Sino-orbital Aspergillosis in Acquired Immunodeficiency Syndrome

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Objective: To describe the clinical features, causes, imaging characteristics, treatment, and outcome of patients with the acquired immunodeficiency syndrome (AIDS) and sino-orbital aspergillosis.

Design: Records of 5 patients were reviewed. Results of imaging and histopathologic examinations and clinical courses of the patients were studied.

Results: There were 3 women and 2 men (mean age, 34.0 years). All had received a diagnosis of AIDS, and mean CD4+ cell count was 0.014 \times 10^9/L (14 cells/mm^3). Computed tomographic scanning exhibited heterogeneous, enhancing sino-orbital soft tissue lesions with bony erosion, and magnetic resonance imaging disclosed soft tissue masses hypointense on T1- and T2-weighted images. The infection involved 1 or more paranasal sinuses, with extension into the right orbit in 3 patients and into the left orbit in 2. Patients were treated with aggressive surgical debridement and intravenous antifungal agents. In addition, local irrigation of amphotericin B was performed in 3 patients. Aspergillus fumigatus was found to be the cause in all 5 patients. Intracranial extension developed in 4 patients, and all subsequently died. The 2 longest surviving patients were the only ones being treated with protease inhibitors. Three patients had a history of frequent marijuana smoking.

Conclusions: Sino-orbital aspergillosis is a progressive, relentless, and usually fatal opportunistic infection of advanced AIDS. Patients are first seen with longstanding headache and proptosis with minimal external inflammatory signs. Marijuana smoking may increase the risk for development of sino-orbital aspergillosis in these patients. Aggressive surgical and medical treatment, combined with newer combination therapies using protease inhibitors, may improve the longevity of these patients.

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Orbital infections are relatively uncommon in patients infected with the human immunodeficiency virus (HIV), but when present, they cause significant morbidity and mortality.\(^1\) Aspergillus, a fungus ubiquitous in our environment, can cause noninvasive or invasive infections in immunocompetent and immunocompromised patients.\(^2,4\) Recently, the association between acquired immunodeficiency syndrome (AIDS) and sino-orbital aspergillosis has been described.\(^1,5-8\) We reviewed 5 patients with sino-orbital aspergillosis and AIDS and studied the predisposing factors, clinical presentations, imaging characteristics, treatments, and outcomes.

RESULTS

We studied 3 women and 2 men with a mean age of 34 years at initial examination. All patients had received a previous diagnosis of AIDS and had been seropositive for HIV from 3 to 10 years (mean duration, 6.4 years). The mean CD4\(^+\) cell count was 0.014 \times 10^9/L (14 cells/mm\(^3\)). The infections involved 1 or more paranasal sinuses and extended into the right orbit in 3 patients and into the left orbit in 2. Computed tomographic findings included heterogeneous, enhancing sino-orbital masses with bony destruction and calcifications; MRI exhibited soft tissue–enhancing masses, hypointense on T1- and T2-weighted images. None of the patients had concomitant pulmonary infection. Surgical excision or debulking of the sino-orbital mass was performed in all patients, and tissue was cultured and examined histopathologically. Fungal cultures in all patients yielded Aspergillus fumigatus, and secondary bacterial infections were found in 3 patients. All patients were treated with systemic antifungal agents in the perioperative period,
PATIENTS AND METHODS

The 5 patients with AIDS and sino-orbital aspergillosis underwent evaluation and treatment at the University of Miami Bascom Palmer Eye Institute and Jackson Memorial Hospital, Miami, Fla, from January 1, 1994, to December 31, 1998. All patients underwent a complete history, physical examination, and ophthalmic evaluation. Diagnostic tests included CD4+ lymphocyte counts; computed tomographic (CT) scans of the sinuses, orbits, and brain; and fungal cultures of surgically excised tissues. Magnetic resonance imaging (MRI) was performed in 3 patients.

and all were available for follow-up. Intracranial extension developed in 4 patients. Three were found to have intracranial extension at initial examination, and intracranial spread developed later in the other one, despite aggressive therapy. All 4 patients with intracranial extension died of fungal proliferation, refractory to aggressive therapies. Only 1 patient is still alive. Two patients underwent orbital exenteration. Intracranial extension developed in 1 of these patients 7 months after sinon and orbital exenteration, and orbital recurrences developed in the other patient 3, 6, and 12 months after initial surgical debridement. The second patient finally underwent orbital exenteration (Table).

