

Isolated Orbital Mucormycosis in an Immunocompetent Adolescent

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Introduction and patient profile: *Mucormycosis is a life-threatening disease that usually affects patients with diabetes and other immunocompromised states. However, recent literature has shown an emergence of this disease in immunocompetent individuals. Here we are presenting a rare case of a healthy 13-year-old adolescent diagnosed to have isolated orbital mucormycosis, previously treated with oral and intravenous corticosteroids. The patient presented with a chief complaint of left eye swelling of 3 weeks' duration, which progressed to proptosis and a visual acuity of no light perception.*

Interventions and outcomes: *Diagnosis of mucormycosis was done using histopathological techniques supported by radiologic imaging. Successful treatment of mucormycosis was achieved via amphotericin B administration and orbital exenteration in this case.*

Discussion: *The use of corticosteroids may weaken the immune system of healthy patients and can cause rapid progression of the disease. Early clinical diagnosis is important because this infection can rapidly be fatal.*

Keywords: *rhinocerebral; zygomycosis; pediatric; amphotericin B; corticosteroids; exenteration.*

INTRODUCTION AND PATIENT PROFILE

Mucormycosis is an extremely rare infection caused by a fungus from the family *Mucorales*. *Rhizopus oryzae* species accounts for 60% of all forms of mucormycosis and 90% of rhino-orbito-cerebral cases.¹ These pathogens are ubiquitous spore-forming saprophytes growing in decaying organic matter and are known to invade host tissues, especially the blood vessels, causing thrombosis, infarction, and eventual necrosis.² The usual portal of entry is the nose; from there they proliferate, spreading to the paranasal sinuses and orbit by direct extension or intravascular dissemination.³ Mucormycosis is a life-threatening disease that usually affects patients with diabetes, prolonged corticosteroid use, hematologic malignancies, chronic renal failure, and other immunocompromised states.⁴ However, recent literature has reported cases involving immunocompetent individuals.^{1,5-7} A case report from Malaysia presented a 40-year-old healthy man who contracted orbital mucormycosis after no known ocular trauma, surgery, sinusitis, or skin infection.⁷ Another report from Iran involved an apparently healthy 2-year-old child who presented with swelling and redness of the left eye after exposure to dust particles.⁵ Due to the rarity of this infection, it is difficult to accurately calculate its incidence. In the United States, the annual

incidence has been estimated at 1.7 infections per million.⁸ It is rare even in high-risk patients, representing 8.3–13% of all fungal infections encountered at autopsy.⁹

This case report is significant because, although a diagnosis of orbital mucormycosis is rare in young immunocompetent individuals, it should remain as a differential in patients presenting with eye inflammation. This disease is highly fatal and must be recognized and treated immediately. Early diagnosis of mucormycosis and initiation of appropriate therapy within 5 days has a survival rate of 83% compared with a 43% survival rate at greater than 5 days.⁵

Mucormycosis in the pediatric population is very rare and of 187 patients reviewed, 65% were male with a median age of 5 years and 24% had preexisting hematologic malignancies and 6% with hematopoietic stem cell transplantation.⁹ Although there is some literature of mucormycosis presenting in healthy individuals, this report is unique because the patient is a healthy 13-year-old adolescent with no risk factors aside from living in a grassy area. In addition, initial laboratory reports suggested classic acute bacterial inflammation, rather than fungal infection. Moreover, the patient did not exhibit the typical presentation of

mucormycosis such as eschar formation and imaging did not show frank invasion of the left orbit from the focal sphenoid sinusitis.

A 13-year-old male from the rural and grassy areas of provincial Philippines, with no known comorbidities, presented with a chief complaint of swelling of the left eye of 3 weeks' duration. The swelling progressed to a slight protrusion of the affected eye. He also noted difficulty raising the eyelid, blurring of vision, diplopia, and limited horizontal movement. The patient consulted a private ophthalmologist where he was prescribed unrecalled eye medication for 4 days, which provided no relief. A week after the first consult, the swelling progressed and the patient consulted another ophthalmologist who prescribed oral prednisone 50 mg/tablet once a day, which provided 10% subjective minimal improvement. His symptoms persisted for another week with continued prednisone treatment, which prompted admission to a local hospital. The patient was treated with oral prednisone 50 mg/tablet increased to twice a day and intravenous amoxicillin-clavulanate. He was discharged after 5 days, with improvement of the affected eye noted by his ability to raise his eyelids, absence of diplopia, and no horizontal limitation. He was advised to continue oral medications and consult an orbit specialist of choice. At follow-up, there was no further improvement, leading to admission at the author's institution soon after.

