PHOTO ESSAY

Rhino-orbital Mucormycosis Treated Successfully with Posaconazole without Exenteration

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ABSTRACT

Mucormycosis is a rare and often fatal opportunistic angioinvasive infection seen mostly in immunocompromised patients, such as those with diabetes mellitus, cancer, or renal failure. Ophthalmic manifestations of orbital mucormycosis include ocular pain, periocular oedema, visual loss, ophthalmoplegia, proptosis, and ptosis. Although therapy for orbital mucormycosis consists of maximally tolerated doses of antifungal agents (e.g., amphotericin B) and extensive surgical debridement, treatment remains ineffective in up to 20% of cases. We describe two patients with rhino-orbital mucormycosis who were successfully treated with posaconazole in conjunction with intravenous (IV) amphotericin B and sinus surgical debridement. These cases highlight several unusual early manifestations of orbital mucormycosis, including disc oedema and amaurosis fugax, as well as the applicability of a new extended-spectrum antifungal agent in management of orbital zygomycosis.

Keywords: Disc oedema, mucormycosis, orbital apex syndrome, posaconazole, rhino-orbital

INTRODUCTION

Mucormycosis is a rare and often fatal opportunistic infection seen mostly in immunocompromised patients, such as those with diabetes mellitus, cancer, or renal failure.¹ Ophthalmic manifestations of mucormycosis include ocular pain, periocular oedema, visual loss, ophthalmoplegia, proptosis, and ptosis. Disc oedema and amaurosis fugax, however, are uncommon manifestations of this disease. First-line therapy for orbital mucormycosis consists of maximally tolerated doses of amphotericin B (AMB), extensive surgical debridement, and reversal of predisposing factors.² However, mortality remains high, with AMB regimens ineffective in up to 20% of cases. We describe two patients with rhino-orbital mucormycosis successfully treated with posaconazole

in conjunction with intravenous AMB and sinus debridement. These cases highlight both unusual manifestations of orbital mucormycosis and the applicability of a new extended-spectrum antifungal agent in management of orbital zygomycosis. To our knowledge, this is the sixth report of orbital mucormycosis treated with posaconazole in which the patients were spared of exenteration.

CASE I

A 60-year-old Caucasian male with a past medical history of poorly controlled type 2 diabetes mellitus, coronary artery disease, hypertension, hyperlipidaemia, fibromyalgia, and chronic recurrent sinusitis presented in June 2010 to the emergency room with

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diabetic ketoacidosis and a 3-week history of headaches, right eye pain, progressive right-sided ophthalmoplegia, right-sided ptosis, and right-sided facial numbness in the V₁ distribution. Glycosylated haemoglobin (HbA1c) on presentation was 14.0% and the patient was afebrile with a normal white blood cell count. After the patient was stabilized, maxillofacial computed tomography (CT) showed inflammation of the right ethmoid, maxillary, and sphenoid sinuses that extended into the orbital apex. Endoscopic biopsy with sinus debridement, orbital decompression, and ethmoidectomy was positive for *Rhizopus oryzae*. The patient was started on intravenous (IV) AMB and oral suspension posaconazole based on susceptibility testing. His medications included aspirin, insulin aspart, irbesartan, simvastatin, milnacipran, and hydrochlorothiazide.

On neuro-ophthalmic examination, best corrected visual acuity (BCVA) was no light perception (NLP) right eye (OD) and 20/20 in left eye (OS). Visual fields were full to confrontation OS. Pupils were 6.0 mm, fixed, and nonreactive OD and 3.0 mm and reactive OS with a reverse relative afferent pupillary defect (RAPD) OD. External examination indicated complete ptosis of the right upper lid without proptosis and the patient had right V₁ distribution numbness extending from the right eyelid to the skull vertex. There was –3 underaction of elevation, depression, and adduction OD and normal motility OS. Intraocular pressure examinations were normal OU. Slit-lamp biomicroscopy examination was normal without uveitis or granuloma formation. Dilated funduscopy examination showed optic disc oedema with peripapillary haemorrhages OD and a normal optic nerve OS with a cup-to-disc ratio of 0.3 (Figure 1). Optical coherence tomography of the optic discs showed diffuse right-sided nerve fibre layer loss and measured 73 microns OS on the global indices.

A cranial magnetic resonance imaging (MRI) study showed enhancement of the right optic nerve, oculomotor nerve, trochlear nerve, and abducens nerve with involvement of the retro-orbital fat, extraocular

muscles, and orbital apex (Figure 2). Magnetic resonance angiogram (MRA) was negative with no evidence of vascular thrombosis. Serial MRI studies following a month of antifungal therapy with IV AMB and oral posaconazole showed stabilization of the rhino-orbital infection. The patient's physical examination had stabilized by that point and he was discharged on a regimen of oral posaconazole and NPH insulin.

