Carotid-cavernous sinus thrombosis caused by *Aspergillus fumigatus*

Case report

**Laligam N. Sekhar, M.D., Manuel DuJovny, M.D., and Gotti R. Rao, M.D.**

Department of Neurological Surgery and Department of Pathology (Neuropathology), University of Pittsburgh School of Medicine, and Veterans Administration Medical Center, Pittsburgh, Pennsylvania

A case is presented of *Aspergillus fumigatus* granuloma involving the sphenoid sinus, sella turcica, cavernous sinus, and the internal carotid artery. The diagnosis was established by a transsphenoidal biopsy. The infection proved difficult to treat and finally remitted after chemotherapy with a combination of amphotericin B, rifampin (rifampicin), and flucytosine (5-fluorocytosine). The spectrum of aspergillosis of the central nervous system is reviewed, and difficulties in treating this infection are considered.

**KEY WORDS**  
aspergillosis  
cavernous sinus  
internal carotid artery  
thrombosis  
sella turcica  
hypophysectomy  
chemotherapy

**FUNGAL** infections of the central nervous system (CNS) have assumed more importance in recent years. There has been an increase in the number of these infections, presumably due to the large number of patients being treated with immunosuppressants and steroids after transplantation and for a growing group of autoimmune disorders. Aspergillosis is second only to candidiasis in the frequency of mycosis among cancer patients. The following case report illustrates a mode of presentation of aspergillosis in the CNS mimicking nasopharyngeal carcinoma. It emphasizes the importance of tissue diagnosis by frozen section at the time of surgery and of culturing neurosurgical biopsy material. The difficulties of treating aspergillosis of the CNS are also exemplified by this case.

**Case Report**

This 37-year-old man was admitted to our service in August, 1978, with the chief complaint of right-sided face and ear pain and double vision. He was employed as a maintenance worker in a factory. He had been married for 10 years and had no children. He was well until March, 1978, when he developed throbbing frontal headache that lasted for 4 days. Before this, he had had a cold with nasal drip and fever. The headache was replaced by severe, dull pain of the right ear and preauricular deep facial region, with radiation to the right upper and lower gums, shoulder, and neck. Six weeks prior to admission, he developed double vision on lateral gaze over a period of 2 days. He had lost 20 lb since the onset of the illness.

**Examination.** He was a tall, thin, eunuchoid male with bilaterally small, soft testes. There was no lymphadenopathy. Neurological examination was normal except for bilateral abducens paresis.

Laboratory examination showed a complete and differential blood count, urinalysis, sedimentation rate, and serological test for syphilis to be normal. Serum antibodies for *Candida, Blastomyces, Histoplasma, Coccidioides,* and *Aspergillus* were absent. Three samples of sputum were negative for acid-fast bacilli and fungi. Sputum cytology was normal.

Serum cortisol, growth hormone, triiodothyronine, thyroxine, and thyroid-stimulating hormone levels were normal. Arginine insulin growth hormone tolerance test (AITT) was normal, indicating a normal pituitary reserve. Serum testosterone levels were 297 and 328 ng/dl (normal 300 to 1200 ng/dl), luteinizing hormone was 35 mIU/ml (normal 7 to 28 mIU/ml), follicle-stimulating hormone, 33 mIU/ml (normal 7 to 28 mIU/ml), and prolactin levels were 22 and 24 ng/ml. Testicular biopsy showed Leydig's cell.
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hyperplasia, focal fibrosis, focal tubular atrophy, and decreased spermatogenesis, strongly suggestive of Klinefelter’s syndrome. However, chromosomal analysis showed 46 chromosomes with normal X and Y chromosomes. Serum protein electrophoresis showed diffuse hypogammaglobulinemia, and immunoelectrophoresis showed depression of immunoglobulin E (IgE), IgA, and IgM. Skin test with mumps, streptokinase-streptodornase (SK-SD), Trichophyton, and Candida antigens produced a positive response to Candida, suggesting an adequate delayed immunity system.

A spinal tap showed normal opening pressure; the cerebrospinal fluid (CSF) contained one lymphocyte, protein content of 22 mg, and a glucose level of 76 mg. Cultures were negative for fungi and bacteria.

Plain films of the skull and sinuses showed haziness of both frontal sinuses, opacity of the inferior aspect of the left maxillary sinus, and opacity in the sphenoid sinus. Tomograms of the posterior fossa revealed normal internal auditory canals and jugular foramina. Tomograms of the sellar region showed erosion of the floor of the sella on the right side; there were three masses in the sphenoid sinus, two round masses located in its anterosuperior and posteroinferior aspects, and a third crescentic mass applied en plaque to its roof (Fig. 1 left). Computerized tomography (CT) scans were performed in the horizontal and coronal planes with no evident abnormalities. A transfemoral arteriogram demonstrated narrowing of the right internal carotid artery, beginning 2 cm above the bifurcation and extending through the cavernous sinus. There was complete occlusion at the level of the clinoid process (Fig. 1 right). The left internal carotid artery was enlarged and filled the right and left middle and anterior cerebral arteries.