INTERVENTIONS AND OUTCOMES

Upon admission, the patient was noted to have proptosis of the left eye, with visual acuity of 20/20 – 1, J + 1. The right eye had a visual acuity of 20/20, J + 1. Initial therapeutics included oral prednisone 20 mg/tablet twice a day, amoxicillin-clavulanate 625 mg/tablet twice a day, and intravenous methylprednisone 1 g bolus per day for 3 days. On the first hospital day, the patient had diplopia on all gazes and pain on lateral gaze of the left eye. A computed tomography (CT) scan done on the same day showed a soft tissue density in the medial aspect of the left orbit with periorbital swelling and focal left sphenoid sinusitis. After the first dose of methylprednisone on the patient's second hospital day, the left eye was notably less erythematous, but still slightly proptosed. A complete blood count revealed increased WBC ($26.3 \times 10^9/L$) predominantly neutrophilic (95%), suggesting acute bacterial infection, inflammatory type. An elevated white count could result from the methylprednisone administered to the patient.

By the third hospital day, another CT scan showed a slight decrease in size of the mass-like lesion. The patient experienced left-sided headache (pain scale 9/10) the following day. His left eye was hyperemic and proptosed with a visual acuity of 20/30 – 1; right eye had a visual acuity of 20/20 J + 1. The patient was given acetazolamide 250 mg/tablet for the headache. Intraocular pressure on the left was initially at 19 mmHg and was brought down to 10 mmHg 1-hour post-acetazolamide; right eye intraocular pressure remained at 10 mmHg. Two days later, he still had a persistent headache (pain scale 9/10) for which he was given tramadol 50 mg IV. His left eye was erythematous, swollen, and proptosed with no light perception (NLP). His left pupil was fixed at 5 mm; right eye had a visual acuity of 20/20, J + 1, full extraocular movements with pupils at 2–3 mm reactive to light. On fundoscopy, the left eye had a pale retina and loss of cupping with blurring of disc borders.

By the sixth day of hospitalization, his left eye was swollen, proptosed, with NLP. Left pupil was fixed at 6 mm with negative extraocular movements. The patient was started on mannitol 150 ml every 6 hours, and underwent an emergency left orbital exploration and decompression with tumor debulking with subsequent transfer to the pediatric intensive care unit. On the following day, his headache decreased in intensity (pain scale 5/10); however, the left eye was still proptosed with NLP. A complete blood count showed a drop in white blood cells ($13.5 \times 10^9/L$) from previous count ($26.3 \times 10^9/L$), predominantly neutrophilic (85%). Magnetic resonance (MR) imaging done on the same day (refer to Fig. 1) revealed a large peripherally enhancing mass primarily located along the extraconal compartment of the left orbital cavity causing marked proptosis of the left globe. There were also multifocal cortical signal abnormalities involving the high frontoparietal regions bilaterally, associated with adjacent leptomeningeal contrast enhancement.

On the eighth day of admission, the patient still had periorbital pain (pain scale 3–4/10) with blood pressure elevations (140–150/100–110) that required clonidine and a nicardipine drip. The patient's condition failed to improve despite tumor debulking and continued antibiotics (refer to Fig. 2) the following day. He was then referred to pediatric infectious disease where a clinical diagnosis of fungal infection was made. Amphotericin B was started at 0.75 mg/kg (36 mg IV) and nicardipine drip was increased for the ongoing high blood pressure.

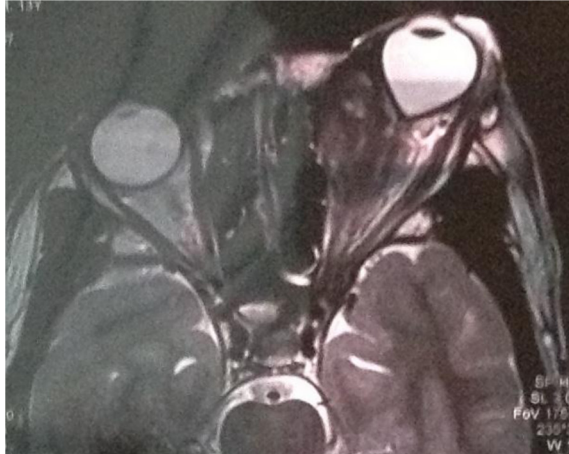


Figure 1. MRI on the seventh hospital day, first post-operative day after left orbital exploration and decompression with tumor debulking. A large peripherally enhancing mass primarily located along the extraconal compartment of the left orbital cavity causing marked proptosis of the left globe.

