

Case reports

Mucormycosis Presenting with Painful Ophthalmoplegia

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Abstract

Mucormycosis is a rare fungal infection that can involve the sino-orbito-cerebral region. Sino-orbito-cerebral mucormycosis is most common in patients who are immunocompromised or have diabetes mellitus, severe malnutrition or burns. This condition can be fatal if it is not diagnosed early and treated aggressively.

This article presents 4 cases of mucormycosis, including 2 with orbital apex syndrome, 1 with cavernous sinus syndrome, and 1 with multiple cranial nerve involvement. All of the patients were presented with painful ophthalmoplegia. The predisposing factors for mucormycosis included diabetes mellitus (three patients) and chronic leukemia (one patient). In all cases, mucormycosis was diagnosed by examining endoscopic sinus drainage material and was treated with surgical debridement and amphotericin B.

Two patients with central nervous system involvement died. The others have survived, but still exhibiting various neurologic abnormalities after aggressive treatment. Patients with mucormycosis rarely present with orbital apex syndrome. The possibility of mucormycosis should be investigated in any patient with painful ophthalmoplegia, and prompt otorhinolaryngologic examination is recommended to ensure rapid diagnosis and treatment.

Key words : Mucormycosis ; ophthalmoplegia ; sinusitis ; treatment.

Introduction

Mucormycosis is an acute, rapidly progressive, and often fatal opportunistic infection caused by fungi of the order *Mucorales*. The rhino-sino-orbital region, respiratory system, gastrointestinal tract, and skin are the most often affected sites (1). Mucormycosis typically develops in warm moist tissues, such as the mucosal folds of the paranasal sinuses. This explains why rhino-cerebral mucormycosis is the most common clinical form (2). Fungi infections of the central nervous system (CNS) can occur via direct invasion from the rhino-orbital region or via hematogenous spread from the respiratory system, gastrointestinal tract or skin (3). Mucormycosis most often affects immunosuppressed individuals and patients with poorly

controlled diabetes (particularly those with ketoacidosis), hematologic malignancies, severe burns or malnutrition (4,5).

Orbital apex syndrome consists of a paralysis of all three nerves supplying the external ocular muscles and a sensory deficit in the distribution of the first division of the trigeminal nerve, combined with an optic nerve lesion (4). Especially, orbital apex syndrome as an initial manifestation of a mucormycosis is a rare condition. The early diagnosis and treatment are very important for decreased mortality (4).

Herein, we report four cases with mucormycosis who presented with painful ophthalmoplegia.

Case 1

A 58-year-old woman with diabetes mellitus was admitted to our emergency department with a headache in her right orbital area and blurred vision for one week. Neurologic examination revealed complete right-sided ophthalmoplegia (palsy of the oculomotor, trochlear and abducens nerves) accompanied by pain and mydriasis, hypoalgesia in the region innervated by the first division of the trigeminal nerve, diminished corneal reflex, and blindness in the right eye (Figure 1). These findings suggested orbital apex syndrome.

Laboratory testing revealed white blood cell count $6 \times 10^3/\text{mm}^3$ with 87% neutrophils ; and fasting blood glucose 206 mg/dL. Urinalysis indicated neither glucosuria nor acetonuria. Cerebrospinal fluid (CSF) analysis showed nothing abnormal, and the results of thyroid tests and other biochemical assessments were normal as well. Testing of visual evoked potentials (VEPs) showed no response in the right eye and late response in the left eye. Orbital computed tomography (CT) and magnetic resonance imaging (MRI) revealed mucosal edema and thickening in the right ethmoidal sinus, sphenoidal sinus and right cavernous sinus with edema of the right optic nerve, and in the medial and inferior rectus muscles and orbita. The affected sites were hyperintense on precontrast and gadolinium-enhanced T1-weighted images (Figure 2a,b).