REPORT OF CASES

PATIENT 1

A 32-year-old woman sought care because of a 4-month history of headache and a recent onset of nausea, vomiting, and decreased vision in the left eye. She had been seropositive for HIV for 4 years and had a CD4+ cell count of 0.010 \times 10^9/L (10 cells/mm³). Previous AIDS-related diseases included Pneumocystis carinii pneumonia, disseminated Mycobacterium avium-intracellulare complex, cryptococcal meningitis, recurrent varicella zoster, and herpes zoster ophthalmicus in the right eye. Her social history included frequent marijuana smoking. Endoscopic biopsy of the ethmoid sinus performed previously at a community hospital revealed a fungal sinusitis. On admission, her visual acuity was 20/30 OD and 20/20 OS. The right eye revealed 5 mm of left axial proptosis, without an afferent pupillary defect. Ocular motility was restricted in all fields in the left eye, and results of fundoscopic examination revealed scattered cotton-wool spots in both eyes. An orbital CT scan showed an enhancing lesion involving both ethmoid sinuses with bony destruction and intracranial and right intraorbital extension (Figure 2). She underwent bilateral endoscopic ethmoidectomy, right medial orbitotomy, and intravenous amphotericin B therapy at doses of 50 to 70 mg/d. In addition, local irrigation with amphotericin B (1 mg/mL) was first seen by us with pain in the right eye, proptosis, and epistaxis of 1 month’s duration in April 1996. His social history was positive for frequent marijuana smoking. Past AIDS-related illnesses included systemic lymphoma and cytomegalovirus (CMV) retinitis in the right eye. Previous frontal sinus surgery revealed invasive aspergillosis. On admission, he was afebrile, and visual acuity was 20/40 OD and 20/20 OS. The right eye revealed 5 mm of proptosis and displacement down and out, with minimal external inflammation (Figure 3). A CT scan showed opacification of the right frontal, ethmoid, and sphenoid sinuses, with a dehiscence of the right orbital roof and intraorbital extension of the mass. He underwent a right endoscopic total ethmoidectomy, frontal and sphenoid sinusotomy, and right orbitotomy with debulking of the lesion. Fungal cultures yielded A fumigatus, and results of histopathologic examination showed typical Aspergillus hyphae. (Figure 4). After several debulking surgeries and treatment with intravenous and local irrigation of amphotericin B, he lost all light perception in the right eye due to massive orbital and sinus recurrence (Figure 5). He underwent orbital and sinus exenteration in May 1997. During hospitalization, he was treated with intravenous
### Clinical Summary of Patients With AIDS and Sino-orbital Aspergillosis*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>HIV Risk Factors</th>
<th>HIV Seropositivity, y</th>
<th>HIV-Related Illness</th>
<th>History of Marijuana Smoking</th>
<th>CD4+ Count, x10^3/L</th>
<th>Duration of Symptoms, mo</th>
<th>Visual Acuity in Involved Eye</th>
<th>Orbital, Paranasal Sinus, and Intracranial Involvement</th>
<th>Duration of Orbital Presentation to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/32</td>
<td>Heterosexual transfer, possible IDU</td>
<td>4</td>
<td>PCP, MAC, cryptococcal meningitis, herpes zoster, hepatitis C</td>
<td>Yes</td>
<td>0.010</td>
<td>4</td>
<td>20/50 OS</td>
<td>Left orbit; bilateral ethmoid, sphenoid; left frontal lobe</td>
<td>14 mo</td>
</tr>
<tr>
<td>2/F/35</td>
<td>Heterosexual transfer, possible IDU</td>
<td>4</td>
<td>None</td>
<td>Unknown</td>
<td>0.001</td>
<td>1</td>
<td>20/20 OD</td>
<td>Right orbit; right frontal, maxillary; bilateral ethmoid; bilateral frontal lobes</td>
<td>7 mo</td>
</tr>
<tr>
<td>3/M/38</td>
<td>Homosexual transfer</td>
<td>11</td>
<td>Lymphoma, CMV retinitis</td>
<td>Yes</td>
<td>0.012</td>
<td>1</td>
<td>20/40 OD</td>
<td>Right orbit; right ethmoid, frontal; sphenoid maxillary; frontal lobes</td>
<td>28 mo</td>
</tr>
<tr>
<td>4/F/34</td>
<td>Heterosexual transfer</td>
<td>10</td>
<td>PCP, CMV retinitis</td>
<td>Yes</td>
<td>0.037</td>
<td>6</td>
<td>20/25 OS</td>
<td>Left orbit; left ethmoid</td>
<td>Still alive</td>
</tr>
<tr>
<td>5/M/31</td>
<td>Homosexual transfer</td>
<td>3</td>
<td>PCP</td>
<td>No</td>
<td>0.011</td>
<td>0</td>
<td>20/25 OD</td>
<td>Right orbit; bilateral ethmoid, sphenoid, maxillary; bilateral frontal lobes</td>
<td>2 wk</td>
</tr>
</tbody>
</table>

