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Sino-Orbital and Cerebral Aspergillosis: Cure with Medical Therapy

Sino-Orbital- und Zerebralaspergillose: Ausheilung durch medikamentöse Therapie

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Schlüsselwörter: Aspergillose – *Aspergillus fumigatus* – Nebenhöhlen – Orbita – Gehirn

Summary: A patient with sino-orbital and cerebral aspergillosis was successfully treated medically without surgical debridement. Anti-fungal agents, including amphotericin B and flucytosine were given over a fifteen month period with improvement in symptoms, resolution of cerebral abscesses by CT scan, and disappearance of serum precipitins to Aspergillus fumigatus. Success was attributed to the long duration of therapy (received in part as an outpatient), the use of agents to which the organism was known to be susceptible, and the maintenance of therapeutic drug levels. Although surgery is important in the management of chronic sino-orbital and cerebral aspergillosis, in patients unable to undergo extensive debridement medical therapy given for extended periods of time may be successful in eradicating the infection.

Zusammenfassung: Eine Patientin mit einer Aspergillose der Nebenhöhlen, der Orbita und des Gehirns wurde erfolgreich medikamentös ohne chirurgisches Debridement behandelt. Antimykotika einschließlich Amphotericin B und Flucytosin wurden über einen Zeitraum von 15 Monaten verabreicht und führten zu einer Besserung der Symptomatik, zu einer Rückbildung der computertomographisch erfaßbaren zerebralen Abszesse und zu einem Verschwinden der Serumpräzipitine gegen Aspergillus fumigatus. Der Erfolg wird der langen Dauer der antimykotischen Chemotherapie zugeschrieben (teilweise ambulant verabreicht), ferner der Anwendung von Präparaten mit ausgetesteter Suszeptibilität des Erregers und der Erzielung und Erhaltung therapeutisch wirksamer Antimykotika-Konzentrationen. Obgleich die Chirurgie in der Behandlung der Aspergillose der Nebenhöhlen, der Orbita und des Gehirns das Vorgehen der ersten Wahl ist, kann die medikamentöse Therapie bei Patienten, an denen ein extensives chirurgisches Debridement nicht möglich ist, bei Langzeitanwendung die Infektion zum Erlöschen bringen.

Introduction

Sino-orbital and cerebral aspergillosis are much less common than other types of *Aspergillus* infection, such as pulmonary aspergillosis. However, in many ways invasive pulmonary and sino-orbital aspergillosis are very similar. The infecting organism is almost always *Aspergillus fumigatus* or *A. flavus* in both types of infection. In both forms, spores are inhaled from the environment and invade the respiratory epithelium to establish infection, and blood vessel inva-

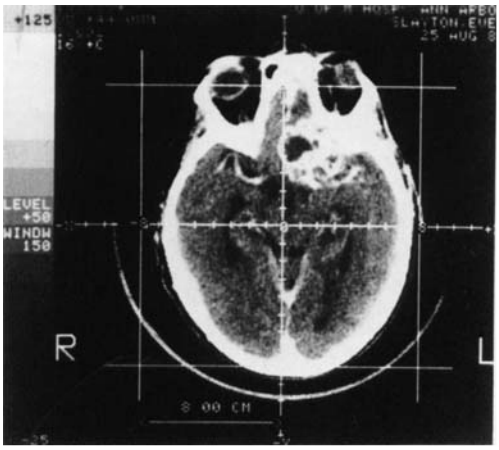
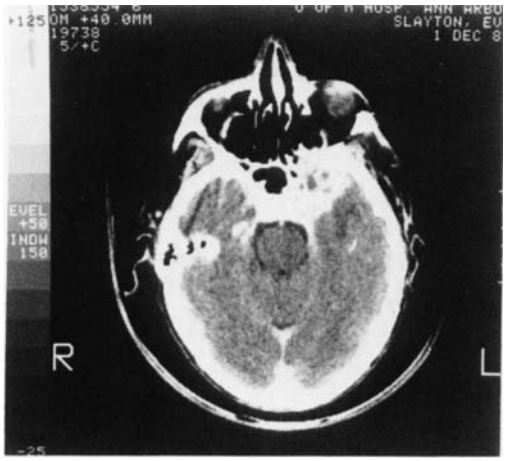


Fig. 2: (December 1983) Following 2.5 gm of amphotericin B and flucytosine a coalescing lesion of the frontal lobe, diminished in size was seen.