At last follow-up, 12 months later, no evidence of active infection was found. Visual acuity remained NLP OD and 20/20 OS. The patient continued to have right-sided global ophthalmoplegia with no improvement on examination. Repeat ophthalmoscopy indicated optic atrophy OD and a normal optic disc OS.

CASE 2

A 59-year-old Caucasian male with past medical history of right lung transplant, immunosuppressed with tacrolimus, presented in January 2012 with a 4-day history of headaches, progressive right-sided visual loss, photosensitivity, periorbital oedema, transient light-induced right-sided visual obscurations lasting seconds to minutes, and right-sided facial numbness in the entire trigeminal nerve distribution. Past medical history was also significant for bladder carcinoma, prostate carcinoma, diabetes secondary to chronic corticosteroid usage, chronic renal failure, and chronic sinusitis. Cranial CT of the head showed opacification of the right ethmoid and maxillary sinuses with extension into the inferior and medial aspects of the right orbit (Figure 3). MRA was negative without any evidence of vascular thrombosis. Endoscopic biopsy with right hemimaxillectomy and ethmoid sinus debridement was positive for *Rhizopus oryzae* and *Staphylococcus epidermidis*. The patient was started on IV AMB, oral suspension posaconazole, micafugin, and hyperbaric oxygen as well as Augmentin and minocycline for bacterial sinusitis.

FIGURE 1 Fundus photographs at presentation showed optic disc oedema with peripapillary haemorrhages OD (A) and a normal optic nerve OS with a cup-to-disc ratio of 0.3 (B).

FIGURE 2 Coronal (A) and axial (B) T1 post-fat saturation cranial MRI sections at presentation indicated enhancement of the right pterygomaxillary fissure and pterygopalatine fossa as well as postoperative changes in the right maxilla. There is right optic nerve enhancement with involvement of the retro-orbital fat, extraocular muscles, and orbital apex.

FIGURE 3 Coronal (A) and axial (B) cranial CT sections at presentation indicated inflammatory processes in the right maxillary sinus with involvement of the soft tissues anterior, posterolateral, and superior to the maxillary sinus including the inferior orbit. There is abnormal soft tissue thickening along the floor of the right orbit inferior to the inferior rectus muscle, with resulting proptosis on the right compared with the left.

His medications included bupropion, fluticasone, metoprolol, tacrolimus, and tamsulosin.

On neuro-ophthalmic examination, the patient was afebrile. BCVA was 20/200 OD and 20/100 OS. Pupils were 3.0 mm in the dark and 2.0 mm in the light with no RAPD. External examination indicated right-sided periocular oedema, periocular erythema, 4 mm upper lid ptosis and 3 mm proptosis. The patient had right-sided facial numbness extending throughout the trigeminal nerve distribution. Corneal sensation was absent OD but normal OS. There was –1 underaction of abduction and adduction OD and normal motility OS. Intraocular pressure examinations were normal OU. Slit-lamp biomicroscopy was normal except for bilateral 2+ nuclear sclerotic cataracts. Dilated fundoscopic examination was normal with no intraocular evidence of infection and cup-to-disc ratios of 0.2 OU. Humphrey visual field test showed nonspecific scatter OD and superior arcuate depression OS.

Serial CT studies at 4 weeks of antifungal therapy with IV AMB and oral suspension posaconazole showed stabilization of the rhino-orbital infection and the patient was continued on a regimen of posaconazole, amphotericin B, and micafugin. At last follow-up, in February 2012, there was no evidence of active infection. Visual acuity had improved to 20/40 OU. The periorbital oedema and ophthalmoplegia had resolved but the patient continued to have right-sided proptosis and numbness in the trigeminal nerve V₂ distribution. He also continued to experience rare episodes of light-induced amaurosis fugax, with a significant decrease in the number of episodes. A follow-up maxillofacial CT scan in April 2012 showed improvements of orbital soft tissue inflammation without acute demineralization of osseous structures (Figure 4). Minimal remnant evidence of paranasal sinus diseases was seen within ethmoid air cells, inferior sinuses, and sphenoid sinuses.

FIGURE 4 A follow-up coronal (A) and axial (B) maxillofacial CT scan in April 2012 showed improvements of right orbital soft tissue inflammation without acute demineralization of osseous structures. There are postoperative changes of right middle turbinectomy and partial ethmoidectomy. Remnants of paranasal sinus diseases within ethmoid air cells, inferior sinuses, and sphenoid sinuses can be noted.