The patient underwent a left orbital exenteration with removal of the left eye, adnexa, and part of the bony orbit under the impression of a rapidly invasive fungal infection on his tenth day of admission. Gram stain showed positive *Mucor spp.* from the orbital mass specimen. A lumbar puncture was obtained and the cerebrospinal fluid specimen submitted on this day showed negative growth of *Mucor spp.* after 5 days.



Figure 2. The patient at the ninth hospital day, third post-operative day after left orbital exploration and decompression with tumor debulking. The patient's left eye is largely proptosed, erythematous, and has no light perception.

However, pathology results revealed filamentous, non-septated, broad fungus morphologically consistent with *Mucormycosis spp.* involving periorbital soft tissue, optic nerve, and intraocular structures. This was also associated with panophthalmitis with retinal detachment, hemorrhage, and subconjunctival hemorrhage. The tissue was also positive for necrosis and infarction.

On the thirteenth day of hospitalization, the patient had no pain in the left eye socket, the dressing was moderately soaked with serosanguinous fluid and he had a normalizing blood pressure. A complete blood count performed on Day 19 demonstrated a continued normalization of white blood cells ($12.8 \times 10^9/L$), predominantly neutrophilic (85%).

In summary, the patient was treated with left orbital exenteration and completed 26 days of amphotericin B. He made steady improvements and was discharged after 39 days in the hospital.

DISCUSSION

Mucormycosis is a life-threatening disease that usually affects patients with diabetes, prolonged corticosteroid use, hematologic malignancies, chronic renal failure, and other immunocompromised states.⁴ A study reporting the epidemiology of zygomycosis shows that the mean age of patients affected was 38.8 years, 65% male. The most common types of infection affected the sinuses (39%), pulmonary organs (24%), cutaneous (19%), and dissemination developed in 23% of cases.¹⁰

Presentation of this disease greatly varies in terms of organs affected and whether or not it would take an indolent or rapid course. In this case, the patient exhibited a rapid progression of the disease despite his previous healthy status. However, the patient was put on corticosteroids for approximately 1 month, thus contributing to immunosuppression. Rapidly progressive rhinocerebral mucormycosis has been reported after a course of prednisone therapy (40–80 mg/day) in an elderly patient with controlled diabetes,¹¹ suggesting that corticosteroids increase the risk of developing mucormycosis. Another study reported the development of *Rhizopus microsporus* infection in a patient with mild steroid-induced hyperglycemia.² It was deduced that the fungus received nourishment from elevated glucose levels in the body¹¹ supporting the prevalence of mucormycosis in patients with poorly controlled diabetes.¹² Corticosteroid treatment affects the ability of mouse bronchoalveolar macrophages to prevent the germination of spores in vitro or after in vivo infection induced by intranasal inoculation.¹³ Chronic corticosteroid based therapy therefore presents

as a risk factor by causing defects in macrophages and neutrophils and/or steroid induced diabetes.⁹

Orbital involvement results from invasion of the nasolacrimal duct spreading through the thin medial orbital wall. This usually presents with proptosis and medial rectus thickening.¹² The initial symptoms of rhino-orbito-cerebral mucormycosis are consistent with those of sinusitis and periorbital cellulitis. This may include eye and/or facial pain and facial numbness, followed by blurry vision. Other symptoms include multiple cranial nerve palsies, unilateral periorbital facial pain, orbital inflammation, eyelid edema, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache, and acute vision loss.⁹ Although this patient had minimal signs of sphenoid sinusitis, there was no break in the mucosa to indicate direct spread from the sinuses. There was no eschar or signs of fungal invasion in the nose. However, eschar is present in only 20–30% of patients.¹² It is theorized that the patient may have inhaled this ubiquitous saprophytic organism while living in a grassy rural area.