1. (August 1983) On admission, a left retroorbital mass was seen extending into the anterior and middle cranial fossae.

sion and necrosis are important components of the pathogenesis of infection (26, 30). One important difference is that invasive pulmonary aspergillosis occurs almost entirely in immunocompromised patients, whereas sino-orbital infection is most frequently seen in immunocompetent hosts (6, 12, 14, 27). Treatment of aspergillosis in an immunocompetent host may be more likely to succeed than treatment in an immunocompromised host. We describe a case of extensive sino-orbital and cerebral aspergillosis with a successful outcome after prolonged medical therapy.

Case History

A 74 year old woman presented to her local hospital with a 3 month history of worsening left-sided facial pain, periorbital swelling, ptosis, and visual loss. A prior temporal artery biopsy had shown no abnormality; empiric trials of prednisone (40 mg daily), phenytoin, and carbemazapine did not alleviate her symptoms.

Roentgenograms of the patient's skull showed no abnormality; computerized tomography (CT) of the orbits and sella turcica revealed mild left proptosis, an ill-defined soft tissue mass surrounding the apex of the optic nerve, and bony destruction. Medial and lateral aspiration biopsy of the left orbit releaved no malignant cells on cytologic examination; cultures of the aspirate were not performed. The patient underwent a left frontal craniotomy, which showed only an enlarged left internal carotid artery partially compressing the optic nerve. The patient was discharged after 2 months in hospital without a diagnosis.

Two months later, the patient was admitted to the University of Michigan Medical Center for further evaluation. Her complaints were essentially the same as during her previous admission except for the development of complete ophtalmoplegia on the left. She denied any prior history of facial infection, sinusitis, dental problems, or diabetes mellitus. Her review of systems was remarkable only for a 30 1b weight loss. Her temperature was 98.5 °F (36.9 °C), blood pressure 130/80 mm Hg, and pulse 86 beats/min. Her left eye exam was significant for proptosis, ptosis, chemosis, periorbital edema, paralysis of extra-ocular muscles and blindness. The chest, cardiac, and abdominal

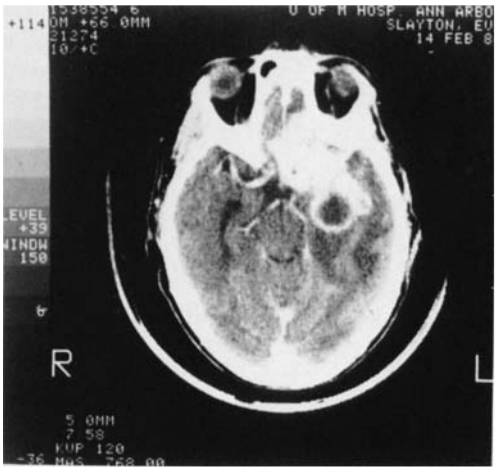


Fig. 3: (February 1984) After 2 months of vibunazole therapy the patient developed a new left temporal abscess.

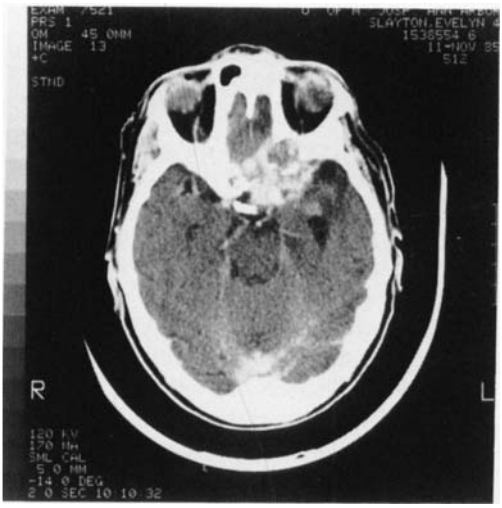


Fig. 4: (November 1985) Following stereotactic aspiration and additional therapy with flucytosine and amphotericin B (2, 9 gm) the abscess resolved and the patient remains clinically stable.

examination were unremarkable. The remainder of her neurologic examination showed normal strength and sensation in all extremities with symmetrical reflexes.

Chest roentgenogram showed no abnormalities. Skull films showed left maxillary sinus mucosal thickening but no bone destruction. CT revealed a left orbital mass involving the apex and ethmoid, sphenoid, and cavernous sinuses extending into the anterior and middle cranial fossae with extensive bony destruction and cerebral edema (Figure 1). A lumbar puncture showed xanthochromic fluid containing one white blood cell, 64 red blood cells, a protein of 86 mg/dl, and a glucose of 98 mg/dl. Cultures of spinal fluid yielded no growth.