*AIDS indicates acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IDU, intravenous drug use; PCP, Pneumocystis carinii pneumonia; MAC, Mycobacterium avium-intracellulare complex; and CMV, cytomegalovirus.

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**Figure 1.** Patient 1. Axial computed tomographic scan of a 32-year-old woman with invasive sino-orbital aspergillosis extending into left orbit and brain.

**Figure 2.** Patient 2. Coronal computed tomographic scan of a 35-year-old woman with invasive aspergillosis involving both ethmoid sinuses and right orbit, with intracranial extension of the infection (arrow).

**Figure 3.** Patient 3. A 38-year-old man following frontal sinus surgery with proptosis and downward displacement in the right eye secondary to invasive aspergillosis.

**Figure 4.** Patient 3. Histopathologic section of orbital tissue exhibits numerous hyphal elements with septae and dichotomous branching, typical of aspergillus (Gomori methenamine silver stain, original magnification × 400).
amphotericin B lipid complex at a dose of 300 mg/d, and
started oral itraconazole therapy, 300 mg twice a day, which
he continued after discharge. Seven months later, he was
found to have asymptomatic intracranial extension on MRI.
He underwent a craniotomy with extensive debridement
of the infection in December 1997, and cultures con-
Fumigatus. He was without clinical
evidence of disease in June 1998, and was being treated with
weekly socket irrigation with amphotericin B, 50 mg/50 mL.
His systemic medications include saquinavir mesylate, a pro-
tease inhibitor, started in June 1996; 2 nucleoside reverse
transcriptase inhibitors, stavudine and lamivudine; and oral
itraconazole. In October 1997, his CD4+ count had in-
creased to 0.148 \times 10^9/L (148 cells/mm^3), and viral load
(HIV-1 RNA detected using polymerase chain reaction
analysis) was less than 400 RNA copies/mL, considered non-
detectable. Recurrent intracranial disease developed in July
1998, and he underwent repeated craniotomy with de-
bridement, but he died of intracranial extension in Au-

PATIENT 4

A 34-year-old woman was first seen by us in July 1997
with severe pain in the left eye of 4 weeks’ duration and
a 6-month history of severe headaches, sinus problems,
and left-sided proptosis. She had been seropositive for
HIV for at least 10 years, and her CD4+ count was
0.037 \times 10^9/L (37 cells/mm^3). Her social history was
positive for frequent marijuana smoking. Previous
AIDS-related illnesses included P carinii pneumonia
and CMV retinitis in the right eye. On admission, she
was afebrile with visual acuity of light perception in the
right eye and 20/25 OS. There was a right exotropia, as
well as a dense cataract and afferent pupillary defect in
the right eye. The left eye revealed 4 mm of proptosis
with minimal inflammatory signs (Figure 6). Magnetic
resonance imaging showed an enhancing soft tissue
mass involving both ethmoid sinuses with extension
into the left orbit (Figure 7, Figure 8, and
Figure 9). She underwent endoscopic total ethmoido-
teomy, frontal sinusotomy, and orbital decompression.
Fungus cultures yielded A fumigatus. Three
months following sinus and orbital drainage, and de-
spite daily intravenous liposomal amphotericin B
therapy, recurrent orbital disease developed, and she
underwent repeated medial orbitotomy and debride-
ment. Another recurrence developed 3 months later,
and she underwent an inferior orbitotomy with debride-
ment. Fungal cultures yielded A fumigatus, and

Figure 5. Patient 3. Non–contrast-enhanced axial computed tomographic
scan showing recurrent heterogeneous mass filling the right orbit and
ethmoid sinus.

Figure 6. Patient 4. A 34-year-old woman nearly blind in the right eye
secondary to cytomegalovirus retinitis and dense cataract, and with
proptosis in the left eye due to left sino-orbital aspergillosis. A drain is in
place from previous frontal sinus surgery.

Figure 7. Patient 4. Magnetic resonance imaging (T1-weighted)
demonstrates hypointense lesion involving both ethmoid sinuses and
invading the left orbit.

