

CASE REPORT

Posaconazole: An Only Oral First-line Antifungal for Rhinocerebral Mucormycosis

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ABSTRACT

Introduction: Mucormycosis is a rare opportunistic invasive fungal infection. The most commonly reported form of the disease is rhinocerebral mucormycosis. Early diagnosis of the disease and aggressive medical and surgical intervention prevent the high morbidity and mortality associated with mucormycosis.

Case report: A 54-year-old diabetic and hypertensive male presented with severe frontal headache and retro-orbital pain of 4 days duration with high-grade fever. On examination, the patient was conscious and oriented with a blood pressure of 210/100 mm Hg. The pupils were anisocoric. Frontal sinus tenderness was present. Anterior rhinoscopy showed deviation of nasal septum to left without edema and nasal mucosal congestion. Eye examination revealed normal vision without any periorbital swelling and normal fundus. Plain axial computed tomography showed soft-tissue density material in sphenoid sinus with focal hyperdense component anteriorly. Cerebrospinal fluid study was negative for meningitis with a normal cerebrospinal fluid pressure. Axial T1-weighted image showed T1 intermediate to high signal soft tissue occluding the sphenoid sinus. Axial T2-weighted image showed T2 high signal soft tissue occluding the sphenoid sinus. Similar signal tissue was seen in the middle and posterior ethmoid air cells on both sides. Axial and coronal postcontrast T1-weighted fat-saturated images showed heterogeneously enhancing soft tissue in sphenoid and ethmoid sinuses. The patient underwent functional endoscopic sinus surgery and tissue sampling, following which antifungal therapy with posaconazole was initiated since biopsy from sinus mucosa was consistent with mucormycosis. The patient responded well to functional endoscopic sinus surgical evacuation of the fungal debris and posaconazole and is doing well on follow-up.

Conclusion: This report highlights the possibility of occurrence of this rapidly fatal condition even with normal-looking nasal mucosa. High index of suspicion is required to prevent the complications as the course of the disease is very rapid. This case report emphasizes the fact that posaconazole is the only available oral antifungal that can be used as a first-line agent in the management of mucormycosis, even in immunocompromised individuals.

Keywords: Headache, Oral antifungal therapy, Posaconazole, Rhinocerebral mucormycosis.

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INTRODUCTION

Mucormycosis (also known as phycomycosis and zygomycosis) is a rare opportunistic invasive infection caused by fungi belonging to the order Mucorales and the family Mucoraceae.¹ It is recognized as one of the most rapidly progressive lethal forms of fungal infection in human beings with a high mortality rate of 70 to 100%.² The incidence of mucormycosis is approximately 1.7 cases per 100,000 population per year.³ The most commonly reported form of the disease is rhinocerebral mucormycosis, characterized by progressive fungal invasion of the hard palate, paranasal sinuses, orbit, and the brain.⁴ The conditions predisposing to mucormycosis are diabetes mellitus, malnutrition, burns, long-term steroid therapy, cirrhosis, immunosuppressive therapy, and hematological malignancies.⁴ Early diagnosis of the disease and aggressive medical and surgical intervention prevent the high morbidity and mortality associated with mucormycosis.⁵

CASE REPORT

A 54-year-old diabetic (since 30 years) and hypertensive male presented with severe frontal headache and retro-orbital pain, aggravated on bending down, of 4 days duration with high-grade fever. There was no history of any nasal/eye discharge, facial pain, vomiting, diplopia, or blurring of vision. On examination, the

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patient was conscious and oriented with a blood pressure of 210/100 mmHg. The pupils were anisocoric. There were no meningeal signs and he did not have any other focal neurological deficits. Frontal sinus tenderness was present. Anterior rhinoscopy showed deviation of nasal septum to left without edema and nasal mucosal congestion. Eye examination revealed normal vision without any periorbital swelling and normal fundus. Laboratory investigations of blood revealed hemoglobin: 12.7 gm%, white blood cells: 9,700/mm³ with 88% polymorphs, 6% lymphocytes, 6% monocytes, and platelets of 220,000. Liver function revealed serum bilirubin 0.5 mg/dl (total) and 0.1 mg/dL (direct) with aspartate transaminase/alanine transaminase: 21/38 and alkaline phosphatase: 53. Renal function showed blood urea 45 mg/dL and serum creatinine 1.2 mg/dL.

