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Rhino-Orbital Mucormycosis

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Abstract

***Background*: Mucormycosis is an aggressive fungal infection caused by filamentous fungi of the Zygomycetes class and Mucorales order. It has a high mortality rate classified by the infection site which includes rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. Clinical hallmarks of this infection is tissue necrosis with black eschar resulting from angioinvasion and subsequent thrombosis. *Case Report*: A 45-year-old white male presented to the emergency department with diabetic ketoacidosis, orbital swelling and pain with left facial numbness. Computed tomography (CT) revealed left maxillary sinusitis with orbital cellulitis. Surgical drainage and debridement was performed and biopsy and culture of the contents revealed inspissated mucopus. A diagnosis of acute left maxillary sinusitis/orbital cellulitis and likely rhino-orbital mucormycosis with left infraorbital enhancing lesions was made and the patient was aggressively treated with antifungals and survived. *Conclusion*: Although the mortality rate of rhino-orbital mucormycosis is high, this infection can be cured. Early diagnosis through tissue biopsy and culture with immediate and aggressive treatment with an anti-fungal, surgical debridement, and reversal of pre-disposing conditions if possible is crucial for a more favourable prognosis.**

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Introduction

Mucormycosis, also referred to as zygomycetes, is an opportunistic invasive fungus that was first described in the literature by German pathologist Paltauf in 1885. It was a case of a systemic infection with gastric and rhinocerebral involvement which he described as "Mycosis Mucorina."[1] The annual incidence rate in 1997 was 0.7 cases per million individuals, then in 2006 it increased to 1.2 cases per million individuals. The annual incidence has almost doubled in a decade. The yearly incidence increased with age from 0.3 per million in children under 9 years old to 3.9 per million in adults 89 years old or older. As risk factors increase, the annual incidence rates increase.[2] This is most apparent among patients with diabetic ketoacidosis which has increased by 400% in incidence between 1991 and 2007.[3] We present a Case Report on successfully treated rhino-orbital mucormycosis in a patient with diabetic ketoacidosis. We will review common signs and symptoms, etiology, treatment, and management for this condition. Proper diagnosis and management will significantly improve survival rate which is why it is crucial for clinicians to be aware of this deadly condition.

Case Report

A 45-year-old white male was referred from the hospital emergency room for an urgent eye exam. He presented to our clinic with 8/10 periorbital pain in the left eye, numbness of the left cheek, acute horizontal diplopia, left lid swelling, and a decrease in visual acuity in the left eye. Ocular history was negative for injury, surgery, and ocular disease. His last eye exam was eight months ago which was unremarkable except for incipient cataracts, low refractive error, and low risk glaucoma suspect OU. Medical systemic history includes poorly controlled type 2 diabetes (for six years), hypertension, depression, alcoholism, obesity (body mass index of 34), and post-traumatic stress disorder.

He was found by a friend to be unresponsive and lethargic, with an altered mental status prior to being sent to the emergency room. About four to six months prior to being admitted he reported heavily drinking (up to twelve packs of beer per day) due to the recent death of his mother. In the emergency department, they found his blood glucose to be 753 mg/dL which resulted in his diabetic