The patient underwent a left lateral orbitotomy and biopsy of the mass lesion. Pathologic examination showed septate hyphae with granulomas and grew *A. fumigatus*. Serum precipitins to *A. fumigatus* were present. Because of the extensive intracranial involvement, surgical debridement was not done and anti-fungal therapy was begun. Amphotericin B, increasing to a maximum daily dose of 1 mg/kg, was given with gradual improvement. Flucytosine (initially 150 mg/kg/day) was added to the regimen after the organism was noted to be sensitive. After two months of therapy (amphotericin B total dose = 2.5 gm), a repeat head CT showed a marked decrease in the size of the frontal lobe lesion (Figure 2). Clinically, the patient had less pain but had no improvement in her visual loss.

Chronic oral suppression was tried with ketoconazole but because of a high minimal inhibitory concentration and poor absorption, the patient was switched to an oral investigational agent, vibunazole (Bayer, Inc.) which had a lower minimal inhibitory concentration and was better tolerated (Table 1).

After 2 months of outpatient therapy with vibunazole, the patient developed an expressive aphasia and disorientation. A repeat head CT scan showed multiple thick-rimmed lucencies 1 – 2 cm in diameter and a large (5 cm) ring enhancing lesion involving the left temporal lobe and basal ganglia (Figure 3). Stereotactic aspiration yielded 10 ml of cloudy yellow fluid. Culture of the fluid yielded no growth. Serum precipitins to *A. fumigatus* were still present. The patient was

Table 1: Drug susceptibilities and serum concentrations

	MIC* (µg/ml)	Daily Dose (mg)	Serum Concentration (µg/ml)
Amphotericin B	0.2	60	Not done
Flucytosine	1.6	1000 – 4000	52 – 80
Ketoconazole	6.2	800	<0.3
Vibunazole	2.0	800	4.4

* MIC = Minimal Inhibitory Concentration

placed back on amphotericin B and flucytosine and was also treated with dexamethasone. After an additional 1 gm of amphotericin B, a repeat head CT showed decreased edema and mass effect with shrinking of the temporal lesion. The serum precipitins were only weakly positive at this point.

The patient continued to receive amphotericin B and flucytosine as an outpatient until an additional 2,9 gm of amphotericin B had been administered. The CT scan showed resolution of the parietal abscess (Figure 4). Serum precipitins became negative. After 15 months of therapy (total of 6.4 gm of amphotericin B) the patient's anti-fungal medications were stopped and she continued to do well for over 2 years. She still has chronic left face pain and loss of vision in the left eye. The CT shows persistent abnormalities in the left orbit and frontal lobe, unchanged for 2 years.

Comment

Aspergillus is a common environmental fungus which may colonize the upper respiratory tract following inhalation. The organism causes infection by hematogenous dissemination or by contiguous spread to local structures, such as the paranasal sinuses, orbit, and brain. While disseminated infection occurs in hosts who are compromised by malignancy, intravenous drug abuse, cytotoxic agents, or glucocorticoids (6, 26, 30), local invasion, especially of the upper respiratory tract and orbit, occurs primarily in immunocompetent patients (12, 14, 27).

When *Aspergillus* sinusitis occurs in the normal host, a more indolent course is seen compared with the acute fulminant disease, reminiscent of mucormycosis, found in patients with malignancy (20, 29). Many cases of chronic *Aspergillus* sinusitis are described in hot, dry, dusty climates, such as the northern Sudan, where *A. flavus* is a common soil isolate and the disease is endemic (21, 28). In other parts of the world, both *A. fumigatus* and *A. flavus* are the predominant pathogens.

Chronic *Aspergillus* sinusitis may be non-invasive or invasive (12, 14, 27). The more common non-invasive form presents with symptoms of unilateral sinus obstruction unresponsive to antibiotic therapy (27). Opacification of paranasal sinuses without bone destruction is seen on roentgenograms. The maxillary sinus is most commonly involved followed by the sphenoid, ethmoid, and frontal sinuses (14). Drainage and debridement af the affected sinus is the primary treatment, and the prognosis is excellent.

In some individuals with chronic *Aspergillus* sinusitis, as noted with our patient, invasion of adjacent structures occurs with destruction of bone, invasion into the orbit, and eventually invasion into the frontal lobes of the brain (9, 11, 13, 18, 32). The predominant host response in these instances is granulomatous, and the process is slowly progressive (9, 18). Why certain individuals are unable to contain the fungus and suffer progressive tissue destruction is not clear. In some instances, it would appear that inappropriate use of antibiotics or corticosteroids, as in our patient, may have con-

tributed to increased growth and tissue invasion by Aspergillus (1, 9, 11). In most instances, however, no risk factors can be delineated.