DISCUSSION

Rhino-orbital mucormycosis is a rare disease entity, with an estimated prevalence of 1.7 per one million in the United States, characterized pathophysiologically by angioinvasion, thrombus formation, and tissue necrosis.¹ Infection often begins as an acute sinusitis that spreads to contiguous structures. As in our two cases, orbital invasion itself occurs primarily by extension of the infection from the ethmoid sinus through the lamina papyracea or from the roof of the maxillary sinus. Damage to the medial rectus, inferior rectus, and inferior oblique muscles are most common, resulting in diplopia and disconjugate gaze often mimicking that of an oculomotor palsy.³ Periorbital and retro-orbital pain are also common presenting symptoms secondary to invasion. Subsequent infarction of cranial nerves can result in facial numbness, weakness, blindness, ophthalmoplegia, and invasion of the cavernous sinus has been known to cause cavernous sinus thrombosis and carotid artery occlusion. Cavernous sinus thrombosis, which can present with a multitude of symptoms including ptosis, chemosis, multiple cranial nerve palsies, papilloedema, headache, and nuchal rigidity, is associated with a poor prognostic outcome. Orbital apex syndrome, a syndrome resulting in damage to cranial nerves III, IV, VI, and the V₁ branch of the

trigeminal nerve in the context of optic nerve dysfunction, is another known complication of orbital mucormycosis with an indolent variant.⁴

Disc oedema, seen in case 1, is a rare finding in rhino-orbital mucormycosis. A review of literature found only two previous documented cases of disc oedema as a physical finding in rhino-orbital mucormycosis without cavernous sinus thrombosis. In one report,⁵ bilateral disc oedema associated with cherry-red spots was seen secondary to ophthalmic artery occlusion in a patient with extensive cerebral involvement. In the other report,⁶ a 21-year-old African American female patient with poorly controlled diabetes presented with unilateral disc oedema suspicious for choroidal infarction in the context of proptosis and ophthalmoplegia. In our first case, MRA was negative for any evidence of macrovascular occlusion. A possible explanation for the disc oedema seen in this patient is angioinvasive ischaemic optic neuropathy following compromise of the short posterior ciliary arteries. Our patient had many of the vasculopathic risk factors often associated with non-arteritic ischaemic optic neuropathy (NAION) but did not present with an abnormal small cup-to-disc ratio, or "disc at risk," seen in the majority of NAION cases.

Amaurosis fugax, seen in case 2, is typically seen in cases of mucormycosis in the context of cavernous sinus involvement or angioinvasive carotid, ophthalmic, or retinal artery occlusion.⁷ Light-induced amaurosis fugax (LIA) has been shown to be strongly associated with carotid artery stenosis, although it has also been reported in cases of macular disease and degeneration of the retinal pigment epithelium.⁸ Although mucor angioinvasion remains the most likely cause of this patient's unilateral light-induced amaurosis fugax, there was no radiographic or physical indication of vascular compromise. The pathogenesis of LIA remains unclear but is thought to be related to retinal ischaemia resulting in a delay in regeneration of photoreceptor pigments. However, as in our case, evidence of venous stasis retinopathy and vascular compromise is absent in many cases of LIA. We were unable to find any previous reports of light-induced amaurosis fugax associated with mucormycosis in the English ophthalmic literature.

Posaconazole is an extended-spectrum triazole shown to have therapeutic value in treatment of zygomycetes infections.⁹ Its utility in rhino-orbital mucormycosis is yet to be established and a review of literature yielded only five previous reports of the use of posaconazole in orbital mucormycosis (Table 1).^{9–13} In previous cases, posaconazole was often utilized late in the disease progression when patient had already received the maximum recommended dosage of AMB and had extensive surgical debridement. In our cases, posaconazole was started early in the disease course (following diagnosis) in conjunction with AMB and other antifungal agents. Despite the extent of

TABLE 1 Summary of previously reported rhino-orbital mucormycosis successfully treated with posaconazole without exenteration.