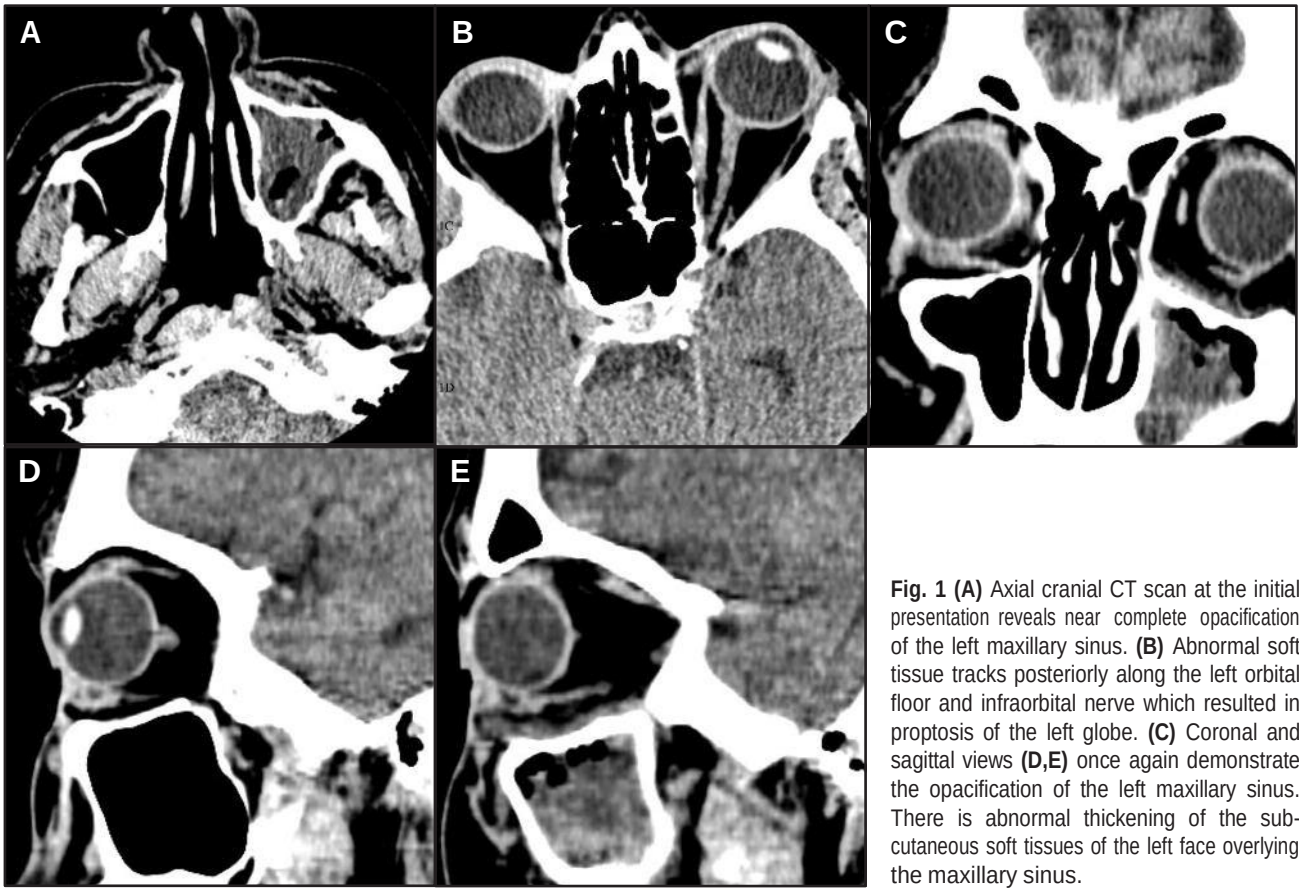

Fig. 1 (A) Axial cranial CT scan at the initial presentation reveals near complete opacification of the left maxillary sinus. **(B)** Abnormal soft tissue tracks posteriorly along the left orbital floor and infraorbital nerve which resulted in proptosis of the left globe. **(C)** Coronal and sagittal views **(D,E)** once again demonstrate the opacification of the left maxillary sinus. There is abnormal thickening of the subcutaneous soft tissues of the left face overlying the maxillary sinus.

coma. He was then placed on an insulin regimen. With good control of his glucose, his diabetic ketoacidosis resolved. However, he developed severe left eye swelling, pain, edema, and redness with subjective blurriness and occasional diplopia upon two days of admission. He was diagnosed with orbital cellulitis during this time with associated left facial numbness, blurred vision, and left maxillary sinusitis. A CT scan revealed left inferior orbital cellulitis, maxillary sinusitis, and preseptal cellulitis (Fig. 1 A-E). He was started on vancomycin and Zosyn® (piperacillin-tazobactam, New York, NY). When his condition was stable, he was transferred into our hospital for management about one week after the initial presentation.

Upon being admitted he reported that the diplopia had resolved. However, he still was symptomatic for subjective left face numbness without paresis, left eye pain, swelling, overall weakness, fatigue, and ongoing headaches. The new concern was for fungal sinusitis with orbital involvement. Head and neck department doctors confirmed that there was no necrosis or black eschar upon examination. Upon consulting with the infectious disease department, the patient was put on liposomal amphotericin B and surgical drainage and debridement of the left maxillary sinus was scheduled for the next day. He then had a same day referral to the eye clinic.

Examination Findings

Ocular examination revealed best corrected visual acuities of 6/6 (20/20) OD and 6/7.5 (20/25) OS with plano — 0.50x100 and +0.50-1.00x100, respectively. Pupils were round and equally reactive to light with no afferent pupillary defect noted OU. Extraocular muscle testing was full. Gross visual fields were full. Primary gaze revealed a flick of exotropia. Exophthalmometry (Hertel) was measured at 19 mm OD and 22 mm OS with a base of 95 mm. Color vision with Ishihara was 9/10 OD and OS. He had decreased sensation along his left maxillary nerve. Intraocular pressure measured 14 mmHg OD and 15 mmHg OS by Goldmann applanation tonometry. Slit lamp biomicroscopy demonstrated no ptosis, mild skin changes with erythema and mild edema. The conjunctiva was white and quiet. The cornea was clear and there was a deep and quiet anterior chamber. The iris was round and reactive with no signs of iris neovascularization. He had trace nuclear sclerosis with a clear vitreous OU. Dilated fundus examination with binocular indirect ophthalmoscopy was unremarkable except for inferior extramacular drusen OU. The cup-to-disc ratios were 0.50 round OD, 0.40 round OS with full rims (Fig. 2 A,B). The macula was flat and even, vessels were within normal

