

Review Article

An aggressive multidisciplinary approach reduces mortality in rhinocerebral mucormycosis

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Abstract

Background: Rhinocerebral mucormycosis occurs in immunocompromised hosts with uncontrolled diabetes, solid organ transplants, and hematologic malignancies. Primary disease is in the paranasal sinuses but often progresses intracranially, via direct extension or angioinvasion. Rhinocerebral mucormycosis is rapidly fatal with a mortality rate of 85%, even when maximally treated with surgical debridement, antifungal therapy, and correction of underlying processes.

Methods: We performed a retrospective chart review of patients with rhinocerebral mucormycosis from 2011 to 2014. These patients were analyzed for symptoms, surgical and medical management, and outcome. We found four patients who were diagnosed with rhinocerebral mucormycosis. All patients underwent rapid aggressive surgical debridement and were started on antifungal therapy on the day of diagnosis. Overall, we observed a mortality rate of 50%.

Results: An early aggressive multidisciplinary approach with surgical debridement, antifungal therapy, and correction of underlying disease have been shown to improve survivability in rhinocerebral mucormycosis.

Conclusion: A multidisciplinary approach to rhinocerebral mucormycosis with otolaryngology, neurosurgery, and ophthalmology, infectious disease and medical intensivists can help reduce mortality in an otherwise largely fatal disease. Even despite these measures, outcomes remain poor, and a high index of suspicion must be maintained in at-risk populations, in order to rapidly execute a multifaceted approach.

Key Words: Invasive fungus, *Mucor*, rhinocerebral mucormycosis, skull base, zygomycetes

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INTRODUCTION

Mucorales is a fungal order in the subphylum mucormycotina that can cause mucormycosis, a fulminant, opportunistic infection in immunocompromised human hosts.^[3] *Mucor* fungi and their spores are found in decaying vegetation and is ubiquitous in the soil and commonly isolated from the sinonasal cavities of healthy, immunocompetent hosts.^[8] The fungus releases spores

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that are inhaled and access the central nervous system (CNS) via the respiratory tract.^[4,8] CNS disease is the most prevalent manifestation of mucormycosis^[8] with an overall mortality of 85%.^[4]

Patients with a lapse in natural immunity, such as diabetes mellitus, hematologic malignancy, and immune suppression after organ transplantation are predisposed to *Mucor* infection.^[1,2,4,5,7-9] Because the relative incidence of fungal sinusitis is low, a high-index of suspicion must be maintained in order to secure an early diagnosis, which has been shown to improve prognoses.^[1] Rapid and extensive surgical debridement of the sinuses as well as initiation of antifungal therapy has been shown to reduce mortality.^[1,4,8] Despite these aggressive measures, overall prognosis remains bleak.

We reviewed four cases of rhinocerebral mucormycosis treated at our institution with rapid surgical and medical multidisciplinary measures, and found an overall mortality rate of 50%, with survivors living over 18 months from

the time of initial diagnosis without evidence of recurrent disease.

METHODS

We performed a retrospective chart review of the four patients with rhinocerebral mucormycosis admitted to our institution from 2011 to 2014. Their medical records were reviewed for basic demographic information, clinical presentation, exam and imaging findings, surgical procedures, medical antimicrobial therapy, and follow-up care. Due to the retrospective design of this case series, Institutional Review Board approval was not required.

RESULTS

From 2011 to 2014, four patients were admitted to the University of Arizona Medical Center with a diagnosis of rhinocerebral mucormycosis. Table 1 summarizes their clinical courses and outcomes. All four patients presented

