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Fungal Orbital Cellulitis: Presenting Features, Management and Outcomes at a Referral Center

Asim V. Farooq, Rakesh M. Patel, Amy Y. Lin, Pete Setabutr, Juliana Sartori, and Vinay K. Aakalu

Department of Ophthalmology, University of Illinois at Chicago College of Medicine, Chicago, Illinois, USA

Abstract

Purpose—To report a series of patients with fungal orbital cellulitis who underwent exenteration surgery and describe presenting features, management and outcomes at a referral center.

Methods—Retrospective case series.

Results—From November 2011 to March 2014, four patients underwent orbital exenteration for fungal orbital cellulitis at the University of Illinois. Three patients had mucormycosis and one had aspergillosis. All patients were treated with intravenous antifungals and underwent orbital exenteration. Two patients were successfully treated with supplemental intra-orbital catheter delivery of amphotericin B. Presenting visual acuity in the affected eye ranged from 20/25 to no light perception. Some level of ophthalmoplegia was present in three patients. Significantly elevated intraocular pressure was found in two patients. All patients with mucormycosis were found to have uncontrolled diabetes mellitus. One patient had a history of myelodysplastic syndrome, chronic hepatitis C infection, polysubstance abuse and Crohn's disease. Another patient had a history of alcoholic liver cirrhosis, Crohn's disease treated with systemic immunosuppression and renal cell carcinoma. The patient with aspergillosis had myelodysplastic syndrome and portal hypertension, and the initial presentation resembled giant cell arteritis. Two of four patients died during their hospitalization.

Conclusions—Fungal orbital cellulitis has a high mortality rate despite aggressive antifungal treatment and orbital exenteration performed soon after the diagnosis is confirmed. Patients often have a history of immunosuppression and the onset may be insidious. There must be a high rate of suspicion for fungal orbital cellulitis given the appropriate signs and medical history in order to avoid treatment delay.

Keywords

Aspergillosis; exenteration; mucormycosis; orbital cellulitis

Correspondence: Asim V. Farooq, Department of Ophthalmology, University of Illinois at Chicago College of Medicine, 1855 W. Taylor Street, Chicago, IL 60612, USA. Tel: (312) 996-9120. asimvfarooq@gmail.com.

DECLARATION OF INTEREST

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

INTRODUCTION

Fungal orbital cellulitis is caused by opportunistic pathogens and is associated with a high mortality rate among affected individuals. One example is mucormycosis, which is caused by a fungus in the order *Mucorales* and is commonly found in the soil and among decaying organic matter. Among disease causing organisms in this order, the *Rhizopus* species is most common.^{1,2} Its rapid pathogenesis is thought to be related to vascular invasion, leading to thrombosis and subsequent necrosis of involved tissues. This mechanism of spread is facilitated by high amounts of iron or glucose in the serum.^{1,3} Mucormycosis often initially involves the maxillary and ethmoid sinuses, with subsequent spread into the orbit and brain.⁴

Invasive aspergillosis is caused by a fungus in the order *Eurotiales* and in the genus *Aspergillus*.⁵ Most organisms in this genus are highly aerobic and are found on plants and other organic matter rich in carbohydrates. Whereas non-invasive aspergillosis may be associated with allergic sinusitis or a fungus ball with local destruction, invasive aspergillosis in the region of the orbit spreads through bony erosion and/or vascular involvement.⁵ Like mucormycosis, the initial site of infection is usually the sinuses with secondary orbital involvement.^{6,7}

After confirmation of the diagnosis of fungal orbital cellulitis based on biopsy and/or culture, aggressive treatment with intravenous antifungals and orbital exenteration was performed in all cases in our series. Here we describe three cases of orbital mucormycosis and one case of orbital aspergillosis that were seen at the University of Illinois from November 2011 to March 2014.

METHODS

The database of patients diagnosed with fungal orbital cellulitis and treated with orbital exenteration surgery at the University of Illinois Hospital and Health Sciences System, Department of Ophthalmology and Visual Sciences, Oculoplastics service from November 2011 to March 2014 was reviewed in a retrospective fashion. Relevant clinical information, radiologic imaging studies and histopathology slides were reviewed. Cases of non-invasive aspergillosis that did not require orbital exenteration were not included in this series.

