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Treatment and Survival Outcomes in Rhino-Orbital Mucormycosis with and without Orbital Exenteration: A Retrospective Case Series and Literature Review

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Abstract: Rhino-orbital mucormycosis (ROM) is a life-threatening, fungal infection, primarily affecting immunocompromised patients. The role of orbital exenteration in treatment remains debated, especially regarding its impact on survival outcomes. This case series presents two patients from our Ophthalmology department and compares them with eight cases from the literature, focusing on treatment outcomes and survival rates. We specifically explore the impact of orbital exenteration and other management strategies. The analysis reveals that survival outcomes are closely linked to the timely initiation of antifungal therapy, the patient's underlying conditions, and the extent of orbital involvement at the time of diagnosis. Our findings, in line with the literature, show that early-stage ROM can be treated successfully with less invasive methods, while advanced cases may require orbital exenteration. The need for exenteration should be evaluated on a case-by-case basis, with early detection and appropriate antifungal treatment being critical factors for survival. This study highlights the importance of early diagnosis and individualized treatment plans, emphasizing that while orbital exenteration may improve survival in severe cases, less invasive interventions should be considered for less advanced ROM. Further research and standardized guidelines are needed to refine treatment strategies.

Keywords: *Mucorales*, orbital apex syndrome, ORBITAL exenteration, rhino-orbital mucormycosis, surgical debridement

Introduction

Mucormycosis refers to a rare and severe opportunistic fungal infection caused by species belonging to the order *Mucorales*.[1,2] The incidence of fungal infections is currently increasing.[1] The main Fungi genera responsible for mucormycosis in humans are *Rhizopus spp., Mucor spp*. and *Absidia spp*., with *Rhizopus arrhizus* the most prevalent globally.[3–5]

The disease has a global distribution, with its incidence increasing as the population of susceptible and immunosuppressed individuals continues to expand.[2] This rising trend underscores the growing significance of understanding and addressing this dangerous fungal infection.[6–12] Globally, the incidence rate of mucormycosis varies from 0.005 to 1.7 per a million population.[13] Reliable national incidence rates of mucormycosis in Israel are currently unavailable.[14] However, several single-center reports suggest that tertiary medical centers typically manage approximately 1 to 4 cases per year.[15,16] Mucormycosis is characterized by angio-invasion, which is associated with high morbidity and mortality.[3,4] The term Mucormycosis encompasses various clinical forms of the disease, including rhino-orbital-cerebral (ROCM), pulmonary, disseminated, cutaneous, and gastrointestinal mucormycosis. Among these, ROCM is the most commonly encountered form.[1,2]

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These opportunistic saprobic fungi are ubiquitous in the environment, and are routinely cultured from the nasal and oral cavities of asymptomatic individuals. Upon spore formation, these fungi become airborne and can be inhaled, allowing entry through the nasal mucosa.[17] In immunocompetent individuals, these spores are typically cleared by the host's phagocytic immune response. However, in immunocompromised patients, the spores may germinate, forming hyphae that enable the fungi to rapidly invade host tissues.[18] This invasive process primarily affects the vasculature, where hyphal growth along the blood vessel's elastic lamina induces endothelial damage and promotes the formation of thrombi.[19] This thrombosis leads to arterial occlusion, tissue ischemia, infarction, and the characteristic black necrotic eschar observed in mucormycosis.[18] Mucormycosis should be strongly suspected in individuals receiving immunosuppressive therapies, including antineoplastic agents or prolonged corticosteroid treatment, as well as in those with predisposing conditions such as diabetes mellitus, diabetic ketoacidosis, alcoholism, acquired immunodeficiency syndrome (eg AIDS), or hematologic malignancies.[17,20–24] Nevertheless, it is noteworthy that mucormycosis have also been documented in immunocompetent hosts, as evidenced by existing literature.[25–27]