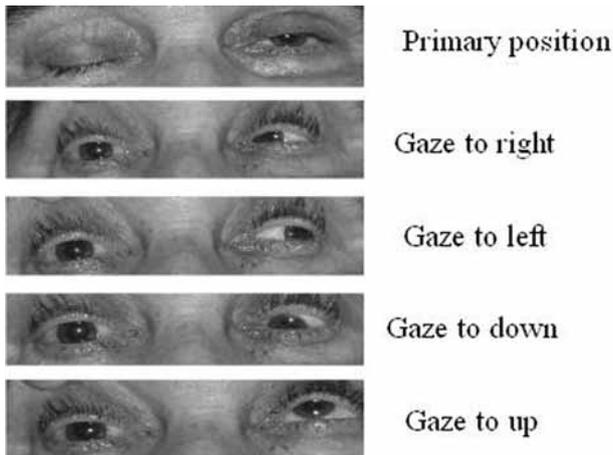
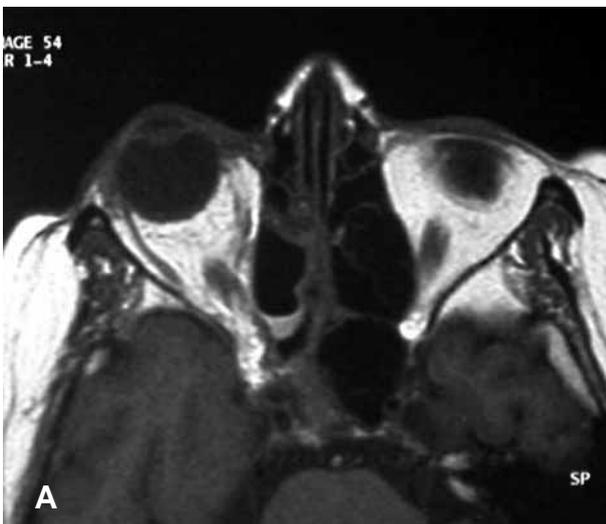


FIG. 1. — A photo of Case 1: the patient exhibited total right-sided ophthalmoplegia with mydriasis.

The otorhinolaryngology department was consulted and the patient's condition was interpreted as fungal sinusitis. Endoscopic sinus drainage was performed and the material was submitted for fungal culture and histopathologic examination. A sample was inoculated into 5% blood agar, eosin-methylene blue and Sabouraud's agar, and the Sabouraud's plate showed growth on the third day (1 week after the patient was admitted to hospital). Lactophenol staining of material collected from the ethmoidal sinus revealed nonseptate fungal hyphae. Based on these findings, the patient was diagnosed as mucormycosis.

The patient's blood glucose levels were brought under control with regular insulin, and then therapy for mucormycosis was started. Test doses of amphotericin B were given initially, and the patient was prescribed a dose of 1 mg/kg/day. The pain was diminished after 1 week of treatment, but then she developed left hemiparesis due to infarction of the right centrum semiovale. Two weeks later, the patient was lost due to respiratory and cardiac failure and overwhelming sepsis.



Case 2

A 60-year-old man with diabetes mellitus was admitted to our emergency department. He had already visited another hospital, and had a dull, moderately severe headache in the right orbital area that had been present for 5 days. Blurred vision accompanied the headache, and he also complained of facial numbness. Nausea, vomiting, photophobia or phonophobia were not described. Neurologic examination revealed complete right-sided ophthalmoplegia (oculomotor, trochlear and abducens nerves) with mydriasis hypoesthesia in the region innervated by the ophthalmic division of the trigeminal nerve, and diminished corneal reflex and blindness on the right. There was no pupillary light reflex in the right eye.

Laboratory investigation revealed white blood cell count $15 \times 10^3/\text{mm}^3$ with 88% neutrophils; blood glucose 350 mg/dL; and erythrocyte sedimentation rate (ESR) 50 mm/hour. Glycosuria and acetonuria were not detected on urinalysis. CSF analysis revealed 60 leukocytes/ mm^3 , protein 159 mg/dL, and glucose 180 mg/dL (simultaneous blood glucose level 199 mg/dL). The results of thyroid testing and other biochemical analyses were normal.

The examination results suggested orbital apex syndrome. Orbital MRI demonstrated edema and thickening of the mucosa in right ethmoidal and sphenoidal sinus, and infiltration of the right orbit and right optic nerve. The affected sites were hyperintense on precontrast and gadolinium-enhanced T1-weighted images. Testing of VEPs yielded no reliable response in the right eye, and a normal cortical response in the left eye.

