Endoscopic Sinus Surgery in the Management of Mucormycosis

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This is a report of the use of endoscopic sinus surgery in the management of three patients diagnosed with rhino-orbital or rhino-orbito-cerebral mucormycosis. A retrospective review was performed of the clinical examinations and imaging studies of three patients who underwent endoscopic sinus surgery as part of their therapy for mucormycosis. In addition to endoscopic surgery, all patients had aggressive control of underlying risk factors (diabetes mellitus, immunosuppression) and prolonged intravenous amphotericin B therapy. All three patients survived and avoided orbital exenteration. In selected patients with rhino-orbito-cerebral mucormycosis, endoscopic techniques can play a valuable role in diagnosis and management.

Key Words: Endoscopic sinus surgery—Rhino-orbital mucormycosis—Rhino-orbito-cerebral mucormycosis.

Rhino-orbito-cerebral mucormycosis is a fungal infection well known to ophthalmologists for its devastating ocular morbidity and high rate of patient mortality. The term "aggressive" best describes the clinical approach for diagnosis and treatment of this condition (1–7).

Traditional surgical therapy entails extensive debridement of all infected tissues, which often requires debridement of the affected paranasal sinuses, coupled with orbital exenteration. The latter procedure has been recommended by some as primary therapy in the presence of even minimal orbital infection (4,7,8). However, several reports have documented patient survival without exenteration in the presence of clinical orbital involvement (3,5,9–28).

We report three patients with mucormycosis in whom endoscopic sinus surgery facilitated diagnosis and management of the disease. All three patients survived without orbital exenteration.

CASE REPORTS

Case 1

A 21-year-old woman experienced left periorbital pain without chills or fever and noted a precipitous loss in vision in her left eye over 2 days. Her medical history was significant for poorly controlled insulin-dependent diabetes mellitus of 16 years' duration. Visual acuity was 20/25 right eye and no light perception left eye. The right pupil reacted briskly to light, the left was nonreactive, and there was a left afferent pupillary defect. There was left periorbital edema and 3 mm of left proptosis. Eye movements on the right were full, whereas on the left there was complete ophthalmoplegia associated with total ptosis. Slit lamp examination findings were normal bilaterally. The right fundus was unremarkable, whereas the left showed edema of the optic disc and peripapillary retina with venous engorgement. General physical and neurologic examinations were otherwise normal.

Contrast-enhanced computed tomography and magnetic resonance imaging (MRI) (Fig. 1) showed left ethmoid sinusitis with orbital inflammation. The patient underwent transnasal endoscopic exploration of the left ethmoid and maxillary sinuses. The inferior turbinate and extensive portions of these sinuses were friable and necrotic in appearance. A left total ethmoidectomy, sphenoideotomy, maxillary antrostomy, and inferior turbinectomy were performed by endoscopy. The lamina papyracea was removed. The orbital fat was examined and found to be healthy. Biopsy specimens from the paranasal sinuses showed invasive fungal elements consistent with mucormycosis.

Complete blood count, serum chemistries, and cerebrospinal fluid analysis were normal. Serum glucose was 82 mg/dl with no ketosis. Therapy consisted of 1 mg/kg intravenous amphotericin B per day, supplemented with intranasal aerosolized amphotericin B and 10 g per day oral 5-flucytosine, later changed to 600 mg per day rifampin.

During the next month, the patient's clinical course stabilized. Serial imaging studies showed persistent sinus and periorbital soft tissue changes but no progression of disease. She was taken back to the operating room on two more occasions for endoscopic evaluation of her sinuses and left orbit to be certain no active infection was present. None was found.

After 1 month, the patient was discharged with intravenous access to complete her course of amphotericin B (total dose of 2 g). Over the ensuing 7 months the patient regained most of the function of the levator palpebrae...
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FIG. 1. Case 1. Contrast-enhanced magnetic resonance imaging shows left paranasal sinusitis with left orbital extension on axial (A) and coronal (B) scans.

and extraocular muscles on the left, although her vision improved only to light perception in the left eye.