Clinical suspicion should be high in patients presenting with facial pain, periorbital swelling, nasal congestion, or visual disturbances, particularly when accompanied by necrotic eschars or cranial nerve palsies. Early diagnosis relies on a combination of clinical evaluation, imaging and histopathology. Contrast-enhanced MRI or CT scans are essential for assessing the extent of sinus, orbital, and intracranial involvement. Nasal endoscopy can reveal mucosal necrosis or discoloration and facilitates targeted biopsies. Histopathological examination of tissue typically shows broad, ribbon-like, pauci-septate hyphae with right-angle branching and vascular invasion. Fungal cultures and molecular techniques, such as PCR, may assist in species identification, although their sensitivity and availability vary. A multidisciplinary diagnostic approach is critical to enable early detection and timely intervention.[28]

The management of mucormycosis requires a comprehensive approach, combining antifungal therapy and surgical intervention.[29] Amphotericin B remains the cornerstone of treatment for systemic mucormycosis.[30] As medical therapy alone seldom achieves a cure; it must be paired with surgical debridement to effectively remove the fungus from necrotic tissues. In cases of rhino-orbital mucormycosis, the standard treatment involves intravenous amphotericin B, extensive sinus debridement, and, in certain cases, orbital exenteration to prevent the infection from spreading intracranially.[18]

Following the COVID-19 pandemic, a notable rise in ROM cases has been observed, likely driven by steroid use, diabetes, and immune dysregulation. This surge, alongside evolving treatment approaches, has underscored the need to reassess management strategies and survival outcomes. Our objective was to compare survival outcomes between patients who received medical treatment alone and those who underwent combined medical and surgical interventions, with or without orbital exenteration. By including a diverse range of cases, we aimed to explore how varying risk factors and comorbidities influence clinical decisions and outcomes in ROM management.

Cases Presentation

Case 1

A 69-year-old male, with a recent history of kidney transplantation due to end-stage renal disease (ESRD), was admitted to the emergency department with complaints of fever, general weakness, and painless swelling of the left orbit. His medical history included type 2 diabetes mellitus, hypertension, and hyperlipidemia. At the time of admission, he was in the post-transplant recovery phase and receiving immunosuppressive therapy. Upon examination, significant orbital involvement was noted, including proptosis, ptosis, mydriasis, and complete ophthalmoplegia in the left eye (Figure 1). Additionally, a necrotic black lesion was observed on the dorsum of the tongue (Figure 2). The lesions depicted in the figures display the characteristic features of tissue necrosis associated with mucormycosis. Initial laboratory evaluation revealed markedly elevated inflammatory markers, with a C-reactive protein (CRP) of 126 mg/L (normal <5 mg/L), erythrocyte sedimentation rate (ESR) of 78 mm/hr (normal <20 mm/hr), and a white blood cell count of 18.5×10^9/L with neutrophilic predominance consistent with an acute inflammatory or infectious process.

A chest X-ray revealed bilateral interstitial infiltrates (Figure 3). Orbital and cranial MRI showed enhancement around the left optic nerve, along with two subacute lacunar infarcts and patchy white matter lesions, suggestive of possible angioinvasive spread. Given the patient's clinical presentation and his immunocompromised state, invasive fungal infection, specifically

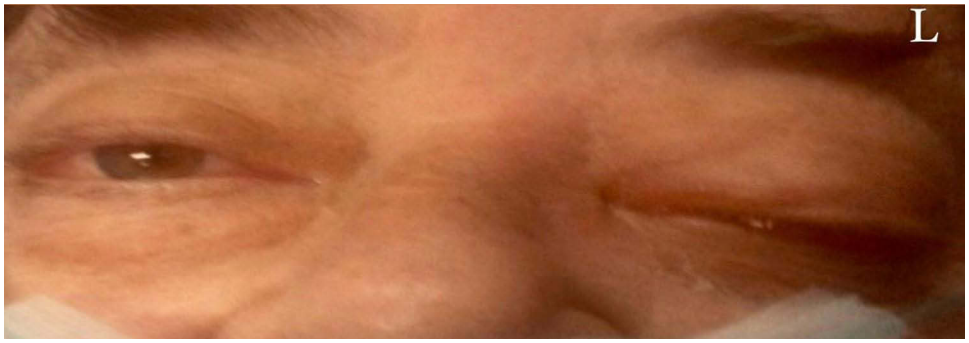

Figure 1 Clinical image of the patient (case 1) with confirmed rhino-orbital mucormycosis, demonstrating advanced involvement of the left periorbital region. There is marked swelling of both the upper and lower left eyelids, accompanied with significant ptosis that nearly obscures the palpebral fissure. Erythema and edema are evident, with distortion of normal periocular anatomy. The right eye remains relatively unaffected. The pronounced asymmetry and severity of left-sided changes are consistent with extensive local fungal invasion, characteristic of mucormycosis in immunocompromised individuals.