RESULTS

Case 1

A 71-year-old Hispanic male presented to our emergency department with an 8-day history of right periorbital swelling and pain. He had been placed on oral clindamycin 2 days prior by an outside provider for signs of preseptal cellulitis, and had worsening symptoms. The patient complained of binocular diplopia in all directions of gaze except primary, and also noted numbness on the right side of his face. He also noted decreased vision OD. He gave a history of pterygium surgery OS 20 years prior as well as refractive error.

The patient also reported a history of hypertension and type II diabetes mellitus (DM). Notably, he was diagnosed with DM one year prior and had discontinued his medications. On examination, his visual acuities at near were 20/50 (pinhole vision 20/30) OD and 20/30

OS. There was no afferent pupillary defect. Ishihara testing was normal. Extraocular movement testing revealed limitations in supraduction, infraduction and abduction OD, and movements were full OS. Hertel exophthalmometry measurements were 24 mm OD and 21 mm OS. Intraocular pressures were 40 mmHg OD and 18 mmHg OS. There was decreased sensation to light touch in the right V1 and V2 distributions.

External examination revealed moderate right upper eyelid edema with mild conjunctival injection and chemosis OD. Anterior segment examination revealed cataracts in both eyes and a nasal pterygium OS. Dilated fundus examination revealed mild hypertensive retinopathy.

His blood glucose level was found to be 326 mg/dl (reference range 65–110). Other relevant laboratory results included a white blood cell count of 12,100 cells/microliter (reference range 3.9–12.0). A computed tomography (CT) scan with contrast revealed cellulitis of the right upper and lower eyelids without clear evidence of post-septal extension, as well as near-complete opacification of the right maxillary sinus (Figure 1). An Otolaryngology consult was ordered and broad-spectrum intravenous antibiotics were initiated. Intraocular pressure (IOP) lowering drops were also added.

A CT venogram was obtained which did not reveal cavernous sinus thrombosis. His vision deteriorated to hand motions OD and an afferent pupillary defect developed in this eye. At this time there was concern for orbital apex syndrome. An Infectious Disease consult was obtained, and amphotericin B was initiated given a suspicion for mucormycosis based on rapid progression while on broad-spectrum antibiotics. A decision was made to take the patient to the operating room. The Otolaryngology service obtained intranasal biopsies that were sent for frozen section analysis and which revealed fungal elements consistent with mucormycosis (Figure 2). A right maxillary antrostomy, ethmoidectomy and inferior turbinate reduction was performed along with extensive debridement of nasal mucosa. Intravenous micafungin was also added.

After a detailed discussion with the patient and his family including risks, benefits and alternatives, a decision was made to return to the operating room with the Oculoplastics service for an orbital decompression and exploration. The orbital floor was found to be positive for mucormycosis on frozen section analysis. A suture tarsorrhaphy was placed along with an irrigation cannula to deliver amphotericin B to the orbit. Neurosurgery was consulted, and a magnetic resonance imaging (MRI) study was obtained which again did not reveal cavernous sinus thrombosis. Subsequently, and after another detailed discussion, the patient returned to the operating room for orbital exenteration. Post-operatively, intravenous antifungals were continued, with transition to oral posaconazole after discharge. He is currently being followed on an outpatient basis.

Case 2

A 59-year-old African American female presented to the emergency department as a transfer from an outside hospital, where she was being treated for diabetic ketoacidosis. During her admission at the outside hospital, the patient reported a history of blurry vision OD along with tearing and periocular swelling for a few days. She was then evaluated by an

ophthalmologist, who noted an elevated intraocular pressure and complete ophthalmoplegia OD, while a CT scan showed signs consistent with orbital cellulitis. She was being treated with broad-spectrum antibiotics, and had also received a dose of intravenous micafungin as well as oral posaconazole and itraconazole prior to transfer to our facility.