The patient's condition was interpreted as fungal sinusitis. Endoscopic sinus drainage was performed by an otorhinolaryngologist. The drainage material was subjected to fungal culture and was histopathologically examined. A sample of it was inoculated into 5% blood agar, eosin-methylene

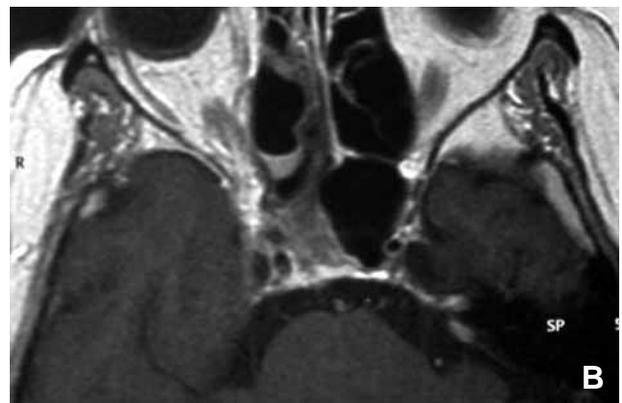


FIG. 2. — Non-contrast (A) and post-contrast (B) axial T1-weighted orbital magnetic resonance image sequences from Case 1 show mucosal thickening in the right ethmoidal and right sphenoidal sinuses.

blue and Sabouraud's agar. On the third day, there was growth on the Sabouraud's plate. Lactophenol staining of the drainage material revealed nonseptate fungal hyphae.

The patient's elevated blood glucose was brought under control with regular insulin. Test doses of amphotericin B were given, and then the drug was administered at a dose of 1 mg/kg/day. After 10 days of this treatment, his creatine level started to rise. The medication was changed to liposomal amphotericin B 1 mg/kg/day, and this was continued for 30 days. At the end of this period, osteomyelitis was detected in the alveolar process of the patient's left maxilla, and inferior maxillectomy was performed. Fungal hyphae were found on the pathological examination of the resected maxillary bone. Six months later, a complete neurological evaluation showed that the total right ophthalmoplegia and right-eye blindness remained; however, the patient's general condition was good and there were no abnormal systemic findings.

Case 3

A 61-year-old man was admitted with left facial weakness, insufficient eyelid closure, headache in the left orbital area, diplopia, and numbness of the left side of the face. He had had these problems for a day. The man had been diagnosed as diabetes mellitus 6 years ago. Neurologic examination at admission revealed numerous findings on the left side of the face: miosis, peripheral facial nerve palsy, abducens nerve palsy, and hypoesthesia in the regions innervated by the trigeminal nerve. Two days later, the patient developed total left ophthalmoplegia accompanied by pain, and 4 days later, he developed peripheral facial nerve palsy on the right.

The results of laboratory tests were white blood cell count $18 \times 10^3/\text{mm}^3$ with 92% neutrophils and 4% lymphocytes; creatinine 1.55 mg/dL; and ESR 52 mm/hour. Urinalysis revealed glycosuria but no acetonuria. CSF examination revealed 20 leukocytes/ mm^3 , mildly elevated protein (47 mg/dL), and glucose 110 mg/dL (and simultaneous blood glucose level of 120 mg/dL). Gram and Giemsa staining of CSF showed nothing remarkable. Thyroid function testing and other biochemical evaluations were normal.

Paranasal sinus CT showed mucosal thickening in the frontal and ethmoidal sinuses bilaterally (with findings more pronounced on the left), and in the left sphenoidal and maxillary sinuses. Cranial and orbital MRI also demonstrated infiltration of the paranasal sinuses, orbits, the left mastoid, and the muscles and adipose tissue of the infratemporal fossa. Cranial magnetic resonance angiography revealed nothing abnormal.

The otorhinolaryngology department was consulted and the patient was suspected to have fungal sinusitis. Endoscopic sinus surgery was performed

and material was drained from the ethmoidal sinus. This material grew nonseptate fungal hyphae in 5% dextrose and Sabouraud's agar, and this led to the diagnosis of mucormycosis.