Invasion of cranial nerves, blood vessels, and extraocular muscles within the orbit leads to a variety of symptoms. In a review of 47 cases of orbital aspergillosis reported in the literature, Hedges et al. noted that proptosis was present in 74% of patients while decreased visual acuity (28%), pain (23%), and extraocular palsies (9%) were less commonly seen (11). Only one case presented with an orbital apex syndrome (decreased vision, corneal hypoaesthesia, and complete ophthalmoplegia), as seen in our patient. Seventy-seven percent of patients had associated sinus disease, and 23% had concomitant central nervous system involvement. With symptoms of visual loss and pain, elderly patients frequently receive corticosteroids for presumptive temporal arteritis (1, 9, 11). The absence of both fever and a markedly elevated sedimentation rate should lead one to question this diagnosis.

Cerebral aspergillosis may occur secondary to local invasion, as in our patient and others with invasive sino-orbital aspergillosis (9, 11). Pathologically, the process is usually a granulomatous tissue response with involvement of pituitary or frontal lobes as a result of direct extension from sinuses (13, 18, 32). Blood vessel invasion with metastatic spread to the cortex and infarction may also occur (5).

Additionally, cerebral involvement occurs frequently during the course of disseminated aspergillosis in immunocompromised hosts (6, 26, 30). In those instances, spread is hematogenous and multiple cerebral abscesses adjacent to blood vessels are the usual pathologic sequelae. A neutrophilic response, if the patient is not markedly granulocytopenic, is usually noted (33).

Patients with *Aspergillus* endocarditis and intravenous drug abusers also develop cerebral aspergillosis. Cerebral involvement may occur as friable vegetations embolize to cerebral vessels in patients with endocarditis (15). In the case of intravenous drug abusers, the source of the *Aspergillus* is unknown, but often felt to be related to an undiscovered pulmonary lesion or from fungi contaminating the drugs (22).

Diagnosis of sino-orbital and cerebral aspergillosis is difficult. Fever and leukocytosis occur only rarely. Examination of the cerebrospinal fluid reveals findings typical of a parameningeal process – increased protein concentration, presence of a few white or red blood cells, and a normal glucose concentration (23, 32). Cultures of the cerebrospinal fluid are rarely positive. Roentgenograms and CT scans are useful in identifying bony erosions and masses but are otherwise non-diagnostic (3, 10). Arteriography may reveal vessel occlusion, particularly of the internal carotid artery, and mycotic aneurysms.

Patients with pulmonary aspergillomas, allergic bronchopulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, and other chronic forms of aspergillosis often have precipitating antibodies to *Aspergillus* in their serum (2, 24, 27). The presence of *Aspergillus* precipitins is suggestive of infection with this organism (14, 25). However, tissue for pathological examination and culture is the only definitive method to make the diagnosis and exclude other causes, such as malignancy. Measurement of *Aspergillus* precipitins may be more useful in following the course of therapy than in establishing the diagnosis of aspergillosis. These antibodies should disappear as the patient clears his infection, as noted in our patient.

Extensive surgical debridement has been the mainstay of therapy for invasive aspergillosis of the sinuses, orbit, and cerebrum. In one review, patients with orbital disease alone had a mortality of 28%, which increased to 80% with cerebral involvement (11). In a setting where the disease is not completely resectable, a few patients have shown improvement with adjunctive amphotericin B therapy (4, 8, 12, 31, 34, 35). Some isolates of *Aspergillus* are only

moderately susceptible or resistant to amphotericin B. Several studies suggest that the combination of amphotericin B and flucytosine or amphotericin B and rifampin may have a synergistic effect in inhibiting some strains of *Aspergillus* (8, 17, 34).

Yu et al. described a patient with sinocerebral involvement whose symptoms progressed despite sphenoidotomy and 1.9 grams of amphotericin B therapy (34). Flucytosine and rifampin were added empirically to the amphotericin B regimen. After having received therapy with a total of 4 grams of amphotericin B, 6 weeks of rifampin, and 8 weeks of flucytosine, the patient was well on follow-up examination 1 year later.

The role played by the adjunctive antifungal drugs is not clear. In general, susceptibility studies should be performed before adding a drug, such as flucytosine, to the anti-fungal regimen. When flucytosine is used, serum levels must be monitored closely to avoid bone marrow toxicity (16).

The role of imidazoles, such as ketoconazole, in treating *Aspergillus* infections is not established. Several of the imidazole compounds, including vibunazole, the experimental imidazole used in our patient, have activity in vitro against *A. fumigatus* (7, 19). However, except for a newer compound, fluconazole, central nervous system penetration has been poor and probably contributed to failure of the therapeutic trial in our patient.

This report documents a case of sino-orbital and cerebral aspergillosis successfully treated medically without extensive surgical debridement. We believe that the successful outcome was due to prolonged therapy with two drugs with careful monitoring of theraputic drug levels. Administration of amphotericin B at home made this a practical regimen to carry out over a long period of time.

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