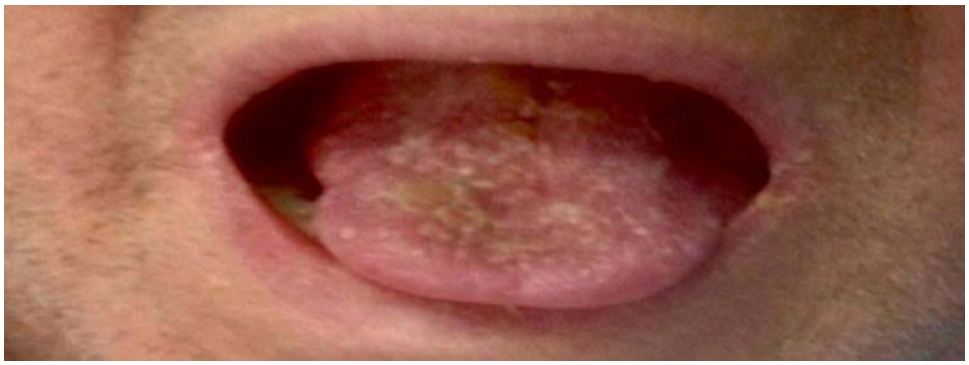

Figure 2 Clinical image (case 1) demonstrating the dorsum of the tongue with irregular, patchy areas of dark brown to black discoloration and surface coating. The lesion exhibits a heterogeneous texture with central pigmentation and surrounding erythematous mucosa, raising concern for possible fungal involvement or ischemic changes in the clinical context described.

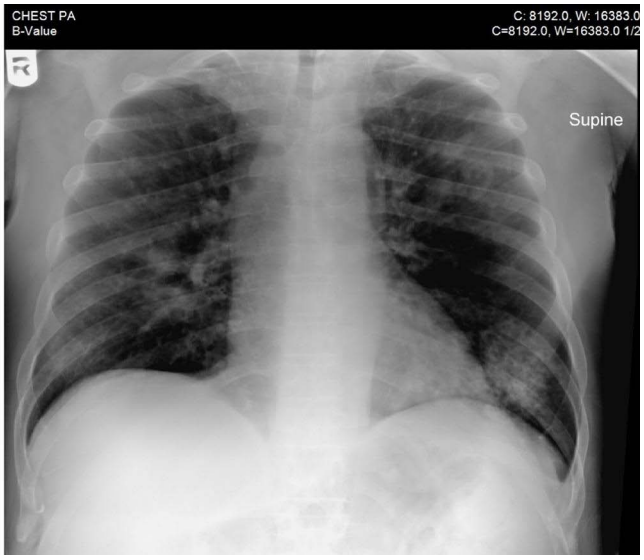

Figure 3 Portable chest radiograph (PA view, supine) of the case 1, revealing bilateral diffuse interstitial infiltrates. The lung fields exhibit a reticulonodular pattern with increased interstitial markings, more prominent in the lower and mid zones, consistent with an interstitial process. Cardiac silhouette and mediastinal contours appear within normal limits. No gross pleural effusion or pneumothorax is identified.

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mucormycosis, was highly suspected. A biopsy of the nasal sinuses was performed. Histopathological examination using hematoxylin and eosin (H&E) staining, followed by Grocott's methenamine silver (GMS) staining, revealed broad, non-septate hyphae with right-angle branching morphologically consistent with *Mucorales*.

The patient was promptly started on intravenous liposomal amphotericin B (100 mg daily) and after multidisciplinary consultation, underwent urgent orbital exenteration due to extensive orbital involvement. Despite aggressive antifungal therapy and surgical intervention, the infection rapidly progressed. The patient's condition deteriorated due to multi-organ failure and he succumbed to the illness nine days after admission.