Operation. With the presumptive diagnosis of nasopharyngeal carcinoma, nasopharyngoscopy was performed under general anesthesia. No masses were visualized and multiple biopsies were taken which showed normal adenoid tissue and epithelium on histological examination. A transseptal, sublabial sphenoidotomy was performed in September, 1978. Three masses were seen inside the sphenoid sinus. Two globular bluish masses with the gross appearance of mucoceles were located in the anterior and posteroinferior portions of the sphenoid sinus. On the roof of the sinus was another mass that was reddish-white in color and bled like granulation tissue on piecemeal removal. The floor of the sella was eroded in places, and upon removal of the bone, similar tissue was found diffusely between the bone and dura of the sella turcica. The dura was firm to touch with instruments, and was apparently not involved. The dura
of the sella turcica was not opened, and the surgical defect in the bone floor was not closed. The rest of the wound was closed as normal.

A frozen tissue section, stained with hematoxylin and eosin, revealed abundant granulation tissue with chronic inflammatory cells, occasional giant cells, and several filamentous septate hyphae. Periodic acid-Schiff (PAS) and methenamine silver techniques subsequently confirmed the presence of fungus, which on fungal cultures of biopsy material was identified as *Aspergillus fumigatus* (Fig. 2).

**Postoperative Course.** Starting on the first postoperative day, amphotericin B was administered intravenously at a dosage of 50 mg on alternate days. On the fourth postoperative day, the patient noted reduction of facial pain and a general sense of well-being. His symptoms steadily improved from this point and completely remitted, except for minimal diplopia on lateral gaze. However, after receiving 1850 mg of amphotericin (2 months postoperatively) he developed persistent fever of 100° to 102°F. This was followed shortly thereafter by the development of right orbital and periorbital pain, which was different from his initial face pain. There was progression of right sixth nerve paresis, and later, third and fourth nerve paralysis developed on the right side, along with cycloplegia, mild proptosis, and eyelid swelling.

A repeat spinal tap showed normal opening pressure; the CSF contained 60 white blood cells with 70% lymphocytes and 30% polymorphonuclear cells, a protein of 44 mg%, and a glucose of 65 mg%. Fungal cultures of the CSF were negative. A CT scan performed at this time showed an enhancing soft-tissue mass in the right side of the sphenoid sinus, and no abnormalities inside the orbit. Tomograms of the sphenoid sinus confirmed the extension of the mass inside the sphenoid. Ultrasonic B-scans of the orbit showed edema of the tissues, but no masses. A transfemoral right carotid arteriogram was repeated, and demonstrated the narrowing of the extracranial internal carotid artery, starting 2 cm above the bifurcation and extending through the cavernous sinus, with complete occlusion at the level of the clinoid process. In the region of the cavernous sinus there was an area of blush, 2 cm in diameter, around the carotid artery, which could represent either an inflammatory...
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granuloma or a small carotid cavernous fistula. The right cavernous sinus did not fill in the venous phase.

Since the granuloma had extended during therapy with amphotericin B, rifampin (rifampicin) was added at a dose of 600 mg twice daily. There was no clinical improvement despite combination therapy with these two drugs, so flucytosine (5-fluorocytosine) was started 15 days after starting rifampin, at a dosage of 2000 mg (37.5 mg/kg body weight) administered every 6 hours. During hospitalization the patient lost an additional 30 lb in weight due to persistent nausea and anorexia. Parenteral hyperalimentation was therefore commenced. One week after starting flucytosine, the patient became afebrile. His orbital pain decreased considerably, and the cranial nerve palsies started to improve.

At this time, in vitro sensitivities of his *A. fumigatus* became available. The organism was sensitive to flucytosine, resistant to rifampin and possibly resistant to amphotericin B. There was no in vitro synergry for the combination of the three drugs. Rifampin was stopped and the patient continued to receive amphotericin B and flucytosine. At the conclusion of drug therapy, the patient had received 4 gm of amphotericin B, a 1-month course of rifampin and a 2-month course of 5-fluorocytosine. A CT scan performed at this time showed marked regression of the sphenoidal mass. On follow-up examination 6 months after conclusion of drug therapy, the patient was free of ocular pain. His exophthalmos had completely resolved. There was marked improvement of the function of oculomotor and trochlear nerves, and some improvement of the function of the abducens nerve.

**Discussion**

In 1729, Micheli described a fungus that he named *Aspergillus* (rough head) because of the microscopic appearance of the spore-bearing structure. The first infection in man attributed to this fungus was described by Sluyer. Since then, over 350 species of *Aspergillus* have been described. *Aspergillus fumigatus* is the most frequent cause of infection, while *A. flavus, A. niger, A. glaucus, A. candidus, A. amstelodami, and A. sydowe* have been frequently implicated as pathogens. *Aspergillus* is a septate fungus that forms branching hyphae in tissues. On culture, it produces conidiospores of a characteristic appearance.