The patient denied any significant past ocular history. Notably, she had a history of type II DM, myelodysplastic syndrome, chronic hepatitis C infection, polysubstance abuse, Crohn's disease, seizures and atrial fibrillation. She also had a prior history of pancreatitis and recurrent urinary tract infections. Visual acuities were 20/400 OD and 20/40 OS at near. There was an afferent pupillary defect on the right. On Ishihara testing the patient read 1 of 11 plates OD (only the test plate) and 11 of 11 plates OS. Extraocular movement testing revealed complete ophthalmoplegia OD and full movements OS. Hertel exophthalmometry measurements were 20 mm OD and 16 mm OS. Intraocular pressures were 38 mmHg OD and 19 mmHg OS. External examination revealed a right-sided ptosis with moderate eyelid edema and conjunctival injection with moderate chemosis OD. Anterior segment examination revealed cataracts in both eyes, and dilated fundus examination revealed vascular sclerosis and tortuosity.

Her blood glucose level was found to be 111 mg/dl (reference range 65–110). Other relevant laboratory results included a white blood cell count of 8,500 cells/microliter (reference range 3.9–12.0) and a serum creatinine level of 2.1 mg/dl (reference range 0.5–1.5). Review of the CT scan performed at the outside hospital revealed right periorbital soft tissue swelling, mild reticulation of right retrobulbar fat and right ethmoid sinusitis (Figure 3). Broad-spectrum antibiotics were continued. Otolaryngology, Infectious Disease and Neurosurgery consults were ordered and IOP lowering drops were initiated.

A decision was made to take the patient to the operating room. Frozen section analysis of intranasal specimens revealed fungal elements consistent with mucormycosis (Figure 4). A right-sided medial maxillectomy, middle turbinate resection and orbital decompression were performed by the Otolaryngology service. Intravenous amphotericin B and micafungin were initiated. An MRI was obtained post-operatively, which did not reveal intracranial extension. After a detailed discussion of the risks, benefits and alternatives with the patient, an orbital exenteration was performed.

Post-operatively, intravenous antifungals were continued and an amphotericin drip was also placed into the right orbit. She unfortunately developed thrombocytopenia as well as hospital-acquired pneumonia, and subsequently required intubation due to increased work of breathing. Her pulmonary, cardiac and neurologic statuses continued to deteriorate, and after detailed discussions with the primary team regarding prognosis, a decision was made by the family to withdraw care.

Case 3

A 65-year-old Hispanic male presented to the emergency department with a 4-day history of irritation and crusting OS. On the day of symptom onset, he had an episode of bilateral lower extremity weakness and noted falling three times at home. He denied ocular or head trauma, and also denied lightheadedness, numbness, tingling, loss of consciousness or

shaking of his extremities. That night, he had awoken with severe left periorbital pain. Since then, he also noted decreased vision as well as tearing in the left eye.

Notably, he had a history of a central retinal vein occlusion (CRVO) OD with anti-vascular endothelial growth factor (VEGF) injections in the past and macular degeneration in both eyes, with a recent evaluation by his retina specialist six days prior to presentation. His past medical history included type II DM with an unknown HbA1c, Crohn's disease treated with mesalamine, renal cell carcinoma status-post nephrectomy and alcoholic liver cirrhosis.

Visual acuities were 20/200 OD and 20/25 OS at near. There was no afferent pupillary defect. On Ishihara testing the patient read 0 of 11 plates OD and 11 of 11 plates OS. Extraocular movements were full OD, and there was moderate restriction of movement in all directions OS. Hertel exophthalmometry measurements were 19 mm OD and 21 mm OS. Intraocular pressures were 13 mmHg in both eyes. External examination revealed a left-sided ptosis with mild eyelid edema and conjunctival injection with mild chemosis OS. Anterior segment examination revealed cataracts in both eyes, and dilated fundus examination revealed findings consistent with his history of CRVO and dry macular degeneration.

His blood glucose level was found to be 439 mg/dl (reference range 65–110). Other relevant laboratory results included a white blood cell count of 22,500 cells/microliter (reference range 3.9–12.0) and a serum creatinine of 3.65 mg/dl (reference range 0.5–1.5). A CT scan without contrast revealed cellulitis overlying the left medial canthal area with post-septal extension as well as ethmoid sinusitis (Figure 5). An Otolaryngology consult was ordered and broad-spectrum intravenous antibiotics were initiated.