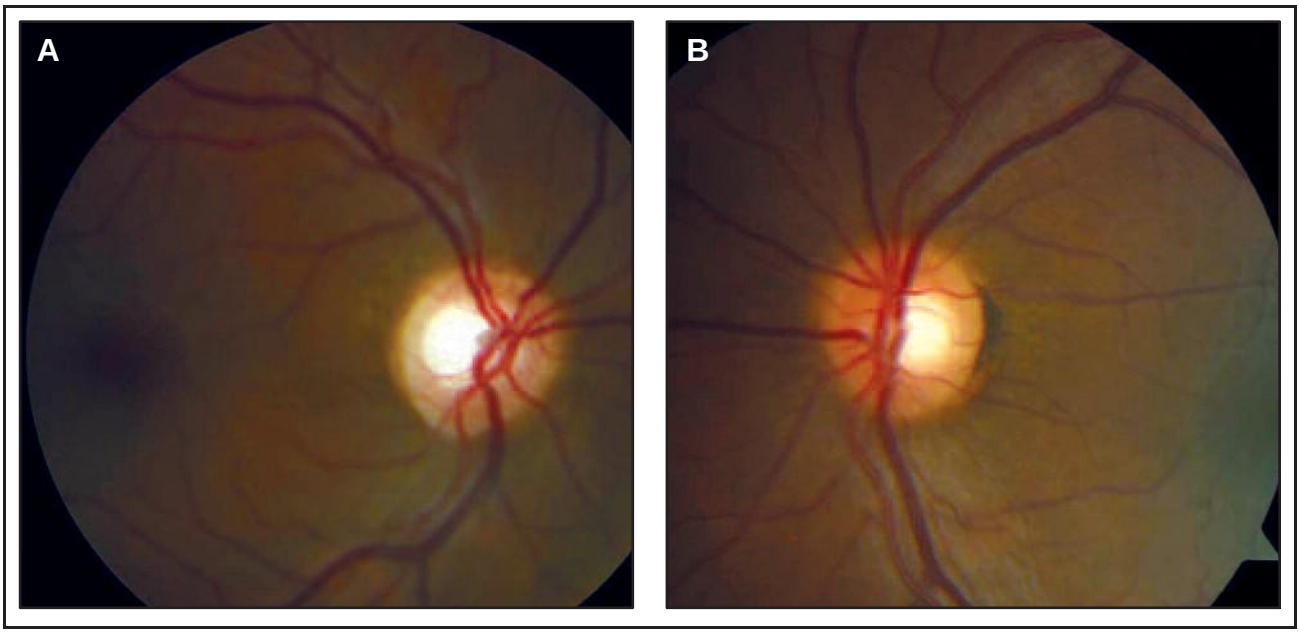

Fig. 2 (A) Fundus photo of the right eye demonstrating a clear view in with a pink and healthy optic nerve with no signs of edema, pallor, or hemorrhages. Cup-to-disc ratios were 0.50 round deep to lamina with unremarkable vasculature. **(B)** Fundus photo of the left eye demonstrating a clear view in with a pink and healthy optic nerve with no signs of edema, pallor, or hemorrhages. Cup-to-disc ratios were 0.40 round deep to lamina with unremarkable vasculature.

limits, and the periphery was intact OU. There was no evidence of intraocular involvement and no signs of orbital compression. The patient was instructed to continue amphotericin B, vancomycin, metronidazole, and Zosyn as prescribed by infectious disease, to proceed with surgical debridement the next day, and to return to ophthalmology post-operatively.

The patient underwent left endoscopic sinus surgery with maxillary antrostomy and anterior ethmoidectomy. Microscopic anatomic pathology revealed non-specific acute and chronic inflammation. Culture of sinus contents revealed positive Gomori methenamine silver (GMS) stain for non-septate broad base hyphae consistent with mucor and maxillary sinus showed inspissated mucopus on the postoperative pathology report. A diagnosis of left maxillary sinusitis/orbital cellulitis, likely rhino-orbital mucormycosis with left infraorbital enhancing lesions was made. His treatment regimen changed to ceftriaxone 2 g IV q.d., metronidzole 500 mg p.o. t.i.d., and liposomal amphotericin 5 mg/kg IV q.d. by infectious disease. He was discharged home once he became stable and was followed-up 3 times per week in the infectious disease outpatient clinic. He was treated with liposomal amphotericin B with taper for two months and treatment was continued until no residual active disease on imaging before discontinuing amphotericin and "mopping up" the condition with posaconzole 200 mg p.o. q.i.d. During the 4-month follow-up he was improving and was clinically stable. Repeat MRI was stable showing thickening with enhancement along the inferior aspect of the orbit with no gross changes. He continued posaconazole for the next few months before discontinuing it.

About two-and-a-half years later, the patient presented for an eye exam and reported four months of sobriety. However, he still had poorly controlled diabetes, as his last glucose finger stick value was 213 mg/dL. There was no diabetic retinopathy OU and no ocular signs of recurrent rhino-orbital mucormycosis was found OU. The patient was encouraged to maintain sobriety and blood sugar control.

Discussion

Epidemiology

Due to the relative rarity of the disease, there are varying estimations of the actual incidence and the incidence varies depending on whether the study was in a developed verse developing country. The literature contains a limited number of population studies. In a population-based surveillance study in San Francisco, California from 1992 to 1993 they found that the annual incidence of mucormycosis was 1.7 cases per 1 million individuals which was about 500 cases per year.[4] A more recent population-based multicenter study in Spain performed throughout 2005, found the incidence was 0.43 cases per 1 million individuals and 0.62 cases per 100,000 hospital admissions.[5]

Table I Clinical presentation of mucormycosis and percentage of diabetics in each study

Clinical Presentation	McCrory (n=40) 2014	Hyo-Lim (n=64) 2013	Spellberg (n=20) 2012	Skiada (n=230) 2011	Chakrabarti (n=178) 2006	Roden (n=929) 2005	Yohai (n=145) 1994	Blitzer (n=179) 1980
Rhinocerebral/ Rhiono-orbito-cerebral	60%	56%	55%	27%	54.5%	48%	**	**
Pulmonary	18%	31%	40%	30%	7%	24%		
Disseminated	10%	4.6%	10%	15%	9%	3%		
Cutaneous	8%	5%			15%	19%		
Gastrointestinal	5%	9%			8%	7%		
Diabetic	58%*	67%*	65%*	9%	81%*	36%*	60%*	70.4%

*Highest risk factor in study
**This study was specific to rhino-orbital-cerebral mucormycosis which they indicated was the most common