Case 2

A 75-year-old female with a medical history of diabetes mellitus, hypertension, and hyperlipidemia presented to the emergency department with complaints of headache and syncope, without any preceding head trauma. Initial laboratory tests showed leukocytosis (WBC: 14.8 $\times 10^9$/L), and chest X-ray revealed bilateral lung shadowing. Based on her clinical symptoms and examination, she was diagnosed with pneumonia and sinusitis. The patient was treated empirically with intravenous ceftriaxone (2 g/day) and azithromycin (500 mg/day) for five days which led to clinical improvement and was subsequently discharged from the hospital. Two weeks after, the patient returned to the emergency department with a three-day history of blurred vision in the left eye alongside persistent headaches. Ophthalmic examination revealed proptosis, ptosis, and complete ophthalmoplegia in the left eye, consistent with orbital apex syndrome (Figure 4). Cranial and orbital computed tomography (CT) scan demonstrated opacification of the left ethmoid and maxillary sinuses, with associated extension into the medial aspect of the left orbit (Figure 5). The patient underwent functional endoscopic sinus surgery (FESS), and a biopsy was performed from the sphenoid sinus. However, the initial biopsy failed to confirm the presence of mucormycosis.

Due to persistent symptoms and increasing suspicion of invasive fungal disease, a chest CT scan was performed and revealed bilateral interstitial infiltrates, suggestive of pulmonary mucormycosis. Despite the negative biopsy, the patient's clinical condition continued to deteriorate, prompting further investigation. A follow-up orbital CT showed focal enhancement within the intra-conal portion of the left orbital apex, raising further suspicion of a fungal infection. Given the radiological findings and high clinical suspicion, the patient underwent additional surgery, which included debridement of the left sinuses and orbital exenteration. During this procedure, a second biopsy taken from the infected orbital tissues revealed broad, non-septated, ribbon-like hyphae with right-angle branching, consistent with mucormycosis. Histopathological examination revealed broad, non-septated, ribbon-like hyphae with right-angle branching, consistent with mucormycosis. The fungal elements were identified using hematoxylin and eosin (H&E) staining, and further confirmed by Grocott's methenamine silver (GMS) stain. These findings were diagnostic of an invasive fungal infection caused by *Rhizopus arrhizus*. The patient was immediately started on antifungal therapy, including intravenous liposomal amphotericin B (5 mg/kg/day) and anidulafungin (100 mg/day). During the orbital exenteration, a cerebrospinal fluid (CSF) leak was identified, likely due to the proximity of the procedure to the Dural structures

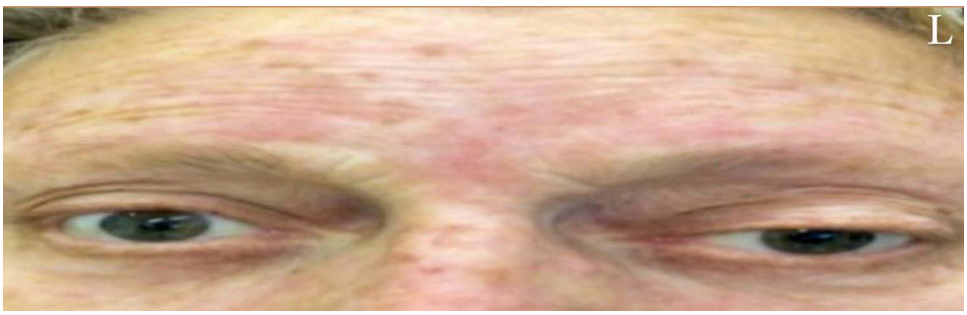

Figure 4 Clinical image of case 2 diagnosed with rhino-orbital mucormycosis. The left eye demonstrates classic signs of orbital involvement, including marked periorbital edema, ptosis, conjunctival injection, and proptosis, in contrast to the unaffected right eye. Erythema and mottling over the nasal bridge and glabellar region suggest cutaneous extension and angioinvasive fungal infiltration. Subtle asymmetry in ocular alignment and lid positioning, more pronounced on the left, raises suspicion for early cranial nerve involvement particularly of the oculomotor and abducens nerves. These findings reflect the fulminant and rapidly progressive nature of mucormycosis.