The patient's blood glucose level was brought under control with regular insulin. Then treatment with liposomal amphotericin B (1 mg/kg/day) was started and he completed a 30-day course. The liposome form of the drug was preferred because the patient had nephropathy. Since the above-mentioned CT examination had revealed infiltration and bone destruction in the left maxilla, maxillectomy was performed. Five months after this surgery, the bilateral peripheral facial nerve palsy, total left ophthalmoplegia, and left trigeminal nerve palsy remained.

Case 4

A 79-year-old man was hospitalized with a diagnosis of chronic myeloid leukemia in our hematology department and was hospitalized. Two days after admission, he complained of headache and dropping of his upper left eyelid. He was consulted to a neurologist and neurologic examination revealed total left ophthalmoplegia accompanied by pain. The patient's headache was throbbing and severe, nausea, vomiting, blindness or facial weakness were not detected. The examination results suggested cavernous sinus syndrome. One-day later, the patient developed right hemiparesis and confusion mentale.

Results of laboratory analyses revealed white blood cell count $15 \times 10^3/\text{mm}^3$ with 22% neutrophils and 16% lymphocytes; hemoglobin 8.3 g/dL; hematocrit 24%; blood glucose 423 mg/dL; blood urea nitrogen 58 mg/dL; creatinine 1.88 mg/dL; and ESR 26 mm/hour. Urinalysis showed glycosuria but no acetonuria. Cranial MRI with contrast injection demonstrated infiltration of the left cavernous sinus and left ethmoidal sinus, and contrast enhancement in the left cavernous sinus area. He was consulted to otorhinolaryngologist, and endoscopic sinus surgery was performed to establish the cause of the sinusitis. The biopsy specimen from the ethmoidal sinus revealed mucormycosis. Cranial MRI was repeated after right hemiparesis occurred. This showed infarction in the mesencephalon, thalamus and capsula interna on the right side.

Although treatment with amphotericin B was started immediately, the patient died on the fifth day of hospitalization.

Discussion

Patients with fungal infection who develop sino-orbito-cerebral syndrome often present with acute headache, fever, facial swelling, sinusitis, ophthalmoplegia and/or blindness (4,8,9). Rhinocerebral

mucormycosis is a relatively common clinical presentation in such cases. Patients with this form of mucormycosis are frequently admitted to otorhinolaryngology clinics with problems of headache, nausea, facial pain and other symptoms of sinusitis. It is rare for individuals with mucormycosis to present with orbital apex syndrome (4,8). The patients presented with multiple cranial nerve involvement are not frequently described. The pathogenesis of cranial involvement is related to direct invasion to nerves (4,8).

There are three stages of rhinocerebral mucormycosis. In stage 1, local infection of the nasal mucosa and sinuses typically causes nasal stuffiness, discharge, localized pain and headache. In stage 2, the *Mucorales* organisms invade the orbital area, causing orbital apex syndrome or superior orbital fissure syndrome. In stage 3, the infection spreads through one or both cavernous sinuses, damaging the internal carotid artery and cribriform plate, resulting in intracranial involvement (3).

Single or multiple ocular nerve palsies combined with pain in one or both eyes are known as painful ophthalmoplegia. There are many possible causes of this condition and the lesions responsible for it may be located in a variety of sites, from the orbit to the superior orbital fissure, cavernous sinus, parasellar area or posterior fossa. The major causes of painful ophthalmoplegia include orbital pseudotumors, metastatic tumors, lymphoma, Tolosa-Hunt syndrome, nasopharyngeal carcinoma, cavernous sinus thrombosis, pituitary adenoma,

intracavernous and posterior communicating artery aneurysm, petrositis, arteritis and diabetes mellitus (10). Mucormycosis and other fungal infections of the sino-orbital region are infrequent causes of this condition (10,11,12). Patients in stage 1 of rhinocerebral mucormycosis can be diagnosed by an otorhinolaryngology clinic. However, if stage 2 and 3 usually referred to a neurology department. If a patient's clinical presentation indicates cranial nerve involvement, it is important that the neurologist should assess for mucormycosis immediately. The clinical findings of sino-orbito-cerebral mucormycosis tend to vary and can include not only painful ophthalmoplegia, but also multiple forms of cranial involvement, as in our third case (12,13).