Another multicenter study from 2005 to 2007, included 15 international European countries and found 230 cases of proven or probable mucormycosis. They noted that there was an increase in frequency of the disease due to the rising prevalence of diabetes, increased use of immunosuppressive treatments, and newer antifungals, in particular voriconazole.[6] During the same time frame there was another study in India from 2006 to 2007 which found 178 diagnosed cases of mucormycosis (mean average of 35.6 cases/year).[7] Lastly, in the largest review of mucormycosis by Roden et al, which compiled a total of 929 cases from 1940 to 2003, they demonstrated an increased incidence over the decades with a decrease in mortality due to the introduction of amphotericin B.[8] Given the acute nature of the condition, there is limited literature reporting the prevalence of the disease. However, in an autopsy series the prevalence of mucormycosis has been 1 to 5 cases per 10,000 autopsies.[9]

Mucormycosis is categorized based on clinical presentation and the primary site of infection at the time of initial diagnosis. The main categories found in literature are: rhinocerebral, rhino-orbital, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous (Table I). Of these, the most common form is rhino-orbital with diabetes as the most common underlying condition.[8-11] Roden et al categorizes infections that are limited to the sinus as its own category rather than labeling it "rhinocerebral" to distinguish patients with localized sinus infections from those with "true" cerebral involvement. In his review of 929 cases, he found that sinus infections, which included rhinocerebral, rhino-orbital, sinusitis, and sinopulmonary, as the most common presentation (39%), followed by pulmonary (25%), cutaneous (19%), cerebral (9%), gastrointestinal (7%), general disseminated (3%), and other (6%) being the least common. He found that diabetes is the most common underlying condition (36% of cases) and that sinus involvement consisting of rhinocerebral, sinus, and rhino-orbital infections are the most common in patients with diabetes (66% of cases).[8] These findings are similar to Chakrabarti's study that found that rhino-orbital-cerebral mucormycosis is the most common presentation at 54.5% and that uncontrolled diabetes (in 73.6% of cases) is a significant risk factor in all types except in renal involvement.[7]

Clinical Presentation

The clinical hallmark of mucormycosis is tissue necrosis resulting from angioinvasion and subsequent thrombosis.[3,10,12,13] The angioinvasion is characterized by a limited inflammatory immune response and is associated with the organism's ability to hematogenously disseminate from the primary site of infection to other surrounding areas. The infection progresses rapidly and unless there is prompt and aggressive treatment, the prognosis will be poor.[3,9] Black necrotic eschar of the nasal mucosa is a characteristic sign of this condition, but its absence does not indicate that mucormycosis is not present.[12,14,15] During the initial presentation, black eschar is noted in 19% to 38%, but as the disease progresses 68% to 80% of patients develop it.[16,17] It presents unilaterally or bilaterally and is thought to be due to thrombosis of the sphenopalatine vessels in the orbit. It should be considered indicative of terminal vessel necrosis rather than the inoculation site of the infection.[14,15,18,19]

Non-ophthalmic signs and symptoms

The common non-ophthalmic clinical presentations of rhino-orbital mucormycosis include: black nasal eschar 68% to 80%, paranasal sinusitis 78%, granular or purulent nasal discharge 74%, fever 26% to 71.4%, rhinorrhea/cold 57%, palatal involvement 29% to 48%, facial edema/pain 20% to 46%, decreased mental function 34%, toothache 24%, facial palsy/numbness 20% to 22%, leukocytosis 23%, headaches 17% to 20%, hemiplegia or stroke 20%, brain abscess 20%, epistaxis 10% to 20%, hemiparesis 17%, facial necrosis 11% to 15%, meningeal signs 11%, and malaise 11% (Table II).[17,19-22]

Table II Summary of non-ophthalmic signs and symptoms.

Signs and Symptoms	Camara-Lemarroy (n=14) 2014	Bhansali (n=35) 2004	Talmi (n=19) 2002	Yohai (n=88) 1994	Blitzer (n=179) 1980
Rhinorrhea/sinusitis	57%	100%		79%	
Fever	71.4%	26%	42%	36%	
Facial edema	14%	46%		30%	26%
Black nasal eschar			94.7%	48%	1%
Nasal discharge/ ulceration		74%	74%	13%	1%
VII nerve palsy/paresis		46%	47%	22%	13%
Palatal involvement (necrosis, ulcer, etc.)		29%	26%	32%	26%
Facial numbness		34%		20%	25%
Mental status change/stupor/coma		29%	31.6%	34%	14.5%
Headache	50%	20%	37%	17%	
Malaise			84%	11%	
Facial pain		20%		23%	
Epistaxis		20%		10%	
Brain abscess		20%		8%	
Toothache		24%		7%	
Hemiparesis/hemiplegia/stroke		17%	15.8%	20%	>1%
Facial necrosis		11%		15%	1%
Seizures			10.5%	2%	>1%

Ophthalmic signs and symptoms

The common orbital signs and symptoms of rhino-orbital mucormycosis are: ophthalmoplegia, unilateral proptosis, vision loss or decrease, chemosis, periorbital edema, periorbital or ocular pain, afferent pupillary defect, trigeminal anesthesia of the ophthalmic division, central retinal artery occlusion, cellulitis, corneal anesthesia, and cavernous sinus thrombosis (Table III).[17,19-22]