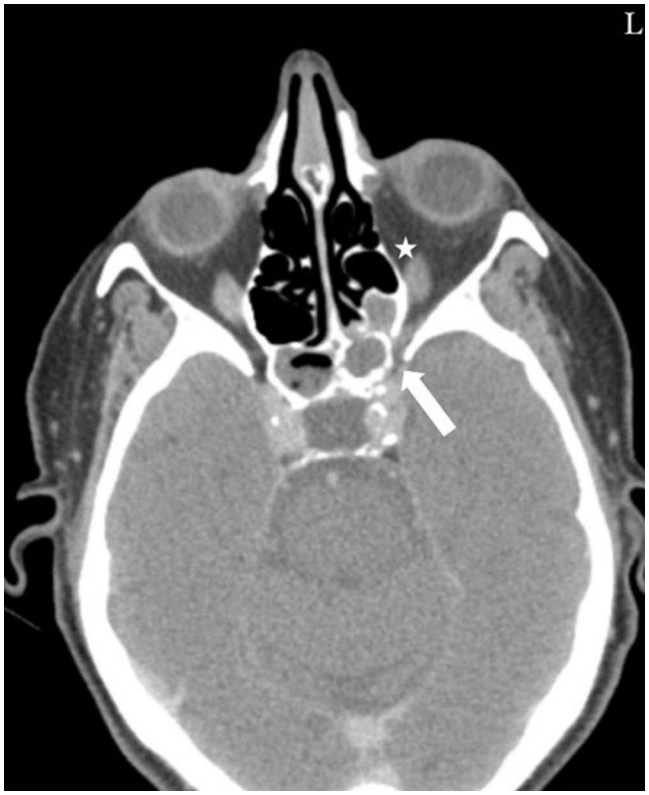

Figure 5 Axial non-contrast CT scan of the orbits and paranasal sinuses of case 2 with rhino-orbital mucormycosis. The scan demonstrates opacification and mucosal thickening of the left ethmoid and maxillary sinuses, with soft tissue attenuation extending into the medial aspect of the left orbit (white arrow) through an area of bony erosion of the lamina papyracea (white star). Mild proptosis of the left globe is evident, along with obliteration of adjacent fat planes and stranding of the intraorbital fat, consistent with early orbital involvement. The right globe is unremarkable, maintaining normal position and contour. The sphenoid sinuses are partially aerated, with subtle mucosal thickening, suggesting early involvement without full opacification at this level.

around the orbital apex. The patient was promptly treated with intravenous ceftriaxone (2g twice daily) for 10 days to prevent secondary central nervous system infection, such as meningitis or encephalitis.

Literature Review

Cases from published reports were identified through a PubMed search, limited to articles published in English between 2021 and 2025 using the keywords: "rhino-orbital mucormycosis", "ROM", "orbital involvement", and "mucormycosis treatment." The selected time frame focused on the period following the COVID-19 pandemic, when the incidence of mucormycosis notably increased. This shift in prevalence and the evolving treatment approaches are crucial for understanding the role of surgical interventions and survival outcomes. The selection of cases was based on specific criteria. Inclusion criteria required biopsy-confirmed mucormycosis with radiologically confirmed orbital involvement, detailed descriptions of treatment approaches (including surgical reports where applicable), and English-language reports. Exclusion criteria included terminally ill patients or those with insufficient clinical or radiological data.

We deliberately selected a diverse range of patients for this case series, representing varying ages, demographics, and clinical presentations. This diversity aimed to capture insights into non-classic ROM cases, highlighting how different immunocompromised states, predisposing risk factors, and comorbidities influence decisions surrounding orbital exenteration. The cases were selected to represent both patients with minimal comorbidities and those with more complex risk profiles, offering a comprehensive understanding of the diverse clinical presentations of ROM. This selection also aimed to evaluate the effectiveness of various antifungal treatments and to assess the role of surgical interventions, particularly in managing severe, advanced cases, across a wide range of patient scenarios.