Figure 8. Patient 4. Magnetic resonance imaging (T2-weighted) also
demonstrates hypointensity (arrow) of the left sino-orbital aspergilloma.
bacterial cultures were negative. She continued treatment with daily intravenous amphotericin B lipid complex at a dose of 5 mg/kg per day. Her systemic medications also included indinavir sulfate, a protease inhibitor started in May 1997, and zidovudine and lamivudine. Her HIV-1 RNA level was 100,222 copies/mL in December 1997. Another orbital recurrence developed in April 1998, and she underwent lateral orbitotomy with drainage of liquid pus and removal of copious cheesy material. Fungal cultures again yielded Aspergillus, and fungal cultures yielded A. fumigatus. Bacterial cultures disclosed a moderate growth of P. aeruginosa and light growth of coagulase-negative Staphylococcus. Despite intensive treatment with systemic amphotericin B, with doses ranging from 30 to 70 mg/d, and broad-spectrum intravenous antibiotics, he died of progressive intracranial disease 2 weeks later.

**PATIENT 5**

A 31-year-old man was first seen by us with facial pain and swelling for 5 days, proptosis and blurred vision in the right eye for 3 days, fever for 24 hours, and epistaxis. He had been seropositive for HIV for 3 years and had a CD4+ count of 0.011 × 10⁹/L (11 cells/mm³). He stopped taking all antiviral medications 2 weeks before admission. He denied any history of marijuana smoking. Previous AIDS-related illnesses included P. carinii pneumonia. He was febrile with a temperature of 38.5°C (101.3°F). Visual acuity was 20/25 − 3 OD and 20/20 OS. His right eye revealed 4 mm of proptosis, with decreased abduction and without afferent pupillary defect. Computed tomographic scan showed bilateral opacification of the ethmoid, maxillary, and sphenoid sinuses, with right intraorbital extension. Erosion of the cribriform plate and intracranial extension with intracranial air were present (Figure 10). He underwent endoscopic bilateral total ethmoidectomies; maxillary, frontal, and sphenoid sinusotomies; and orbital and intracranial decompression. A potassium hydroxide wet mount of excised tissues showed septate hyphae consistent with Aspergillus, and fungal cultures yielded A. fumigatus. Despite intensive treatment with systemic amphotericin B, with doses ranging from 30 to 70 mg/d, and broad-spectrum intravenous antibiotics, he died of progressive intracranial disease 2 weeks later.

**COMMENT**

Aspergillus is usually considered a harmless saprophyte, which is ubiquitous in our environment.³ It uncommonly causes infection in immunocompetent hosts, where it can be invasive or noninvasive. Noninvasive infections include allergic Aspergillus sinusitis and sinonasal aspergilloma.⁸ Most invasive infections in immunocompetent individuals have been reported from hot humid climates and Sudan,⁴,¹⁰ where the infection starts in the paranasal sinuses and initiates a fibrosing, granulomatous reaction.⁴ Secondary orbital and intracranial extension is due to the slow, progressive, and often painless nature of the disease.¹⁰-¹² Aspergillus flavus is the usual causative organism.¹⁰ This invasive fungal infection is difficult to eradicate using surgical debridement combined with systemic and local antifungal agents, and there is a high mortality rate due to intracranial extension.⁴

Invasive aspergilliosis occurs more often in immunocompromised hosts, including patients undergoing transplantation, neutropenic patients receiving chemotherapy,¹³ and patients with AIDS.¹⁴ Pulmonary infections are the most common,¹⁴ but other organs can be infected, including brain, paranasal sinuses, and orbit. Immunocompromised individuals can have a slowly progressive or an abrupt onset of orbital inflammation, proptosis, and pain.⁹,¹³,¹⁵ Fulminating Aspergillus infection of the nose, paranasal sinuses, and orbit, often associated with intracranial extension, has been reported to develop in immunocompromised patients without AIDS.¹⁵ Treatment includes extensive surgical debridement and/or exenteration, combined with aggressive intravenous antifungal treatment and local irrigation or packing with amphotericin B. Despite this aggressive therapy, the mortality rate is high.¹⁶

Infection with HIV results in a selective loss of a critical component of the immune system, the population of T-helper (CD4+) lymphocytes, and low CD4+ cell counts are associated with the development of opportunistic in-
In addition, bacterial cultures of the orbit and sinuses yielded positive results in 3 patients in this study, including infections with *P. aeruginosa* and coagulase-negative *Staphylococcus*. All patients were treated with broad-spectrum intravenous antibiotics during the perioperative period.