Presenting signs and symptoms are orbital and sinus findings consistent with sinusitis or periorbital cellulitis.[19] These are followed by rhinorrhea, fever, nasal mucosal ulceration/necrosis, periorbital and facial swelling, decreased vision, ophthalmoplegia, headache, facial pain, and change in mental status within the first 72 hours.[17] Many case reports have also indicated elevated white blood cell count.[11,21-26] As the infection usually spreads from the ethmoid sinus to the orbit, it affects the extra-ocular muscle function and can cause proptosis as it invades the orbit. Marked chemosis can be seen. Chemosis, proptosis, and loss of extraocular muscle function occur as a result of vascular compromise and indicates the infection has traveled into the orbit. The infection can then spread into neighboring tissues. Onset of ophthalmoplegia and diplopia suggest a cavernous sinus thrombosis, which is an ominous sign. Since the cavernous sinus holds not only the cranial nerves, but also the internal carotid vasculature, the infection can quickly spread systemically and into the central nervous system, causing an extensive infection and indicates a grave prognosis.[9,21]

Etiology, Pathogenesis

Rhizopus oryzae is the most common organism isolated causing mucormycosis. It accounts for 47% to 90% of the cases of mucormycosis, followed by *Mucor spp.*, and *Lichtheimia corymifera*.[6-8,22,23,27,28] They are saprophytic ubiquitous fungi occurring in soil, air, bread molds, decaying or rotten fruits and vegetables, and dung.[12,23,26] *R. Oryzae* have an active ketone reductase system and thrive in high glucose and acidotic conditions. These conditions decrease phagocytic activity of the host because of the resulting impaired gluthione pathway.[20] They are primarily opportunists and require some break-down in immune system defenses to cause infections in humans. Once an infection is established, it spreads readily due to their angioinvasive nature and their ability to grow at or above core body temperature.[29]

Most infections occur secondary to the inhalation of spores into the sinuses and lungs. Infections caused by *R. Oryzae* typically involve the rhinocerebral and pulmonary sites.[29] Other, less common ways of transportation are by ingestion, direct contact via injured skin (burns), trauma with infected soil, and intravenous (IV) drug users.[8,20,30] After the spore gets inhaled into the nasal cavity it travels into the paranasal sinuses, spreads inferiorly to the palate, posteriorly to the sphenoid, and laterally to the cavernous sinus which can invade the orbits and cranial cavity.[12,14,31]

Table III Summary of ophthalmic signs and symptoms.

Clinical Ophthalmic Signs and Symptoms	Camara-Lemarroy (n=14) 2014	Bhansali (n=35) 2004	Talmi (n=19) 2002	Yohai (n=80) 1994	Blitzer (n=179) 1980
Ophthalmoplegia		89%	74%	40%-67%	30%
Proptosis	7%	83%	68%	64%	26%
Vision loss/decrease	21.4%	80%	68%	65%	20%
Chemosis		74%	79%	24%	
Periorbital edema	21.4%	66%	74%	43%	
Ocular/Periorbital pain	28.6%	43%		19%	
Afferent pupillary defect				38%	
Trigeminal anesthesia (V1)				26%	
CRAO		20%		16%	
Orbital cellulitis				20%	
Eyelid necrosis		14%			
Corneal anesthesia				14%	
Cavernous sinus thrombus				13%	
Periorbital necrosis				11%	
Corneal edema/clouding				6%	
Orbital abscess				6%	
Endophthalmitis		6%		1%	
Diplopia				4%	>1%

Mucormycosis have an affinity for blood vessel walls and spread along vascular and neuronal structures. In doing so it infiltrates the walls of blood vessels and may cause cavernous sinus and internal carotid artery thrombosis which can result in soft-tissue infarction. It can also erode the bony walls of the ethmoid sinus which results in the infection progressing into the orbit and brain.[31,32] As the infection progresses into the cavernous sinus it clinically manifests as ophthalmoplegia, a loss of consciousness, and neurological signs. Spread from the cavernous sinus or internal carotid may lead to distant cerebral infarction and/or abscess, usually ipsilateral to the initial disease. Bony destruction is relatively uncommon, but can occur.[13,18,26,33]

Role of iron

Iron is an essential growth factor for Mucormycosis which obtains iron from the host by secreting siderophores. Siderophores are low-molecular weight iron chelators that bind iron to be used by the fungi for cell growth and development. Transferrin is a plasma protein which binds serum iron, thus not allowing the fungi to invade and proliferate its host.[3,26,34] The impact of iron metabolism on the growth and pathogenicity of *R. Oryzae* is linked to diabetes mellitus, particularly with ketoacidosis due to the acidosis state preventing the normal fungistatic action of serum toward *R. Oryzae*.[35] In an acidic pH, like in ketoacidosis, transferrin has a decreased affinity to bind iron which allows more iron to be available and utilized by the fungus[3,7,30]

Deferoxamine

Deferoxamine is a naturally occurring siderophore and is used by *R. Oryzae* to facilitate fungal growth.[3,26,30] Deferoxamine strips ferric iron from transferrin and attaches itself on the mold through an inducible receptor. There have been many studies that have demonstrated deferoxamine's role as a siderophore to *R. Oryzae*.[35-38] De Locht et al found that *R. Oryzae* efficiently used deferoxamine as an iron source in iron overloaded and dialysis patients which increases the risk of mucormycosis in deferoxamine treated patients.[36] Boelaert et al demonstrated that human serum inhibits growth of *R. Oryzae*. This is reversed in an acidosis state. Deferoxamine acts as a siderophore allowing significant iron uptake by *R. Oryzae*. In vitro studies of radiolabeled iron uptake from deferoxamine in serum showed that *R. Oryzae* is able to incorporate 8-fold and 40-fold more iron than can *Aspergillus fumigatus* and *C. albicans* (respectively).[35,37] Modern iron chelators like deferiprone and deferasirox do not have the same siderophore activity for *R. Oryzae*.[3]

