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 × 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–enhancing 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.

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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 sinus 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 on upgaze in the right eye. Results of funduscopic 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 performed. Intraocular injections of amphotericin B, at doses of 25 to 35 mg/d, was administered, and daily transnasal sinus irrigation with amphotericin B (1 mg/mL) was performed. In addition, intravenous ofloxacin was given. She remained disease free for 12 months, but then began experiencing severe right-sided headaches, and MRI disclosed an abscess of the right frontal lobe. Despite debridement of the abscess and treatment with systemic amphotericin B, she died 2 months later of intracranial extension of the infection.

PATIENT 2

A 35-year-old woman was first seen by us with fever and right periorbital swelling for 1 month. She had a history of chronic sinusitis, had been seropositive for HIV for 4 years, and had a CD4+ cell count of 0.001 \times 10^9/L (1 cell/mm³). On admission, her visual acuity was 20/20 OU. She had 5 mm of right axial proptosis, without an afferent pupillary defect. Ocular motility was restricted on upgaze in the right eye. Results of funduscopic 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 was performed. A potassium hydroxide wet mount revealed fungal elements, and fungal cultures yielded A fumigatus. Bacterial cultures showed a light growth of coagulase-negative Staphylococcus. She died of recurrent intracranial disease involving the left frontal lobe 7 months later.

PATIENT 3

A 38-year-old man who had been seropositive for HIV for 11 years and had a CD4+ count of 0.012 \times 10^9/L (12 cells/mm³) 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 downward and outward, 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 confirmed infection with *A 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 protease inhibitor, started in June 1996; 2 nucleoside reverse transcriptase inhibitors, stavudine and lamivudine; and oral itraconazole. In October 1997, his CD4+ count had increased 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 debridement, but he died of intracranial extension in August 1998.

**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. Magnetic resonance imaging showed an enhancing soft tissue mass involving both ethmoid sinuses with extension into the left orbit (Figure 6). Magnetic resonance imaging also demonstrated hypointensity (arrow) of the left sino-orbital *aspergilloma* (Figure 7, Figure 8, and Figure 9). She underwent endoscopic total ethmoidectomy, frontal sinusotomy, and orbital decompression. Fungus cultures yielded *A fumigatus*. Three months following sinus and orbital drainage, and despite daily intravenous liposomal amphotericin B therapy, recurrent orbital disease developed, and she underwent repeated medial orbitotomy and debridement. Another recurrence developed 3 months later, and she underwent an inferior orbitotomy with debridement. Fungal cultures yielded *A fumigatus*, and...
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 bacterial 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 × 10^9/L (11 cells/mm^3). 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. 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.

Aspergillus is usually considered a harmless saprophyte, which is ubiquitous in our environment. It uncommonly causes infection in immunocompetent hosts, where it can be invasive or noninvasive. Noninvasive infections include allergic Aspergillus sinusitis and sinonasal aspergillosis. Most invasive infections in immunocompetent individuals have been reported from hot humid climates and Sudan, where the infection starts in the paranasal sinuses and initiates a fibrosing, granulomatous reaction. Secondary orbital and intracranial extension is due to the slow, progressive, and often painless nature of the disease. Aspergillus flavus is the usual causative organism. 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.

Invasive aspergillosis occurs more often in immunocompromised hosts, including patients undergoing transplantation, neutropenic patients receiving chemotherapy, and patients with AIDS. Pulmonary infections are the most common, 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. Fulminant Aspergillus infection of the nose, paranasal sinuses, and orbit, often associated with intracranial extension, has been reported to develop in immunocompromised patients without AIDS. 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.
developed in many.22 Sinusitis is common in HIV-infected patients,21 and fungal sinusitis more commonly affects patients in the later stages of AIDS, when the CD4+ count is less than 0.050 \times 10^9/L (50 cells/mm^3).20 Aspergillus is the usual fungal pathogen.8 The clinical findings in our patients with AIDS and sino-orbital aspergillosis were usually not abrupt, but slowly progressive. Most patients complained of moderate to severe headaches, which preceded the onset of proptosis, visual changes, and motility disturbances by months. All 5 patients had advanced AIDS, and the mean CD4+ count was 0.014 \times 10^9/L (14 cells/mm^3). The clinical examination, there were minimal external inflammatory signs. Visual acuity was minimally affected, with visual acuity on initial examination ranging from 20/20 to 20/50. It appears that patients with AIDS and invasive sino-orbital aspergillosis have a different clinical course compared with those not infected with HIV. Mauriello et al22 described 5 patients without AIDS and with invasive sino-orbital aspergillosis. Risk factors in their patients included alcohol abuse, steroid therapy, diabetes mellitus, and advanced age. Their patients had the abrupt onset of proptosis and debilitating periorbital pain, with precipitous visual loss. Similar to our patients with AIDS, their patients showed minimal external inflammatory signs, fungal cultures in all yielded A fumigatus, and secondary bacterial infections developed in many.22

Imaging studies are helpful in differentiating sino-orbital aspergillosis from other disease processes. Findings on CT scans included heterogeneous soft tissue masses with bony erosion and calcifications. Orbital lymphoma in patients with AIDS can be accompanied by bone erosion also, when the tumor extends to or from a paranasal sinus. Magnetic resonance imaging exhibited contrast-enhancing soft tissue sino-orbital masses hypointense on T1- and T2-weighted images, with surrounding mucosal inflammation. Zinreich et al described CT and MRI findings in patients with fungal sinusitis and found fungal sinusitis to be characterized by serpiginous areas of increased attenuation on CT scan. The heterogeneous image may be attributable to the presence of iron, manganese, or calcium in fungal concretions. Bone destruction is thought to be due to pressure necrosis and destructive effects by multiple mediators of inflammation released by eosinophils. Magnetic resonance imaging demonstrates contrast-enhancing lesions, which are hypointense on both T1- and T2-weighted images, surrounded by mucosal inflammation. In contrast, neoplasms and bacterial infections are hyperintense on T2-weighted images.25

Definitive diagnosis of aspergillosis is based on fungal culture findings, and all 5 of our patients were found to be infected with A fumigatus. A potassium hydroxide preparation is useful in confirming a fungal infection while awaiting final culture results. Two previous case reports of sino-orbital aspergillosis in patients with AIDS found A fumigatus to be the causative organism,26 and another study found 13 of 14 patients with AIDS and Aspergillus sinusitis were also infected with A fumigatus.7 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.1 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.20

Treatment of invasive sino-orbital aspergillosis involves aggressive surgical debridement combined with systemic antifungal agents.22 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,27 and oral itraconazole.12,26,29 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.30 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.28 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.32 Adjuvant local irrigation of amphotericin B also has been recommended.10 For patients unable or unwilling to undergo surgery, intrasosional injection of amphotericin B has been used successfully as a palliative treatment.6 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.16 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.13,5,7 Teh et al17 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.37-39 Marijuana can be a highly contaminated source of Aspergillus.39,40 This fungus has been cultured from marijuana cigarettes.39 Marijuana has been considered the likely source of infection in immunocompromised patients with invasive pulmonary aspergillosis40 or allergic bronchopulmonary aspergillosis.38 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 exenteration 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.