In this case series, we present 10 patients diagnosed with ROM. Table 1 summarizes patient demographics, clinical presentation, diagnosis and outcome from published reports. The majority of patients (eight out of ten) were

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Table 1 Overview of Patient Demographics, Clinical Presentation, Diagnosis, Treatment and Outcomes From Published Reports

Reference	Age, Gender	Underlying conditions	Symptoms	Diagnosis	Treatment	Outcome
Tsisar et al, 2025[31]	20 Male	Longstanding poorly control-led DM type 1 (HbA1c 9.7% at admission)	Facial swelling, propto-sis, blurred vision in the left eye, facial pain, na-sal obstruction, purulent rhinorrhea, epistaxis	Sinus and orbital CT scan findings: dif-fuse densification of left intraorbital adi-pose tissue, thickened inferior rectus muscle, inflammatory process in fron-tal, maxillary, and sphenoid sinuses Histology and microbiological studies: *Rhizopus arrhizus* complex	Liposomal amphotericin B (10 mg/kg/day), Isavucona-zole, surgical debridement of necrotic tissue, hyperba-ric oxygen therapy	Clinically stable, positive evolution, suppressive therapy with Isavucona-zole for over 2 years
Tuo et al, 2023[32]	43 Male	DM type 2	Fever, general malaise, nasal congestion, pain in left ocular and left orbitofrontal region ra-diating to the occipital region, facial cellulitis, black eschars and ne-crotic ulcers on left na-sal alar, white purulent spots on left palate	Sinus and orbital CT scan findings: scan showed irregular swelling on the left side of the face and maxillary sinus along with left ethmoid, maxillary, and sphenoid sinusitis. Chest CT scan re-vealed a 20 mm high-density nodular shadow in the upper lobe and a 30 mm multi-density mass shadow in the lo-wer lobe of the right lung	Intravenous liposomal amphotericin B (70 mg/day), oral Posaco-conazole (400 mg bid), facial debridement.	Improved general condition, discharged after 3 weeks
Godinho et al, 2021[33]	20 Female	Poorly control-led diabetes	Sudden headache, pain-ful right eye, hypoesthe-sia of right hemi-face, vomiting, proptosis, pto-sis, fixed mydriasis, oph-thalmoplegia, loss of right nasolabial fold, vi-sual acuity reduction (light perception - OD vs 20/20 - OS)	Laboratory findings: Leukocytosis and Diabetic ketoacidosis. Biopsy and my-cobacterial study revealed *Mucorales spp*. Sinus and orbital CT scan findings: fil-ling of right sphenoidal, ethmoidal, and maxillary sinus, with ipsilateral extraco-nical extension, abscess in the right hemiface extending to the apex of the orbit. Further CT showing expansion of the abscess with intra- and extraconi-cal components	Amphotericin B, hyperbaric oxygen surgical interventions: un-ciformectomy, maxillary an-trostomy, endoscopic eth-moidectomy, orbital explo-ration, orbitotomy, debride-ment and exenteration.	Patient survived with cured infection with good general condition at 1-year follow-up