Angioinvasion

Angioinvasion with thrombosis and tissue necrosis is a characteristic pathophysiological feature of mucormycosis.[21,29] It is thought to account for their ability to rapidly spread and invade tissues.[30] Mucormycosis hyphae invade blood vessels and form endovascular thrombi causing tissue necrosis. Necrotic tissue provides fertile

Table IV Differential diagnosis of rhino-orbital mucormycosis.[13,17,27,31,70,71]

Condition	Diagnostic Test
Wegener's granulomatosis	Chest X-ray, PFTs, tissue biopsy for granulomatous lesions, lab work (ANCA serology, CBC, urinalysis, ESR, RF, C-reactive protein)
Bacterial sinusitis	Mainly clinical diagnosis, CT scan of sinus and tissue culture of sinus contents PRN
Grave's ophthalmopathy	Thyroid function tests (T3, T4, TSH), MRI of orbit (ideally T2-weighted images)
Bacterial orbital cellulitis	Lab work (CMC with differential, blood cultures), CT or MRI of brain and orbit
Cavernous sinus thrombosis	Mainly clinical diagnosis, (+)headaches, ophthalmoplegia, diplopia, fever, tachycardia, MRI/CT (if no MRI available), CBC, cerebral angiography PRN
Bacterial endophthalmitis	Mainly clinical diagnosis, positive culture from aqueous or vitreous, blood culture PRN
Preseptal cellulitis	Mainly clinical diagnosis and case history

media for fungal growth.[21] It can also prevent delivery of leukocytes and antifungal agents to the site of infection. Angioinvasion likely contributes to the capacity of the organism to hematogenously disseminate to other neighbouring areas.[28]

Host defenses

Macrophages and neutrophils are the main host defenses against the invasion of mucormycosis.[7,39] Prolonged corticosteroid therapy and diabetes affect circulating neutrophils by impairing their ability to mobilize and migrate to the site of inflammation and their phagocyte function which increases susceptibility to infections. Normally, the metabolic activity of *R. Oryzae* hyphae is suppressed by the host defenses, but this effect is negated by severe ketoacidosis. An acidic and hyperglycemic environment mediate the invasion and damage to the host and provide a good environment for the fungus to grow.[3,14,21,23,30,40,41] Diabetic ketoacidosis patients have elevated levels of free iron in their blood stream which supports growth of *R. Oryzae* at an acidic pH (7.3-6.88), but not at an alkaline pH (7.78-8.38). Artis et al demonstrated that acidosis temporarily disrupts the capacity of transferrin to bind to iron in acidic environments and suggested this alteration abolishes an important host defense mechanism that permits the growth and proliferation of *R. Oryzae*.[42]

Risk Factors

The major risk factors for mucormycosis are uncontrolled diabetes with or without ketoacidosis, deferoxamine therapy in patients receiving hemodialysis, prolonged and severe neutropenia, malignancy, chronic renal failure, organ or hematopoietic stem cell transplant, prolonged use of corticosteroids, IV drug use, and major trauma patients [3,20,27,28,43,44] Of the risk factors, uncontrolled diabetes is reported to be the top underlying disease in rhino-orbital mucormycosis specifically (60% to 88.2%) and in all types of mucormycosis (36%).[8,17,22,45] Independent predictors of sinus mucormycosis are diabetes and injection drug use.[8] The rise in the number of patients with mucormycosis may be correlated with an increasing population of diabetics in developing and tropical countries. Uncontrolled diabetes which can result in ketoacidosis is predisposes people to infection as low serum pH diminishes the phagocytic effect of macrophages and chemotactic and oxidative burst of neutrophils.[7]

Differential Diagnoses

There are a number of different conditions that present with similar clinical signs and symptoms of rhino-orbital mucormycosis. They can be differentiated by imaging, lab work, and associated findings both ocular and systemic. A summary of differential diagnosis is found in Table IV.

Management

Successful treatment and management of mucormycosis require four steps: first, early diagnosis; second, reversal of any underlying predisposing risk factors; third, aggressive surgical debridement when possible; and fourth, prompt antifungal therapy.[9,15,30,32,43]

Early diagnosis

In a review by Yohai et al, survival rates declined if treatment was not initiated within six days from the time of initial presentation. In non-diabetics, there were no survivors after 12 days of the disease without treatment.[17] These findings are supported by a more recent retrospective study which found that delaying amphotericin B-based therapy among patients with mucormycosis for 6 days or more after the onset of symptoms resulted in a two fold increase in mortality rate and a <20% survival rate at 12 weeks after diagnosis. This effect of delayed treatment was more evident in multivariate analysis and was independent of all other risk factors.[46] Thus, early diagnosis is essential to minimize mortality rates.