The following morning, the patient was found to have a decline in vision OS to 20/200. A decision was made to take the patient to the operating room. Frozen sections revealed non-septate hyphae consistent with mucormycosis (Figure 6). Intravenous amphotericin B was initiated intraoperatively. The Otolaryngology service performed a left ethmoidectomy, maxillectomy and orbital decompression, while the Oculoplastics service performed a left anterior orbitotomy with placement of an indwelling catheter for delivery of amphotericin B to the orbit. An Infectious Disease consult was ordered and intravenous micafungin was added.

Post-operatively, the patient was found to have a decline in mental status. Psychiatric consultation was obtained and the patient was felt to have delirium related to multiple medical problems. After discussion of risks, benefits and alternatives with his family, informed consent was obtained for orbital exenteration. Post-operatively, an MRI of the brain revealed acute ischemia of the distal straight gyrus of the inferior left frontal lobe. This was felt to be related to either the recent surgery or intracranial extension of the infectious process. Neurosurgical consultation was obtained, and no acute surgical intervention was planned. Intravenous amphotericin B was continued, with a transition to oral posaconazole after discharge. The patient is currently being followed on an outpatient basis.

Case 4

A 55-year-old Hispanic male presented to the emergency department with a history of right-sided headache and decreased vision in the right eye that started about one month prior. He had presented to the emergency department at the onset of his headaches, and a CT scan at the time had revealed mild sinusitis (Figure 7). Within 2 weeks prior to presentation, he had presented to an outside ophthalmologist with no light perception (NLP) vision in the right eye and reportedly had an otherwise normal ophthalmologic examination. He then underwent an MRI that revealed sinusitis and was then referred to an otolaryngologist who performed a nasal endoscopy and did not see any signs of fungal sinusitis. Erythrocyte sedimentation rate at the time was 62 mm/hr (reference range 0–20) and C-reactive protein level was 8 mg/L (reference range 0–0.8), which were ordered due to a concern for giant cell arteritis.

Upon arrival to our emergency department, the patient reported a history of jaw claudication, right-sided headache, scalp tenderness and weight loss over the past month. He described that his vision had decreased in the right eye over the course of one week. His past ocular history was unremarkable. His past medical history included myelodysplastic syndrome and portal hypertension. Temporal artery pulses were palpable bilaterally. Visual acuities were NLP OD and 20/50-2 OS at distance. Extraocular movements were full bilaterally. There was an afferent pupillary defect on the right. Anterior and posterior segment examinations were otherwise unremarkable.

After review of the outside MRI findings, an Otolaryngology evaluation was recommended. He underwent a repeat MRI, which revealed findings of pan-sinusitis, right optic nerve enhancement and an intracranial abscess in the right frontal lobe (Figure 7). Blood cultures were drawn and intravenous antibiotics as well as antifungals were initiated. The patient was admitted for further management. Upon arrival to the floor he was found to be febrile with a temperature of 38.3 degrees Celsius. The Otolaryngology service performed a right ethmoidectomy, maxillary antrostomy and sphenoidotomy during which inflamed sinus mucosa and mild purulence were noted, and cultures were also obtained at the time. A biopsy specimen revealed fungal elements consistent with aspergillosis (Figure 8).

Repeat imaging revealed an abscess encasing the right optic nerve. The culture results confirmed the diagnosis of invasive aspergillosis. He subsequently underwent a right orbital exenteration. Further imaging revealed signs of septic emboli to the brain. His condition declined during this hospitalization, and he developed acute hypoxic respiratory failure requiring intubation, hypotension requiring the use of vasopressors and acute renal failure. His family ultimately chose to withdraw care.

DISCUSSION

We have presented here a series of patients at the University of Illinois who were diagnosed with fungal orbital cellulitis and who underwent orbital exenteration surgery. All of these patients were found to have underlying medical conditions predisposing them to invasive fungal infection. These patients were co-managed with multiple consulting services. It

should be noted that all of these cases were felt to be severe enough to warrant exenteration surgery, with the primary objective of preventing mortality.