While the source of aspergillosis of the CNS may sometimes be difficult to establish, the usual route of entry is in the blood from the lungs or intestines. This appears to be the common portal of entry in the immunosuppressed host. Extension from the orbit and ethmoid sinus, and sphenoid sinus are the other routes of entry. Our patient may fall into the category of invasion through the sphenoid sinus. While *Aspergillus* invasion of the maxillary and frontal paranasal air sinuses is common, involvement of the sphenoid sinus is quite rare. Anaerobic conditions within the sinus due to the presence of mucoceles or chronic hypertrophic sinusitis are considered a predisposition for invasive sinus aspergillosis. The presence of mucoceles in the sphenoid sinus of our patient should be noted in this regard.

Iatrogenic introduction of *Aspergillus* into the CNS is a rare route of entry. Examples would include infection introduced by spinal tap, and transsphenoidal implantation during placement of radioactive yttrium for pituitary ablation. In many patients, however, the portal of entry is not identified.

The pathology of aspergillosis of the CNS usually depends upon the presence or absence of the compromised host (Table 1). Thus, the disseminated form of the infection occurs commonly in patients with leukemia or lymphoreticular neoplasms, those on immunosuppressant drugs following renal or cardiac transplantation, and those on long-term steroid therapy. In patients with normal immune mechanisms, the disease will more likely be limited to a portion of the CNS.

The two main features of the pathogenesis of CNS aspergillosis are chronic granulomatous inflammation and angiitis. Although *Aspergillus* species produce an endotoxin that causes severe local tissue necrosis and edema in animals, the pathological changes of aspergillosis in humans are usually those of a granulomatous inflammation. The acute exudative meningitis reported by Linck, and the vasculitis may perhaps be due to damage from the toxin.

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Aspergillosis abscesses may be single or multiple, and have been reported in every part of the brain, in the sella, and in the spinal epidural space. Aspergillosis has also been reported to resemble tumors in the frontal lobe, fourth ventricle, posterior fossa (extra-axially), and cervical spinal cord.
Spread of aspergillosis infection frequently occurs from the paranasal sinuses into the orbits and cranial cavity. A chronic granulomatous basal meningitis results, with or without a granulomatous encephalitis of the adjacent brain tissue. Many cases of this variety have been reported from the Sudan, although this undoubtedly occurs in other parts of the world where there are farmlands. 

The granulomas consist of giant cells, epithelioid cells, mononuclear cells, plasma cells, and fibroblasts. Special stains like PAS and methenamine silver demonstrate the presence of the fungal filaments in these granulomas.

Aspergillus (and other fungal species) invade cerebral blood vessels of all sizes. This causes intense inflammation of all layers of the arterial wall with thrombosis, rupture, and mycotic aneurysm formation. McKee and Oppe reported cases of intracranial carotid thrombosis presumed to be due to Aspergillus infection. McCormick, et al., described a case of disseminated aspergillosis with thrombosis of the intracranial carotid, middle cerebral, and anterior cerebral arteries. The orbit, optic nerve, and cavernous carotid were involved, but the cavernous sinus was apparently not involved. Green, et al., described three cases of sino-orbital aspergillosis with thrombosis of the internal carotid and/or middle cerebral arteries. Kaufman, et al., described a case where the intracranial and extracranial carotid arteries were involved by aspergillosis. Cases of hemorrhagic infarction and intracerebral hemorrhage have been reported frequently, presumably due to thrombosis or rupture of the intracerebral blood vessels involved in Aspergillus angiitis. Horten, et al., reported a mycotic aneurysm of the middle cerebral trifurcation, and reviewed three other cases of fungal aneurysms in which the differences between fungal and bacterial mycotic aneurysms were emphasized. Fungal aneurysms are generally larger sized (5 to 10 mm), and occur on the vessels of the circle of Willis, and its major branches (the internal carotid artery-ophthalmic bifurcation, basilar artery, and posterior communicating artery), in contrast to the smaller-sized bacterial aneurysms that affect smaller and more peripheral arterial branches. They also felt that the pathogenesis of these two aneurysms was different, with the bacterial aneurysm tending to arise by occlusion of the vasa vasorum, and the fungal types due to direct invasion of the wall.

Diagnosis of CNS aspergillosis is notoriously difficult. Blood cultures are invariably negative. Cerebrospinal fluid examination often shows elevation of protein and pleocytosis when there is an Aspergillus menigitis, but the organism is almost never cultured from the CSF. Serological tests to detect circulating Aspergillus antibodies or endotoxin are being studied, but are not presently of any use. Thus, the mainstay of diagnosis remains culture and pathological examination of tissue obtained at surgery or autopsy.

The importance of fungal cultures should be emphasized, since most reports in the literature are not documented by culture, and the increasing availability of different antibiotic drugs may make appropriate identification crucial.

Treatment of Aspergillus infections is very unsatisfactory at present. Amphotericin B administered intrathecally and/or intravenously, and flucytosine administered orally are the two forms of therapy that have demonstrated clinical usefulness, although in contrast to other fungi Aspergillus species are relatively resistant to both antibiotics. Experimental evidence and some case reports suggest that combination chemotherapy of amphotericin B and rifampin, and amphotericin B and flucytosine may have an additive or synergistic effect on this serious infection. There is a great need for developing more effective therapy for this increasingly common disease.

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References

11. Good RA, Vernier RL, Smith RT: Serious untoward reactions to therapy with cortisone and adrenocor-
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