There is currently no specific skin, blood, or serologic polymerase chain reaction (PCR) — based test for the diagnosis of mucormycosis so diagnosis is based on biopsy of infected tissues. Proven mucormycosis is based on the revised definitions of invasive fungal disease found in the

European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG). A proven case is defined as a histopathologic, cytopathologic, or direct microscopic examination of the specimen obtained by needle aspiration or biopsy revealing broad-based, aseptate, ribbon-like hyphae consistent with Mucorales with evidence of associated tissue damage.[9,23,26,44,47-49]

Radiographic findings are generally inconclusive and not specific. Magnetic resonance imaging (MRI) is typically more sensitive than computed tomography (CT) scans for detecting orbital and central nervous system involvement. Both of these can be normal or present with subtle findings initially. The most common finding on CT scans of the head or sinuses is subtle sinus mucosal thickening or thickening of the extraocular muscles.[12,13,17,21,27]

Reversal of any underlying risk factors

Chamilos et al found that reversing any underlying predisposing factors (as listed in the risk factor section) and neutrophil recovery was associated with improved survival rates.[46] Spellberg et al, reiterates this point by emphasizing that correcting or controlling predisposing host conditions is vital for improving the prognosis. They noted deferoxamine treatments and immunosuppressive medications, particularly corticosteroids, should be minimized or discontinued, if possible. Aggressive management in diabetic ketoacidosis patients to promptly restore euglycemia and normal acid base status is just as vital as treating the mucormycosis.[9,50,51]

Surgical debridement

Angioinvasion resulting in blood vessel thrombosis and tissue necrosis results in poor penetration of antifungal therapies to infected tissues. Even if the causative organism is susceptible to the treating antifungal agent in vitro, the antifungal maybe ineffective in vivo. Therefore, surgical debridement of all necrotic tissues, when possible, will allow systemic medications to penetrate and be more effective.[13,21,52] Ideally, the infected tissue should be removed until normal bleeding is encountered.[17] There has not been a study that defined the extent and timing of surgical debridement necessary to maximize outcomes of mucormycosis.[52] Surgical debridement and resection appears to increase survival (78% survived in debrided patients vs. 57.5% in non-debrided patients). Combined amphotericin B and radical surgery further improved survival especially in diabetics by 89%.[53] This is further supported by Roden et al, which showed that 64% of patients treated with an antifungal alone survived, 57% of patients treated with surgery alone survived, while 70% of patients who were treated with both an antifungal and surgery survived.[8] It is clear that surgical debridement in combination with appropriate antifungal therapy increases favorable prognosis.

In rhino-orbital-cerebral mucormycosis, aggressive sinus and palatal disease debridement should be performed wherever possible. This helps reduce the infection load within the sinuses and provides tissues for histopathological diagnosis. Exenteration should only be performed in advanced involvement of the orbit and generally should be considered for an actively infected orbit with a blind, immobile eye. Bhansali et al showed extensive orbital involvement by Mucorales required orbital exenteration in 42% of patients and of those patients 82% survived.[22] Surgical debridement earlier in the disease progression has shown higher cure rates (91%).[26,45] Chakrabarti et al found that a combination of debridement surgery and amphotericin B therapy yielded significantly better survival rates compared to treatment with amphotericin B alone (79.6% vs. 51.7% survival, respectively).[7] This emphasizes once again how important early diagnosis in combination of surgical debridement and treatment is.

Antifungal Therapy

Polyenes

It is well established that the primary antifungal treatment of choice is a polyene, whether its amphotericin B or its lipid formulation. Amphotericin B is a polyene antimicrobial that acts by binding to ergosterol in the fungal cell membrane which results in altering the membrane permeability. It is the only FDA approved antifungal agent for primary therapy of mucormycosis. It is highly protein bound and poorly dialyzable. Therefore, it is important to regularly test creatinine clearance and blood urea nitrogen (BUN) levels to monitor for toxicity. If the serum creatinine exceeds 3.0 mg/100 mL or the BUN levels exceed 40 mg/100 mL, decreasing dosage is recommended. Starting doses of 1 mg/kg/day. Amphotericin B improves the survival rate in diabetics (79% in amphotericin B treatment, versus 37% non-amphotericin B).[10,20,52,53] However, it is shown to not be an effective treatment in some cases, particularly in late stage or disseminated disease.[29]

Liposomal amphotericin B is less nephrotoxic compared to amphotericin B. This allows higher doses to be safely administered in greater concentration and circulation time in infected tissues with increased capillary permeability compared to amphotericin B.[10,21,44] The lethal dose of lipid based amphotericin B is approximately 10 to 50 times higher than amphotericin B.[54] Lipid formulations may enable better solubility into the central nervous system and are currently the preferred first-line treatment for mucormycosis with a preference for liposomal amphotericin.[50] The recommended dosage is 5 mg/kg/day.[10,26] It is FDA approved for treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy. Walsh et al investigated the efficacy and safety of lipid based amphotericin B and

found that 71% of patients demonstrated stable and 21% demonstrated improved serum creatinine by end of therapy and 71% of patients with mucormycosis had a complete or partial response. This study demonstrated a significant improvement in renal function following the initiation of therapy with amphotericin B lipid complex, particularly in patients with amphotericin B-induced nephrotoxicity or primary renal dysfunction.[55] A more recent study by Spellberg et al found similar results with high treatment and survival rates in patients treated with liposomal amphotericin B.[47]

Azoles

Azoles work by altering the fungal cell membrane by inhibiting ergosterol synthesis which results in either fungal cell death or inhibition of cell growth. The currently available triazoles are fluconazole, intraconazole, voriconazole, and posaconazole.[50,56,57] In a study examining the in vitro activities of four triazoles and amphotericin B against 37 clinical isolates of mucormycosis (including *Mucor spp*. and *Rhizopus*), they found that overall, the isolates were generally susceptible to posaconazole, itraconazole, and amphotericin B. Of the azoles, posaconazole was the most potent and was shown to have good in vitro activity against mucormycosis. Its minimal inhibitory contribution was about 1.6-fold lower than itraconazole, 33-fold lower than voriconazole, and 47-fold lower than fluconazole. Though it was not as effective as amphotericin B, it has potential to be used to treat mucormycosis.[58] It's standard dose is typically 400 mg given twice daily orally and is highly lipophilic, orally absorbed, and extensively distributed in tissues.[10,51] Previous studies have examined the efficacy of posaconazole in patients who were refractory or intolerant to the standard treatment of amphotericin B and showed that it had 60% to 82.2% survival following treatment with posaconazole.[57,59] Overall, posaconazole should be considered as salvage therapy.