Case report	Patient	Comorbidities	Locations involved	Microorganism	Treatment course	Follow-up period	Final outcome
Rutar and Cockerham (2006) ¹¹	22/M	ALL on induction chemotherapy	Paranasal and periorbital soft tissue Maxillary sinus	<i>Rhizopus mucorales</i>	Amphotericin B for 20 days then switched to posaconazole for 5 months. Surgical debridement.	5 months	Complete resolution of visual acuity and ocular motility. Complete resolution of all radiological, pathological, and microbiological studies.
Kok et al. (2007) ⁹	66/M	DM1, CRI, retinopathy, and microvascular disease	Ethmoid and maxillary sinuses	<i>Rhizopus oryzae</i>	Liposomal amphotericin B on and off for 16 weeks. Posaconazole started on day 7 and continued for 12 months. Repeated surgical debridements.	17 months	Complete resolution of all radiological, pathological, and microbiology studies.
Kok et al. (2007) ⁹	45/F	DM1, renal transplant	Sphenoid and ethmoid sinus	<i>Rhizopus oryzae</i> , <i>Staphylococcus aureus</i> , <i>Enterobacter cloacae</i>	Liposomal amphotericin B for 7 days. Meropenem and clindamycin for 14 days. Oral posaconazole for 12 months.	12 months	Complete resolution of all radiological, pathological, and microbiology studies.
Gelston et al. (2007) ¹⁰	7/F	DM1	Ethmoid and sphenoid sinus extending to the orbit Carvenous sinus, internal carotid artery thrombosis	<i>Mucor</i> species	Amphotericin B for 6 days and surgical debridement, interferon gamma, and hyperbaric oxygen therapy. Then posaconazole was added and continued for 12 months.	12 months	Improved visual acuity from 20/100 to 20/60. Near-complete resolution of ophthalmoplegia.
Tarani et al. (2009) ¹²	12/F	DM1, DKA, and coma	Pansinus, nose, periorbit, frontal lobe of the brain	<i>Rhizopus</i> spp.	Amphotericin B, granulocyte colony-stimulating factor, and hyperbaric oxygen therapy for 25 days. Amphotericin replaced with posaconazole and continued for 21 months. Surgical debridements and reconstruction.	30 months	Loss of vision. Complete resolution of <i>Rhizopus</i> infection in all affected areas.

Abbreviation: ALL = acute lymphoblastic leukaemia; DM1 = diabetes mellitus type 1; CRI = chronic renal insufficiency.

infection, neither of the patients presented required orbital extenteration or required further surgical debridement following initiation of posaconazole therapy. Furthermore, neither of our patients suffered any side effects from posaconazole therapy. Posaconazole is known to have few drug interactions and utilizes the cytochrome P450 complex less than other extended-spectrum antifungals.⁹ Previous reports have recommended that patients undergo at least a 12-month regimen for satisfactory therapeutic response, but significant clinical improvement was seen in both of our patients following less than a month of posaconazole therapy. We believe that ophthalmologists should be aware of the potential benefit of early posaconazole usage in patients with orbital mucormycosis and that this approach may spare patients from exenteration and other disfiguring aggressive surgical procedures.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Note: Figure 1 of this article is available in colour online at informahealthcare.com/oph

REFERENCES

- [1] Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-orbital-cerebral mucormycosis. *Curr Infect Dis Rep* 2012;14:423–434.
- [2] Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. *Laryngol Otol* 2011;125:807–810.
- [3] Hosseini SM, Borghei P. Rhinocerebral mucormycosis: pathways of spread. *Eur Arch Otorhinolaryngol* 2005;262:932–938.
- [4] Songu M, Unlu HH, Gunhan K, Ilker SS, Nese N. Orbital exenteration: a dilemma in mucormycosis presented with orbital apex syndrome. *Am J Rhinol* 2008;22:98–103.
- [5] Song YM, Shin SY. Bilateral ophthalmic artery occlusion in rhino-orbito-cerebral mucormycosis. *Korean J Ophthalmol* 2008;22:66–69.
- [6] Newman RM, Kline LB. Evolution of fundus changes in mucormycosis. *J Neuroophthalmol* 1997;17:51–52.
- [7] Anderson D, Matick H, Naheedy MH, Stein K. Rhinocerebral mucormycosis with CT scan findings: a case report. *Comput Radiol* 1984;8:113–117.
- [8] Kaiboriboon K, Piriyaawat P, Selhorst JB. Light-induced amaurosis fugax. *Am J Ophthalmol* 2001;131:674–676.
- [9] Kok J, Gilroy N, Halliday C, Lee OC, Novakovic D, Kevin P, Chen S. Early use of posaconazole in the successful treatment of rhino-orbital mucormycosis caused by *Rhizopus oryzae*. *J Infect* 2007;55:e33–e36.
- [10] Gelston CD, Durairaj VD, Simoes EA. Rhino-orbital mucormycosis causing cavernous sinus and internal carotid thrombosis treated with posaconazole. *Arch Ophthalmol* 2007;125:848–849.
- [11] Rutar T, Cockerham KP. Periorbital zygomycosis (mucormycosis) treated with posaconazole. *Am J Ophthalmol* 2006;142:187–188.
- [12] Tarani L, Costantino F, Notheis G, Wintergerst U, Venditti M, Di Biasi C, Friederici D, Pasquino AM. Long-term posaconazole treatment and follow-up of rhino-orbital-cerebral mucormycosis in a diabetic girl. *Pediatr Diabetes* 2009;10:289–293.
- [13] Yoon YK, Kim MJ, Chung YG, Shin IY. Successful treatment of a case with rhino-orbital-cerebral mucormycosis by the combination of neurosurgical intervention and the sequential use of amphotericin B and posaconazole. *J Korean Neurosurg Soc* 2010;47:74–77.