Table 1: Patient demographics, presentation, and clinical course

| Patient | Demographics | Presentation | Exam findings | Medical history | Radiographic findings | Surgical procedures | Antimicrobial treatment | Outcome |
|---------|--------------|---|---|---|--|---|--|----------|
| 1 | 61, male | 5 weeks malaise 2 weeks lethargy 2 days ptosis and nonproductive cough | Periorbital edema Ptosis Ophthalmoplegia Altered mental status | Type 2 diabetes Hypertension Hyperlipidemia | Bifrontal cerebritis Internal carotid artery occlusion Anterior skull base infiltration Orbital apex infiltration | Sinus debridement Bedside sinus debridement Sinus debridement #3 | Amphotericin B, lipid complex | Deceased |
| 2 | 76, male | 2 weeks Periorbital cellulitis Facial edema Decreased visual acuity Hearing loss Diabetic ketoacidosis | Periorbital cellulitis Decreased visual acuity Hearing loss Facial edema | Type 2 diabetes Methicillin - sensitive <i>Staphylococcus aureus</i> Bacteremia Hypertension Gout | Frontal sinus and orbit disease Cavernous sinus and ophthalmic vein thrombosis | Sinus debridement Sinus debridement #2 Orbital exenteration | Liposomal amphotericin B | Living |
| 3 | 29, female | 2 weeks frontal headache Photophobia Orbital pain | Orbitofrontal tenderness | Type 1 diabetes Lupus nephritis Bone marrow transplant Renal transplants CMV viremia Hypertension Coronary artery disease | Pansinusitis | Sinus debridement Sinus debridement #2 | Amphotericin B, lipid complex Posaconazole | Living |
| 4 | 53, female | Orbital pain 3 days epistaxis, headache, lethargy, nausea | Blindness Ophthalmoplegia Periorbital edema Ptosis V2-V3 distribution numbness | Type 2 diabetes Renal transplant Hypertension CMV viremia Hyperlipidemia Obesity Retinopathy | Sinusitis with orbital infiltration | Bedside sinus biopsy Sinus debridement Orbital exenteration Sinus debridement #2 Sinus debridement #3 Skull base debridement Sinus debridement #4 | Amphotericin B, lipid complex Micafungin Posaconazole Isavuconazole | Deceased |

CMV: Cytomegalovirus

with some degree of headache, facial and orbital pain, with ophthalmologic symptoms ranging from pain, ptosis, and proptosis to ophthalmoplegia and blindness. All patients had a diagnosis of diabetes mellitus, while half also were immunosuppressed following renal transplants. The patients had magnetic resonance imaging [Figure 1] and computed tomography findings consistent with fulminant sinusitis, but fungal, specifically *Mucor*, sinusitis was diagnosed based on histopathology.

The patients all underwent several sinus debridements with otolaryngologists with intraoperative neurosurgical collaboration, and then subsequently were treated with amphotericin B. Half of the patients also underwent orbital exenteration of the infiltrated globe with ophthalmology. Ultimately 50% of the patients succumbed to their disease. Overall time to diagnosis was an average of 7 days. There was an average of four surgical debridements in the four patients. Both antifungal therapy and surgical debridement were launched on the day of diagnosis, and average prognosis after the presentation was approximately 51 days in the two patients who died [Table 2]. The other two patients have survived 18–24 months at the time of publication.

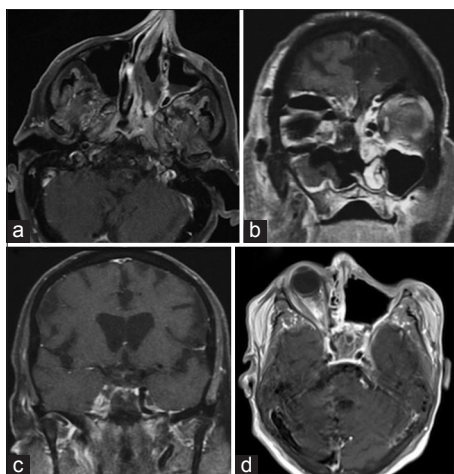


Figure 1: Axial and coronal T1-weighted, gadolinium enhanced, magnetic resonance imaging showing (a and b) sinonasal and (c and d) cavernous sinus invasive fungal infiltration

DISCUSSION

Rhinocerebral mucormycosis often occurs in patients who are immunocompromised, most commonly secondary to hematologic malignancy, diabetes mellitus, or iatrogenically following organ transplantation.^[1,4,8] Patients with diabetes mellitus are predisposed to the rhinocerebral variant of mucormycotic infection.^[1,4,7,8] With the increasing prevalence of diabetes in the US and around the world and ubiquitous nature of the filamentous fungi, an increased incidence of rhinocerebral mucormycosis, is expected.^[1,5,7]