Plain axial computed tomography (Fig. 1) showed soft tissue density material in sphenoid sinus with focal hyperdense component anteriorly. Cerebrospinal fluid (CSF) study (Table 1) was negative for meningitis with a normal CSF pressure. Magnetic resonance imaging of brain was also done. Axial T1-weighted image (Fig. 2A) showed T1 intermediate to high-signal soft tissue occluding the sphenoid sinus. Axial T2-weighted image (Fig. 2B) showed T2 high-signal soft tissue occluding



Fig. 1: Plain axial computed tomography showing soft tissue density material in sphenoid sinus with focal hyperdense component anteriorly

Table 1: Cerebrospinal fluid study

CSF pressure	16 cm H ₂ O
CSF protein	35 mg/dL
CSF sugar	170 mg/dL
Cells	No cells
Gram stain	Negative
AFB stain	Negative
CSF culture	No growth

CSF: Cerebrospinal fluid; AFB: Acid-fast bacteria

the sphenoid sinus. Similar signal tissue was seen in the middle and posterior ethmoid air cells on both sides. Axial and coronal postcontrast T1-weighted fat-saturated images (Figs 2C and D) showed heterogeneously enhancing soft tissue in sphenoid and ethmoid sinuses.

The patient underwent functional endoscopic sinus surgery (FESS) and tissue sampling, following which antifungal therapy with posaconazole (syrup Noxafil 5 mL 8th hourly for 2 weeks) was initiated because biopsy from sinus mucosa showed severely inflamed and focally infarcted sinonasal mucosal tissue with a focus of epithelioid granuloma. The center of granuloma showed fungal hyphae, which were broad and nonseptate with obtuse angle branching, morphologically consistent with mucormycosis (Figs 3A and B). The patient responded well to functional endoscopic sinus surgical evacuation of the fungal debris and posaconazole, following which headache subsided and he was discharged with oral antifungals for 2 weeks, and is doing well on follow-up.