A series of patients treated with limited debridement (without exenteration) was described by Kohn and Hepler.⁸ The authors attributed the success in treatment with limited debridement to early diagnosis and management. In our series, patients had either already developed significant orbital involvement at the time of transfer or progressed rapidly after arrival to our facility.

A comprehensive review of the literature in 1977 described cases of cerebro-rhino-orbital phycomycosis.⁹ Seven cases were found at the Duke University Medical Center over a 46-year period. Five of these patients died as a result of the infection during the follow-up period. Among other cases that were reviewed, the vast majority had diabetes mellitus, and other associations included renal transplantation with immunosuppression, leukemia and acute pancreatitis. Another review published in 1994 found several factors to be associated with a high risk of mortality, including renal disease, leukemia, hemiparesis and bilateral orbital involvement.¹⁰

Several studies have demonstrated that uncontrolled diabetes mellitus remains the most commonly associated condition in orbital mucormycosis.¹¹ Amphotericin B along with aggressive surgical debridement remains the mainstay of treatment, particularly in the presence of significant comorbidities.^{11,12} Due to the severe side effect profile of amphotericin B, a liposomal form of the drug may be considered, particularly in combination with micafungin.^{11–14} There is also a potential role for hyperbaric oxygen as an adjunctive therapy that has been described.^{11,15}

In our series, visual acuity in the affected eye at the time of our assessment ranged from 20/25 to NLP (Table 1). An afferent pupillary defect was present in two of four patients. Color vision was decreased in one patient, and could not be performed in one patient (due to NLP vision). We found that all of the patients in our series had one or more orbital sign(s) at the time of our evaluation. Two patients had significantly elevated intraocular pressure in the affected eye, and intraocular pressure was not recorded in one eye (with NLP vision).

Unilateral exophthalmos as measured by Hertel exophthalmometry was found in three patients, and was not recorded in one patient. All three patients with mucormycosis had uncontrolled diabetes at the time of our assessment. Two of these patients had significant additional comorbidities including chronic hepatitis C, myelodysplastic syndrome and alcoholic liver cirrhosis (Table 1). The patient in our series with invasive aspergillosis had a history of myelodysplastic syndrome and portal hypertension.

The invasive aspergillosis case was also notable for aspects that appeared to mimic giant cell arteritis (GCA), including a history of jaw claudication, right-sided headache, scalp tenderness and weight loss. The ESR and CRP were also elevated. The patient's history of myelodysplastic syndrome, sinusitis seen on recent radiographic imaging and normal optic nerves on examination prompted consideration of an infectious etiology; we therefore obtained repeat imaging as described in the case history. There have been selected case reports of aspergillosis masquerading as GCA.^{16,17} It has therefore been suggested that in

cases of suspected GCA with atypical features and an appropriate clinical history, invasive aspergillosis should also be considered.

An important feature of the patients in our series is that each of them had an apparently insidious period of symptom onset. Three of four patients had initially presented to outside providers prior to evaluation at the University of Illinois. In the first case, the patient was felt to have preseptal cellulitis and was initially placed on oral antibiotics. In the second case, the patient was admitted elsewhere for diabetic ketoacidosis management and was secondarily evaluated for a complaint of diplopia. In the third case, the patient had been seen by a retina specialist less than one week prior and had been asymptomatic, and initially presented with unilateral irritation and crusting. In the fourth case, the patient had symptoms of headache for one month and an outside CT scan had shown sinusitis without orbital involvement. In each case the patient ultimately required orbital exenteration, and two of four died during their hospitalization.