**Orbital Infections** are uncommon in patients with AIDS, whereas opportunistic infections involving the eye occur much more frequently. The differential diagnosis in an HIV-infected individual with an orbital mass includes lymphoma, bacterial orbital cellulitis, orbital cellulitis due to toxoplasmic panophthalmitis, orbital infection with *P. carinii*, and sino-orbital aspergillosis.

Treatment of invasive sino-orbital aspergillosis involves aggressive surgical debridement combined with systemic antifungal agents. Intravenous amphotericin B has been the mainstay of medical therapy, but toxic side effects, especially renal, require discontinuing the medication in some patients. New systemic antifungal medications include liposomal amphotericin B preparations, with fewer renal toxic effects, and oral itraconazole. Liposomal amphotericin B, a formulation of liposome-encapsulated amphotericin B, was reported to be successful in the treatment of *Aspergillus* rhinosinusitis after therapy with conventional amphotericin B failed. Oral itraconazole, a synthetic triazole antifungal agent, is an alternative therapy for invasive aspergillosis, and response rates are reported to be comparable with those of amphotericin B. This medication was successfully used in the treatment of recurrent sino-orbital aspergillosis in an immunocompetent woman after combined surgery and intravenous amphotericin B failed, and was recommended for use in patients who are unable to tolerate amphotericin B. Adjuvant local irrigation of amphotericin B also has been recommended. For patients unable or unwilling to undergo surgery, intralesional injection of amphotericin B has been used successfully as a palliative treatment. Four patients in our series were treated in the perioperative period with intravenous amphotericin B. Two were later treated with intravenous liposomal amphotericin B and continued to receive this medication at home after discharge from the hospital. Both of the surviving patients have been maintained with oral itraconazole after discontinuation of intravenous liposomal amphotericin B therapy. Three patients underwent frequent sinus and orbital irrigation with amphotericin B at a concentration of 1 mg/mL.

Patients with AIDS and invasive pulmonary aspergillosis have a dismal prognosis, usually dying within 2 to 4 months of diagnosis. Patients with AIDS and sino-orbital aspergillosis are also reported to have a poor prognosis, with most dying of intracranial extension even after aggressive medical and surgical treatment. Teh et al described 3 patients with AIDS and invasive *Aspergillus* sinusitis, and reviewed 15 additional patients described in the literature. Seven of the 18 had brain involvement, 3 had orbital extension, 3 had con-
Marijuana smoking may increase the risk for development of sino-orbital aspergillosis. This fungus has been cultured from marijuana cigarettes. Marijuana has been considered the likely source of infection in immunocompromised patients with invasive pulmonary aspergillosis or allergic bronchopulmonary aspergillosis. Three of our patients admitted to habitual use of marijuana. One patient was not specifically asked about marijuana use, but had a history of intravenous drug use and may have smoked marijuana. One patient denied marijuana use. Patients with advanced AIDS, especially those with low CD4+ counts, should be warned of the possible association between marijuana smoking and the development of invasive aspergillosis.

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REFERENCES

A look at the past . . .

ATTLETT protests against operative interference in cases of sarcoma of any of the tissues of the orbit, as an operation always hastens their development. In support of this he offers the following cases: Case I. Subperiosteal pulsating sarcoma in the floor of the left orbit of a child of nine; rapid growth; duration six months; death; metastatic deposits in brain, cerebellum, and internal organs. In this case, removal of orbital contents was quickly followed by a recurrence of the growth. Case II. Large subperiosteal myeloid sarcoma of the inner wall and roof of the orbit. Death in six months after first local manifestation. Case III. Girl of three and one-half years. Tumor completely filling the orbital cavity. Eye removed. Child died four weeks later. Case IV. Large tumor (sarcoma?) of right orbit. Duration three months. No operation. Metastasis to brain and internal organs. Case V. Encapsulated (?) soft, round-celled sarcoma in floor and apex of orbit in a girl of four years. Great protrusion. Operative exteneteration of the orbit. Recovery. Case VI. Subperiosteal alveolar round-celled sarcoma. Slow growth, exploratory operation. Death in three and one-half years. Case VII. Enormous osteo-sarcoma of left orbit. No operation. Death. Duration six years. Patient aged sixty-two. Case VIII. Osteo-sarcoma of the walls of the orbit; enucleation and exenteration. Tumor slowly returned, but patient disappeared from observation.