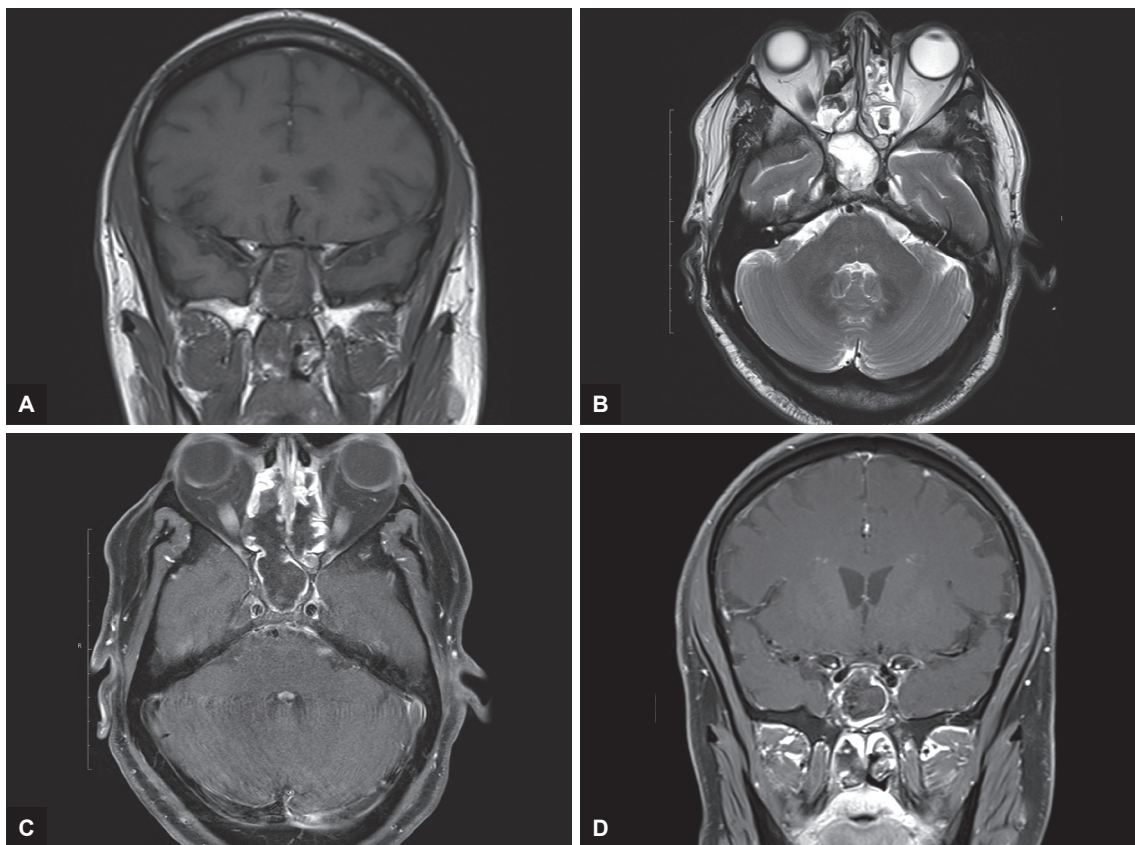
DISCUSSION

Mucormycosis was first described by Paultauf in 1885.¹ Based on the clinical presentation and the involvement of a particular anatomic site, mucormycosis can be classified into six clinical categories:

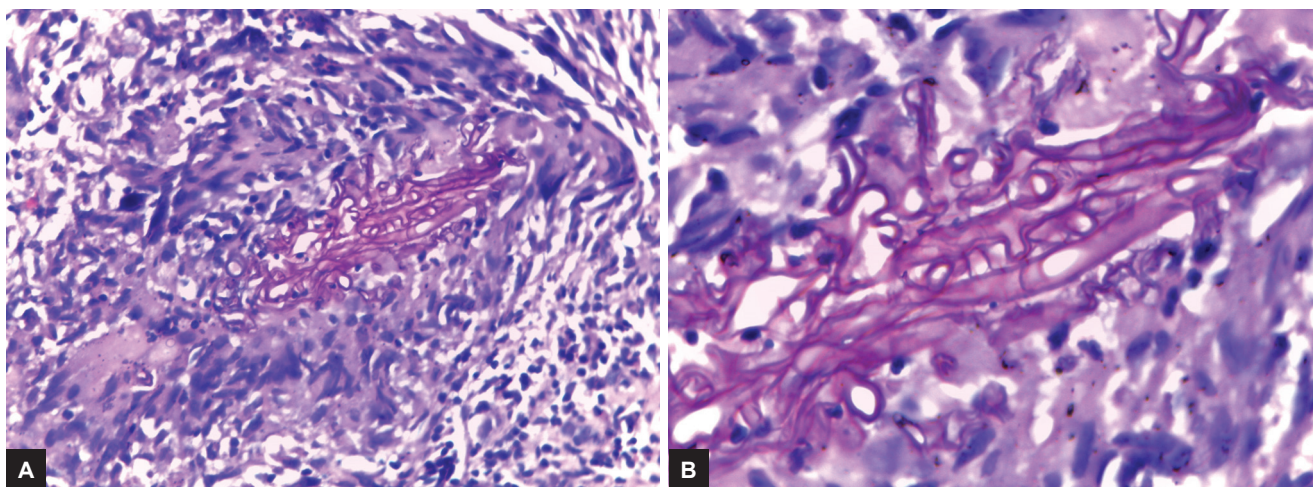
1. Rhinocerebral
2. Pulmonary
3. Cutaneous
4. Gastrointestinal
5. Disseminated
6. Miscellaneous.

Chakrabarti et al⁶ observed that rhino-orbito-cerebral type (44.2%) was the commonest presentation in their retrospective analysis for 10 years in India. It accounts for one-third to one-half of all cases of mucormycosis. Rhino-orbito-cerebral mucormycosis can be subdivided into rhinomaxillary and rhino-oculocerebral forms, the latter being characterized by a high mortality rate.