All of our patients were treated with intravenous antifungals and in two cases we successfully employed intra-orbital catheter delivery of amphotericin B; in the second case the patient died from complications of pneumonia, and it is unclear whether the intra-orbital amphotericin B delivery would have been successful. This has been described previously in the literature in three patients with mucormycosis, one of whom was living at the time of publication.^{18,19} In the other two patients, the infectious process was felt to have been treated successfully.¹⁹

CONCLUSION

The management of fungal orbital cellulitis includes intravenous antifungals and early surgical debridement, which remain the mainstays of treatment. Amphotericin B is our initial drug of choice for mucormycosis, with transition to oral posaconazole on an outpatient basis. Intra-orbital catheter delivery of amphotericin B may be useful as adjunctive therapy. For invasive aspergillosis, amphotericin B or voriconazole may be used. In cases of suspected GCA with atypical features and an appropriate clinical history, invasive aspergillosis should also be considered, although it is rare. Multiple consulting services must be involved in cases of fungal orbital cellulitis and care must be coordinated to manage co-morbidities. In our series, we found that the initial clinical presentation of fungal orbital cellulitis was insidious, and was followed by a rapidly progressive period that required urgent surgical intervention. Although an infrequent diagnosis, there must be a high index of suspicion for this entity in order to prevent treatment delay.

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FIGURE 1.

Axial computed tomography scan from Case 1. This initial imaging study demonstrated right-sided eyelid swelling and ethmoid sinusitis without clear evidence of post-septal extension.

FIGURE 2.

This biopsy specimen from Case 1 shows bone and angioinvasive fungal hyphae consistent with a diagnosis of mucormycosis (hematoxylin and eosin 200×).

FIGURE 3.

Axial computed tomography scan from Case 2. This initial imaging study revealed right-sided eyelid swelling, mild reticulopathy of retrobulbar fat and ethmoid sinusitis.

FIGURE 4. This biopsy specimen from Case 2 shows an area of fat necrosis along with fungal hyphae consistent with a diagnosis of mucormycosis (hematoxylin and eosin 200×).

FIGURE 5. Axial computed tomography scan from Case 3. This initial imaging study revealed cellulitis overlying the left medial canthal area with post-septal extension as well as ethmoid sinusitis.

FIGURE 6.

This biopsy specimen from Case 3 shows an area of the inferior turbinate with angioinvasion by fungal hyphae and associated vessel thrombosis consistent with a diagnosis of mucormycosis (hematoxylin and eosin 20 $\times$).

FIGURE 7.

The top image is an axial computed tomography scan from Case 4. This initial imaging study (performed one month prior to our evaluation) revealed mild ethmoid and sphenoid sinus mucosal thickening. The lower image is an axial post-contrast T1-weighted magnetic resonance image from the same patient. This imaging study was performed about one month after the initial computed tomography scan. It demonstrated persistent sinusitis, along with enhancement in the right optic nerve and in the region of the right gyrus rectus.

FIGURE 8.

Biopsy specimens from Case 4. The image on the left shows septate hyphae in necrotic debris consistent with a diagnosis of aspergillosis (hematoxylin and eosin, 400×). The image on the right also shows septate hyphae, some with 45 degree branching (Gomori Methenamine Silver, 400×). These specimens were taken from the ethmoid sinus.

TABLE 1

Presenting features of patients with fungal orbital cellulitis.

	Eye involved	Initial VA	APD	Ishihara	Ophthalmoplegia	Exophthalmos (asymmetry)	IOP (mmHg)	Underlying disease(s)
Case 1	Right	20/30 (PH near)	No	11/11	Yes; partial	Yes (3 mm)	40	Diabetes
Case 2	Right	20/400 (near)	Yes	1/11	Yes; complete	Yes (4 mm)	38	Diabetes, myelodysplastic syndrome, chronic HCV, polysubstance abuse, Crohn's disease
Case 3	Left	20/25 (near)	No	11/11	Yes; partial	Yes (2 mm)	13	Diabetes, renal cell CA, alcoholic liver cirrhosis, Crohn's disease treated with immunosuppressive medication
Case 4	Right	NLP	Yes	Unable	No	N/A	N/A	Myelodysplastic syndrome, portal hypertension

VA= visual acuity, APD = afferent pupillary defect, IOP = intraocular pressure, PH = pinhole, mm = millimeters, HCV = hepatitis C virus, CA= carcinoma, NLP = no light perception, and N/A= not available.