Case 2

A 46-year-old man reported the onset of diplopia associated with left ptosis and left periorbital pain. The patient had a 20-year history of insulin-dependent diabetes mellitus and 11 years previously had undergone a right vitrectomy for treatment of a macular hole. Visual acuity on the right eye had stabilized to 20/200. Acuity of the left eye had been 20/40 after focal macular laser photocoagulation for diabetic macular edema. Visual acuity was 20/400 OU. Pupils measured 3 mm and were briskly reactive to light, with no relative afferent pupillary defect. Eye movements were normal on the right but on the left were consistent with a partial left oculomotor nerve palsy. Corneal sensation was intact. There was 6 mm of left ptosis and no proptosis. Both fundi showed diabetic retinopathy with laser photocoagulation scars and a right macular hole.

Over the next week the patient experienced worsening vision on the left associated with left facial pain. Acuity remained 20/400, right eye, but declined to hand motions on the left. Four millimeters of left proptosis was present with total left ptosis and ophthalmoplegia. The fundi were unchanged.

The patient was immediately admitted to the hospital. Contrast-enhanced MRI showed bilateral ethmoid and sphenoid sinusitis with left orbital involvement (Fig. 2) and enhancement of the basal meninges and falx cerebri (Fig. 3).

Endoscopic exploration of the ethmoid and sphenoid sinuses was performed. Gross necrosis was apparent, necessitating left middle turbinatectomy, right total ethmoidectomy, and bilateral sphenoid sinusotomies, all by way of endoscopy. An external left ethmoidectomy including removal of the lamina papyracea was performed. Inspection of the left orbit showed no signs of necrosis. Biopsy specimens from the paranasal sinuses were consistent with mucormycosis.

Therapy consisting of intravenous amphotericin B and rifampin was begun, as well as aggressive control of the diabetes mellitus. Over the next 12 days, despite improvement in periorbital edema and proptosis, vision deteriorated to light perception. During this period the patient underwent three bilateral endoscopic explorations of the medial orbit and maxillary and ethmoid sinuses. No evidence of necrosis was found, and each procedure was terminated with irrigation of the sinus cavities and amphotericin B solution.

The patient received a total dose of 1.8 g amphotericin B and has been clinically unchanged during 12 months of follow-up.

FIG. 2. Case 2. Contrast-enhanced axial magnetic resonance scanning reveals extensive bilateral ethmoid sinusitis with left orbital involvement.
Case 3

A 49-year-old man who had undergone cardiac transplantation one month previously reported right jaw pain associated with nasal discharge. The patient had had insulin-dependent diabetes for 13 years. Medications included prednisone, cyclosporine, azathioprine, and insulin. Otolaryngologic examination revealed erythema and edema of the nasal turbinates on the right. Plain radiographs were consistent with right maxillary sinusitis, but transnasal culture of the sinus revealed no pathogenic organisms. Within 24 hours, right upper and lower lid edema and mild chemosis was noted, but after 3 days of intravenous antibiotics the symptoms had improved, and the patient was discharged with a course of azithromycin.

Sixteen days later, right facial weakness developed associated with numbness in the distribution of the maxillary and mandibular divisions of the right trigeminal nerve. Facial edema of the right parotid region was present, but examination of a specimen obtained in fine-needle biopsy of the parotid gland was unremarkable. Eye examination showed acuity of 20/200 right eye, 20/30 left eye. Marked chemosis on the right was associated with proptosis and limited eye movements in all directions. The optic discs were normal, and retinal examination showed mild nonproliferative diabetic retinopathy. Contrast-enhanced MRI showed right maxillary, sphenoid, and ethmoid sinusitis (Fig. 4), with adjacent cerebritis of the right temporal lobe (Fig. 5).

Endoscopy of the paranasal sinuses was performed revealing extensive disease. Total ethmoidectomy, sphenoidotomy, maxillary antrostomy, resection of turbinates, and removal of the lamina papyracea were effected by right nasal endoscopy. Orbital fat appeared healthy without signs of necrosis. Specimens obtained were consistent with and cultures were positive for Rhizopus species.

The patient underwent excision of the right temporal lobe tip and underlying dura and bone. Histologic examination revealed mucormycosis in the brain specimens (Fig. 6). Treatment was begun with intravenous amphotericin B (1 mg/kg/day).

The following day, the patient was noted to have left hemiplegia, and cranial MRI showed an infarct in the right motor cortex. Over the ensuing 6 weeks the neurologic deficits improved. Dosage of his immunosuppressive medication was carefully decreased. Periorbital
edema and chemosis resolved, with restoration of full extracocular movements on the right. Visual acuity remained poor in the right eye. The patient received a total of 3.5 g amphotericin B intravenously.