Our patient was diabetic, and uncontrolled diabetes can alter the normal immunologic response of patients to infections. Such patients have decreased granulocyte phagocytic ability with altered polymorphonuclear leukocyte response. Reports have suggested that the ability of serum of immunocompromised patients to inhibit fungus *in vitro* is reduced, which makes them suitable hosts to opportunistic infections.⁷ Flow Chart 1 shows the pathophysiology of mucormycotic infection in a diabetic patient. The fungus invades the arteries, forms thrombi within the blood vessels that reduce blood supply, and causes necrosis of hard and soft tissues. Once entered into the arteries, the fungus can spread to orbital and intracranial structures.⁷



Figs 2A to D: (A) Axial T1-weighted image showing T1 intermediate to high signal soft tissue occluding the sphenoid sinus; (B) Axial T2-weighted image showing T2 high signal soft tissue occluding the sphenoid sinus. Similar signal tissues seen in middle and posterior ethmoid air cells on both sides; and (C and D) Axial and coronal postcontrast T1-weighted fat-saturated images showing heterogeneously enhancing soft tissue in sphenoid and ethmoid sinuses

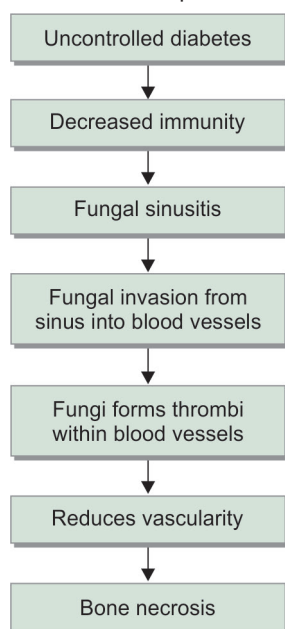


Figs 3A and B: (A) Biopsy showing severely inflamed mucosal tissue with granulomatous reaction to fungal hyphae (hematoxylin and eosin 40 \times); and (B) High-power view showing broad nonseptate fungal hyphae (hematoxylin and eosin 100 \times)

Nasal congestion, headache, earache, and facial pains are some of the most common features, which are not at all characteristic. Depending on the affected site, adjacent structures like the orbit or the central nervous system may be involved. Periorbital edema, ophthalmoplegia, and deterioration of eye are of high probability.

Extension into cavernous sinus may cause cavernous sinus thrombosis. Through the cribriform plate of the

ethmoid bone or the supraorbital fissure, the infection may spread intracranially, affect cranial nerves, and cause abscesses or sagittal sinus thrombosis. Perineural invasion has also been reported.⁸ Differential diagnosis mainly includes necrotizing fasciitis, especially if facial edema is present.⁸ A histopathological diagnosis is generally considered more precise than simple culture due to the depth of invasion of the infection.⁹

Flow Chart 1: Pathophysiology of mucormycotic infection in a diabetic patient

Four factors are critical for treating mucormycosis:

1. Rapidity of diagnosis
2. Reversal of underlying predisposing factors (if possible)
3. Appropriate surgical debridement of infected tissue, and
4. Appropriate antifungal therapy.¹⁰

Surgical resection and debridement are associated with improved outcomes. Amphotericin B and posaconazole are the only antifungal agents currently available that are active against *Mucorales*.¹¹ Considering the safety profile in terms of nephrotoxicity, liposomal amphotericin remains a better option in treating mucormycosis. It is also superior to the conventional Amphotericin B in patients with hematological malignancies. Posaconazole is the only antifungal formulation available as an oral preparation. It has been used as an oral step-down agent after successful response with Amphotericin B or for salvage therapy in case of refractory disease or intolerance to side effects of Amphotericin B.¹¹ Here, we attempted to treat mucormycosis with posaconazole as the first-line agent following FESS and the patient responded very well to it. Peet et al¹² and Singh et al had successfully used posaconazole as a first-line agent in the treatment of mucormycosis in systemic lupus erythematosus patients.

CONCLUSION

This report highlights the possibility of occurrence of this rapidly fatal condition even with normal-looking nasal

mucosa. High index of suspicion is required to prevent the complications as the course of the disease is very rapid. In our patient with a very short history of symptoms of 4 days duration, the diagnosis was difficult with the disease involving predominantly the posterior group of sinuses. Surgical debridement of the fungal debris with strict diabetes control and prompt medical management with posaconazole showed good clinical response. This case report also emphasizes the fact that posaconazole is the only available oral antifungal, which can be used as a first-line agent in the management of mucormycosis, even in an immunocompromised individual.

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