It is essential for the clinician to maintain a high index of suspicion in populations at risk, as early diagnosis can be life-saving.^[4] Clinical symptoms usually begin as nonspecific malaise and headache, progressing to acute sinusitis, facial edema and pain, orbital symptoms, rhinorrhea, and eventual ophthalmoplegia, blindness, and lethargy.^[8] This can make differentiation from the more common and less morbid bacterial sinusitis challenging, and often these patients fail antibiotic treatment prior to histopathologic diagnosis of fungal sinusitis and commencement of appropriate antimicrobial therapy.^[1]

Mucor sinusitis can rapidly progress from isolated sinus involvement to direct orbital extension leading to pain, ptosis, proptosis, ophthalmoplegia, and eventual blindness.^[1,8] Intracranial extension occurs in 80% of cases and causes encephalopathy, cerebritis, and angioinvasion leading to cavernous sinus thrombosis and cerebrovascular accidents.^[2,5,8] Early diagnosis and subsequent treatment has been shown to portend higher survivability.^[1,4,8]

A review of 929 reported cases of mucormycosis showed survivability was only 3% in patients who were untreated, none of whom had the rhinocerebral variant of the disease.^[7] The mainstay of treatment remains aggressive surgical debridement, antifungal therapy, and reversal of underlying predisposing factors. Surgical debridement is often performed primarily by otolaryngologists with the involvement of ophthalmologists and neurosurgeons for orbital and intracranial extension, respectively. Often multiple, progressively aggressive debridements are required. Pharmacologic treatment should also be

Table 2: Timing of presentation and treatment

| Patient | Demographics | Symptom onset to presentation (days) | Presentation to UMC from OSH (days) | Time to diagnosis* (days) | Time to start of antifungal therapy** (days) | Surgical procedures | Time to first surgery** (days) | Time to death* (days) |
|---------|--------------|--------------------------------------|-------------------------------------|---------------------------|--|---------------------|--------------------------------|-----------------------|
| 1 | 61, male | 35 | 1 | 2 | 0 | 3 | 0 | 13 |
| 2 | 76, male | 14 | 15 | 15 | 0 | 3 | 0 | - |
| 3 | 29, female | 15 | - | 10 | 0 | 2 | 0 | - |
| 4 | 53, female | 3 | - | 2 | 0 | 7 | 0 | 88 |
| Average | | 17±13 | 8±10 | 7±6 | 0 | 4±2 | 0 | 51±53 |

*From presentation to medical care (including OSH), **From diagnosis. OSH: Outside hospital, UMC: University Medical Center

commenced rapidly with intravenous amphotericin B. Specifically, liposomal formulations of amphotericin B are preferred to classic preparations of the antifungal agent as they have more favorable side effect profiles and are far more tolerable in these already systemically compromised patients. Liposomal amphotericin B has also been shown to have fewer adverse reactions than amphotericin B lipid complex, though the latter is much less costly and, therefore, more readily available, though highly variable between organizations. Aside from discontinuation of therapy from intolerable side effects, no difference has been shown in efficacy between the three formulations of the drug.^[6] Some studies have shown that addition of posaconazole as a second line agent might improve survivability in refractory cases.^[9]

The key to management of this rapidly progressive fulminant disease is swift commencement of multidisciplinary treatments. These patients should be treated in tertiary care centers with the availability of otolaryngology, ophthalmology, neurosurgery, and infectious disease specialists so as to execute efficient and expeditious treatment. We feel that the rapid initiation of an aggressive multifaceted surgical and medical treatment regiment can confer an improved overall prognosis, and propose treating rhinocerebral mucormycosis as any other neurosurgical emergency.

CONCLUSION

Given the high morbidity and mortality of invasive rhino-orbito-cerebral fungal infections, a comprehensive and efficient multidisciplinary approach must be executed. This includes early and aggressive surgical debridement of disease in the paranasal sinuses, foramina of the skull base, and intracranial components, as well as

initiation of a robust anti-fungal medical regimen with close follow-up. Despite aggressive measures, the overall mortality of rhinocerebral mucormycosis remains high, and future studies must focus on avenues of securing an early diagnosis, enacting aggressive multidisciplinary management, and pursuing new avenues of treatment.

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Conflicts of interest

There are no conflicts of interest.

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