<td>[13] 1978 No</td>
<td>A. fumigatus</td>
<td>Seizures, coma, subarachnoid hemorrhage</td>
<td>Intracranial aneurysm of the CA</td>
<td>None</td>
<td>None</td>
<td>Died</td>
<td>Destruction of the arterial wall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B; CA, carotid artery; NC, not communicated.
sinusitis. Therefore, in cases for which elective surgical ligation cannot be achieved or when prodromal bleeding requires urgent intervention, alternative nonsurgical approaches have been pursued.

Open surgical procedure is generally accepted as the technique of choice for extracranial carotid noninfectious aneurysms. Ligation of the affected artery was the treatment of reference during the 1970s and 1980s [6, 13, 24, 25]. However, recent reports have advocated the use of minimally invasive endovascular therapy as an alternative approach for such aneurysms [1, 26]. Hurst et al. [10] have reported an internal carotid artery aneurysm caused by invasive Aspergillus sphenoidal sinusitis. Although the aneurysm was obliterated by endovascular coils, it extended intradurally and caused fatal subarachnoid hemorrhage. Gonda et al. [27] also reported successful endovascular treatment of an extracranial carotid artery aneurysm complicated by a bacterial parapharyngeal abscess. In this latter case, coil occlusion was unsuccessful, and surgical ligation of the internal carotid artery was required [27]. Endovascular treatment with stents or occlusion, as in our case, may offer an effective but less invasive therapeutic alternative for fungal internal carotid aneurysms [26, 28]. Such techniques have commonly been used in cases of traumatic or atherosclerotic aneurysms [1, 16].

Our case demonstrates that nasal bleeding in the course of Aspergillus sphenoidal sinusitis may be caused by internal carotid aneurysm and emphasizes the potential benefit of urgent coil embolization. Following endovascular embolization, the prolonged administration of antifungal drugs, as given to our patient, was associated with control of the disease. The coils could be a potential nidus for persistent infection [26], and a theoretical risk of infection of foreign material and abscess formation also exists [29]; however, such subsequent infection has never been reported [30].

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References