Our report describes 4 patients who developed painful ophthalmoplegia due to mucormycosis. Painful ophthalmoplegia was the main presenting symptom in all these cases. The patients in Cases 1 and 2 presented with orbital apex syndrome, the third patient had bilateral multiple cranial nerve involvement, and the fourth had cavernous sinus syndrome. The clinical findings, cranial MRI and outcome of cases were shown in Table 1.

The difficulties of diagnosing sino-orbito-cerebral mucormycosis are well known. This condition occurs in all age groups. It usually affects patients with debilitating diseases, but can also affect people in good health. The most common risk factor for mucormycosis is diabetes mellitus. The predisposing factors in our four cases were diabetes mellitus and chronic leukemia. Apart from the

Table 1
Clinical findings, cranial MRI and outcome of cases

Case no	Age/Sex	Clinical findings	Cranial MRI	Outcome
1	58 Female	Right-sided orbital pain Oculomotor/trochlear/abducens palsy Blindness in the right area	Mucosal edema and thickening in the right ethmoidal sinus and right cavernous sinus, edema of the right optic nerve, and edema in the medial and inferior rectus muscles and orbit.	Exitus
2	60 Male	Right-sided orbital pain oculomotor/trochlear/abducens palsy blindness on the right area	Edema and thickening of the mucosa in the right ethmoidal sinuses and in the right sphenoidal sinuses and infiltration of the right orbit and right optic nerve.	Alive Right total ophthalmoplegia and total blindness in the right eye
3	61 Male	Miosis, peripheral facial nerve palsy, abducens nerve palsy, and hypoesthesia on the left side. 2 days later, total left ophthalmoplegia and pain ; 4 days later right peripheral facial nerve palsy	Infiltration of the left cavernous sinus and left ethmoidal sinus, and contrast enhancement in the left cavernous sinus area.	Alive Total left ophthalmoplegia Bilateral peripheral facial palsy Left trigeminal nerve palsy
4	79 Male	Left ophthalmoplegia Headache One day later right hemiplegia	Infiltration of the left cavernous sinus and left ethmoidal sinus, and contrast enhancement in the left cavernous sinus area. One day later mesencephalon, thalamus and capsula interna infarct was found in right side.	

finding of leukocytosis, routine laboratory assessment did not assist with diagnosis. The CSF findings analyses in our cases of mucormycosis were nonspecific, and CSF cultures were not helpful. Although CT may show sinusitis in patients with mucormycosis, the CT findings can mimic benign mucosal disease. Dhiwakar and colleagues found paranasal cellulites to be the most frequent early clinical sign of mucormycosis, whereas CT in our cases revealed only minimal thickening of the paranasal sinus mucosa (14). In contrast, cranial and orbital MRI can more clearly demonstrate fungal infection of the sino-orbito-cerebral region, with hyperintense lesions on T1-weighted images.

An article by Nithyanandam and coworkers stresses that debridement of the sinuses is necessary in all cases of sino-orbito-cerebral mucormycosis diagnosis in the early stages requires astute investigation (15). In our four cases, the definitive diagnosis was made based on detection of mucormycosis hyphae in cultures of biopsy specimens obtained via endoscopic examination of the nasal cavity or paranasal sinuses. In Case 1, the diagnosis was established on the seventh day of the admission and Case 3 was diagnosed on the 10th day of hospitalization.

We emphasize that any diabetic or immunosuppressed patient with painful ophthalmoplegia should undergo immediate otorhinolaryngologic evaluation to rule out mucormycosis. This is extremely important, as the radiological, CSF, and hematologic/biochemical assessments in these cases are nonspecific. Timely diagnosis of mucormycosis requires a high level of suspicion and immediate biopsy of sinus mucosa. It cannot be stressed enough that early diagnosis and treatment are essential. The reported survival rates for cases in which treatment is delayed more than 12 days after the onset of symptoms range from 36% to 42%, whereas the range for patients treated within 6 days of onset is 76% to 81% (1). Intracranial mucormycosis involvement also has a poor prognosis, as demonstrated by 2 of our cases.

In conclusion, our 4 cases of mucormycosis with painful ophthalmoplegia (orbital apex syndrome, cavernous sinus syndrome, multiple cranial involvement) underline the importance of early diagnosis, of correcting predisposing conditions such as hyperglycemia and ketoacidosis, of administering early intravenous amphotericin B therapy, and of performing radical surgical debridement as early as possible.

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