DISCUSSION

Prompt diagnosis of rhino-orbito-cerebral mucormycosis requires a high index of clinical suspicion in any patient with diabetes and in debilitated or immunosuppressed patients who report facial or orbital pain, diplopia, or diminished vision (2,4,7,28). Every effort should be made in such patients to perform a biopsy and to culture material from the nose, palate, paranasal sinuses, or orbit (2,4,7,28). With histopathologic evidence of the disease, certain aspects of management are essential. Multidisciplinary care should include aggressive control of underlying systemic disease (2,3,11-14,16,17,19,20,28-32); reduction in dosage or discontinuation of immunosuppressive drugs, if possible (2,8,13,21,33,34); and administration of intravenous amphotericin B in therapeutic doses (2,3,10-14,16,17,29-21,28-31,33).

Surgical removal of all necrotic tissue is essential in the treatment of rhino-orbito-cerebral mucormycosis (1,2,5-7). However, there are no clear guidelines for achieving this goal. For example, there are reports of patients with rhino-orbito-cerebral mucormycosis surviving without undergoing orbital exenteration. They had orbital signs (ophthalmoplegia, proptosis) and received intravenous amphotericin B. Surgical therapy included biopsy alone or was combined with selective excision of nonviable orbital tissue. None of these patients was found to have extensive necrosis within the orbit (3,5,9-28).

In a review of 179 patients with mucormycosis, Blitzer et al. (3), although showing a clear benefit with surgery, were unable to show a detrimental effect in delaying it. In fact, 35% of their survivors had surgery more than a week after initial diagnosis of mucormycosis. Similar findings were reported by Peterson et al. (28) in their study of 28 patients with mucormycosis. Thus, in selected cases, it appears that with close observation and serial imaging, orbital contents can be spared until clinical deterioration mandates exenteration.

It should be emphasized that none of our patients showed necrosis of the orbital tissues. Necrosis was absent despite clinical findings of amaurosis, proptosis, ophthalmoplegia, and imaging studies showing orbital inflammation. It is possible that these findings were the result of *Mucor* cellulitis (35) or spillover inflammation from the adjacent paranasal sinuses. If extensive necrosis had been found, most authorities would have performed orbital exenteration (2,5,18). Therefore, direct inspection...
of orbital contents, looking carefully for signs of necrosis, is critical in determining the need for paranasal sinus surgery alone or more aggressive surgical therapy, including exenteration.

Endoscopy provides an effective surgical approach in the diagnosis and management of patients with rhino-orbito-cerebral mucormycosis. This procedure can often be performed in an outpatient setting with modified local anesthesia, and unlike traditional anterior rhinoscopy, allows visualization of the posterior nasal cavity and sinuses. It allows the surgeon to inspect infected tissue, selectively remove necrotic material, and spare healthy structures. It affords repeat examinations and debridement of the paramaxillary sinuses and orbital contents in monitoring response to therapy (36).

Ophthalmic complications have been reported after endoscopic sinus surgery (37,38). Neuhaus classified these into four categories: nasofrontal sac or duct injury, extracranial muscle injury, intracerebral hemorrhage/empyema, and optic nerve injury (38).

In addition, the endoscopic approach is limited in its access to the orbit. It primarily allows visualization of the medial and inferomedial orbit through the ethmoid sinuses (3,5,21). Factors contributing to the ease of spread include the thickness of the lamina papyracea, the thinnest orbital bone, congenital dehiscences often present along the medial wall, and the perforation of the medial orbital wall by arteries and veins (41).

A number of other methods hold promise in the treatment of rhino-orbito-cerebral mucormycosis. Local application of amphotericin B (cases 1 and 2) allows increased concentration of the agent at the site of active infection (5,8,13,19,26,29,34,42,43). Hyperbaric oxygen may prove beneficial, because members of the family Mucoraceae are susceptible to increased oxygen tension (22,24,31,42). Liposomal preparations of amphotericin B may prove beneficial, because members of the family Mucoraceae are susceptible to increased oxygen tension (22,24,31,42). Liposomal preparations of amphotericin B may prove beneficial, because members of the family Mucoraceae are susceptible to increased oxygen tension (22,24,31,42).


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