Echinocandins

Caspofungin, a member of the echinocandin antifungal class, has no activity against mucormycosis in standard in vitro susceptibility tests.[50,60] However, Reed et al. demonstrated that in combination therapy (polyene with caspofungin), the overall success rate in patients with rhino-orbital mucormycosis with CNS disease at 30 days hospital discharge was 100% vs 45% among polyene monotherapy.[60] The typical standard intravenous dose is 100 mg daily.[10]

Iron chelation therapy

Deferasirox is FDA approved for the treatment of chronic iron overload.[61] Considering that there is a link between iron availability and mucormycosis, Ibrahim et al explored the potential for deferasirox as a possible treatment option. They found that deferasirox was fungicidal by 24 hours for clinical isolates of mucorales in vitro and that deferasirox's cidality was time dependent rather than concentration dependent. In diabetic ketoacidosis mice with disseminated mucormycosis, deferasirox was as effective as liposomal amphotericin B (LAmB) therapy. Additionally, combination deferasirox/LAmB therapy synergistically improved survival (80% survival for combination vs 40% monotherapy vs 0% placebo).[62] This study is contrasted by Spellberg et al which demonstrated that when deferasirox was added to LAmB in a small (n=20) double blind, prospective, placebo-controlled study, the combination treatment group (deferasirox with LAmB) had a higher mortality rate than the LAmB only group (82% vs 22%) at 90 days. There were more active malignancies, neutropenia, and corticosteroid therapy patients in the combination group, along with less diabetics which could account for the higher mortality.[47]

Adjunctive therapies including hyperbaric oxygen

Several case reports and studies have shown that adjunctive hyperbaric oxygen improved the overall survival rate, ranging from 83% to 100%.[17,25,27,63,64] Hyperbaric oxygen treats the lactic acidosis which promotes oxidative action of amphotericin B. It contributes to tissue healing by several mechanisms. It enhances leukocyte-mediated phagocytosis, it significantly elevates tissue oxygen levels which increases the rate of tissue healing, and it significantly elevates the levels of growth factors, which promotes angiogenesis and healing.[64,65] The hyperbaric oxygen exerts a fungistatic effect.[26] This is demonstrated in experimental studies using 100% hyperbaric oxygen at 1-3 atmospheres.[66] There is no clear guideline in terms of how long the duration of therapy should be as the optimal duration of treatment has not been studied prospectively and is generally unknown. However, it is recommended that treatment should be continued until the clinical signs and symptoms are resolved, there is resolution or stabilization of residual radiographic signs of disease on serial imaging, and underlying immunosuppression is reversed. This is determined on a case by case basis.[52,63,67,68] Whether hyperbaric oxygen itself has a significant effect on prognosis has not been established by clinical trials due to the rarity of this condition.

Prognosis

The mortality rate depends on the underlying disease, the infection site, and how advanced the condition is.[43] If the fungus penetrates the CNS or enters the major intracranial vasculature, mortality is substantially increased.[9] The lowest survival rates were associated with periorbital necrosis (33%) and cavernous sinus thrombosis (40%). There is no significant decrease in survival with increased number of sinuses involved.[17] Prognosis is significantly improved with amphotericin B treatment (either as monotherapy or in combination with posaconazole) or

with posaconazole and other antifungals (in combination or sequentially). Surgical treatment decreased the risk of death by 79%.[6,8] Roden et al found that overall mortality was 54%, mortality from rhino-orbital mucormycosis was 25%, and once there was cerebral involvement, mortality from rhinocerebral was 62%. They noted that mortality had improved from 84% in the 1950s to 47% in the 1990s and mortality had been overall stable since the introduction of amphotericin B in the 1960s.[8]

Complications

This infection is rapidly progressive and results in death unless underlying risk factors are reversed (if possible) and aggressive treatment with antifungal agents and surgical excision is promptly initiated.[12] Adverse reactions to treatments is something that must be monitored. There are several adverse reactions to amphotericin B, but the most significant is nephrotoxicity (serum creatinine level of greater than or equal to 2.5 mg/dL in adults). Nephrotoxicity may occur in up to 80% of patients and prevents administration of maximally effective therapy. Renal function must be closely monitored by measurement of serum creatinine, blood urea nitrogen, serum magnesium, serum sodium, and serum potassium levels.[20,55,69] Posaconazole also has adverse effects which include fever, nausea, vomiting, diarrhea, abdominal pain, dry mouth, headache and fatigue.[56] Rare adverse effects of hyperbaric oxygen are spontaneous pneumothorax, seizures from oxygen toxicity, and difficulty equalizing middle ear pressure.[66]

Conclusion

In conclusion, mucormycosis remains a severe infectious disease with poor prognosis if diagnosis and treatment is delayed. With the increasing incidence of diabetics and their risk for rhino-orbital mucormycosis, especially if uncontrolled, it is vital that eye care providers are aware of this condition as diagnosis can often be difficult. Prompt and appropriate referrals are of the essence as early diagnosis, reversal of any underlying predisposing risk factors, aggressive surgical debridement when possible and prompt antifungal therapy will increase the prognosis for these patients. □

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