In immunocompetent patients, the nose and/or maxillary sinuses appear to be the predominant source of infection of the respiratory tract. If sporangiospores are larger than 10 μm , they may remain localized to the upper airways, giving an isolated form. Otherwise, they may colonize the distal alveolar spaces involving the pulmonary tract. Once infection has colonized the nose and paranasal sinuses, it should be promptly diagnosed and treated. If there is a delay, infection may invade the base of the skull through blood vessels, disseminating to the central nervous system, giving the rhino-orbito-cerebral form, as seen in this case.⁸ Since the mucosal epithelium and endothelium serve as effective barriers against tissue and angioinvasion, *Mucor* infection in such patients seems to be attributed to the ability of the fungus to attack the epithelium previously damaged by prior infection, cytotoxic agent, or direct trauma. It is likely that *Mucor* sporangiospores secrete several toxins or proteases that destroy endothelial cells in mucosal membranes.¹⁴

It has been hypothesized that a chronic local insult, such as chronic sinusitis, might act as a predisposing factor for possible development of *Mucor* infection in immunocompetent individuals. There is a disruption of the first-line barrier defense of upper airway caused by an impaired mucociliary clearance.⁸ In addition, patients with chronic sinusitis have a reduction in several molecules involved in the epidermal differentiation complex, such as S100 and SPINK5, which are

necessary in maintaining the barrier function of the upper airways and sinuses.¹⁵ The patient in this case showed signs of sphenoid sinusitis. It is unclear whether this was an acute or chronic insult; however, it is hypothesized that the *Mucor* infection spread to the orbital region from the sphenoid sinus.

Survival depends upon early diagnosis and adequate treatment. As the disease progresses beyond the boundaries of the sinuses, orbit, brain, skin, or lung, the prognosis worsens.¹ The earliest sign of infection is facial edema followed by proptosis, chemosis, and extraocular muscle paresis. Other manifestations include perinasal cellulitis, paresthesia, periorbital edema, mucopurulent rhinorrhea, and nasal crusting.^{6,9,10,12} Early diagnosis of mucormycosis and initiation of appropriate therapy within 5 days has a survival rate of 83% compared with a 43% survival rate at greater than 5 days.⁵ Pre-operative contrast enhanced CT is useful in defining the extent of the disease which would show edematous mucosa, fluid filling the ethmoid sinuses, and destruction of periorbital tissues and bone margins. MR imaging is useful in identifying intradural and intracranial extent of the infection. Contrast-enhanced MR imaging can also demonstrate perineural spread. However, imaging studies are not confirmatory tests for mucormycosis. Diagnosis should be made via histopathological identification of fungal tissue invasion. *Mucorales* is identified by culture and microscopic visualization of broad, non-septated hyphae.⁹

Treatment is a combination of systemic amphotericin B at the highest tolerable dose,^{1,3–5,7,10–13} orbital exenteration, and adjacent tissue debridement.^{1,4,5,7,10–13} A survival rate of 70% was attributed to cases treated with antifungal and surgical management; 61% for cases treated with amphotericin B deoxycholate only; 57% for cases treated with surgical management only; and 3% for cases that were not treated.⁸ Blood vessel thrombosis and resulting tissue necrosis prevents the penetration of the anti-fungal medications. Therefore, surgical debridement greatly improves survival.¹³

In conclusion, although mucormycosis commonly affects immunocompromised patients, there have been emerging reports of this rare disease among healthy individuals, as is the case presented here. The initial symptoms of rhino-orbito-cerebral mucormycosis are consistent with those of sinusitis and periorbital cellulitis. As the infection spreads, it can manifest as headaches, proptosis, ophthalmoplegia, acute vision loss, and multiple cranial nerve palsies.⁹ This can be a rapidly fatal infection, and timely diagnosis and aggressive treatments are therefore essential. Although

imaging studies are used to determine the extent of involvement, definitive diagnosis is done by a biopsy, which will show broad, non-septated hyphae. Mucormycosis is adequately treated with amphotericin B and surgical debridement. In retrospect, the administration of steroids during the initial presentation of the patient could have weakened the immune system and may have accelerated the rate of invasion. As presented above, the use of corticosteroids over a long period of time is a risk factor for the development of mucormycosis.

LEARNING POINTS

1. Clinical diagnosis is important because this infection can rapidly be fatal. Early diagnosis of mucormycosis and initiation of appropriate therapy within 5 days has a survival rate of 83% compared with a 43% survival rate at greater than 5 days.
2. Mucormycosis infection is most commonly seen in immunocompromised patients, but can also occur in immunocompetent individuals, and even including those on chronic steroids, with hematological malignancies, or with chronic kidney disease.
3. Although imaging can determine the extent of the infection, a confirmatory diagnosis is done with a biopsy showing broad, non-septated hyphae.
4. Judicious use of steroids is emphasized because it can accelerate the speed of invasion of mucormycosis.
5. Successful treatment of mucormycosis involves both amphotericin B and surgical debridement leading to increased survival with the combination.

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