Dhiyantari et al, 2024[34]	22 Male	Otherwise healthy, no history of dia-betes or immu-nodeficiency	Open wound at inner corner of right eye, right facial protrusion, thick yellowish fluid secretion, pain in right periorbital area radiating to the head, no light perception or ocular motility in right eye	Orbital CT scan findings: orbital celluli-tis and proptosis, 2.9 cm of right ocular bulb, cutaneous-subcutaneous abscess Biopsy and histology: ribbon-like hy-phae with pauciseptate, 90° branching – *mucoraceae spp*. family	Debridement surgery with Weber-Ferguson techni-que, exenteration of right orbital tissue, Amphotericin B (50 mg/ day for 5 weeks), Itraconazole (200 mg q 8 hours for 6 months)	Significant improvement after surgery and anti-fungal treatment, resolu-tion of infection, no re-currence at 6-month follow-up, maxillary sinus fistula present
Farojov et al, 2016[35]	24 Female	Acute liver fai-lure due to acute Budd-Chiari syndro-me, liver trans-plant recipient	Swelling and pain at left side of face and eye, necrotic tissue in hard palate, fever, visual loss in the left eye	Sinus and orbital CT scan findings: left orbital proptosis, inflammatory chan-ges in retro-orbital space, necrosis in inferior rectus muscle, abscess forma-tion in maxillary sinus and retro-orbital space Biopsy and histology: broad, ribbon-like, septate hyphae suggesting mucormycosis	Amphotericin B (3 mg/kg/ day, increased to 8–10 mg/ kg/day), debridement sur-gery (left partial maxillecto-my), orbital enucleation, sinus debridement	Significant improvement post-surgery, complete resolution of infection, permanent visual loss in left eye, patient stable at 5-year follow-up, no recurrence, stable liver function, and discharged after 93 days
Chandran et al, 2024[36]	62 Female	Poorly control-led diabetes, hypertension, treated cervi-cal cancer	Sudden onset of painful visual loss in the right eye, proptosis, redness, ptosis, NLP in right eye, swollen optic disc, cherry red spot at macula	Sinus and orbital CT scan findings: orbital cellulitis, sinusitis Facial and orbital MRI findings: invasive sinusitis extending into right pterygopalatine fossa, no intraorbital or intracranial involvement, sub-periosteal abscess with orbital extension	IV Ceftriaxone (for orbital cellulitis), IV Amphotericin B (for fungal sinusitis), en-doscopic debridement, right subtotal orbital exentera-tion, Posaconazole (oral for 6 months)	Good recovery, no recurrence at 1-year follow-up, awaiting ocular prosthesis and undergoing cosmetic rehabilitation

(*Continued*)

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Table 1 (Continued).

Reference	Age, Gender	Underlying conditions	Symptoms	Diagnosis	Treatment	Outcome
Siriwardena et al, 2024[37]	35 Female	Otherwise healthy, diagnosed with AML, under-going chemo-therapy (Flu-darabine and Cytarabine re-gimen for resi-dual disease)	Severe right-sided hea-dache, pain in right ear, mild right eye proptosis, right eye blind-ness, res-triction of medial eye movement, blood-stai-ned discharge from right nostril	Sinus X-ray findings: bilateral haziness in maxillary sinuses Sinus and orbital CT scan findings: Enlarged lacrimal gland (extra-medullary AML deposit), proptosis, mucosal disease in bilateral sphenoid and maxillary sinuses MRI: Bilateral pan-sinusitis with right intra-orbital extension, optic nerve compression FESS with biopsy performed: necrosis of nasal septum and inferior turbinate. Biopsy: Fungal infection consistent with *Rhizopus spp*. isolated in fungal culture	IV liposomal amphotericin B (5 mg/kg/day) for six weeks. IV amphotericin continued weekly during chemothera-py	Resolution of proptosis and ophthalmoplegia. Persistent right eye blindness due to optic nerve damage. Regular follow-ups with ENT and Oncology teams. Clini–cally asymptomatic des-pite right eye blindness
Siriwardena et al, 2024[37]	42 Male	AML, under-going induc-tion chemothe-rapy with Dau-norubicin and Cytarabine.	Right-sided headache, facial swelling, pares-thesia, right eye proptosis	Sinus and orbital CT scan findings: sinusitis of the right-side maxillary and right-side ethmoid sinus with involvement of the inferior part of orbital fossa through eroded orbital floor causing proptosis FESS: necrotic debris in the right-side maxillary sinus and inferior orbital sinus were removed and samples were negative by fungal culture	IV liposomal amphotericin B (5 mg/kg/day) for 6 weeks, FESS (2 times)	Clinical improvement, resolution of headache, no visual impairment or ophthalmoplegia, successful continuation of chemotherapy

Abbreviations: DM, Diabetes Mellitus; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; FESS, Functional Endoscopic Sinus Surgery; IV, Intravenous; NLP, no light perception; OD, Right Eye; OS, Left Eye; AML, Acute Myeloid Leukemia.

immunocompromised due to underlying conditions such as acute myeloid leukemia (AML), hematopoietic stem cell transplantation (HSCT), poorly controlled diabetes, post-liver transplantation, and post-COVID steroid use. These conditions create a susceptibility to opportunistic infections, including mucormycosis.[17,20–24] The clinical presentation of ROM is often marked by several common symptoms. Proptosis, which occurred in 80% of the cases, is a hallmark of orbital involvement and was the most frequently observed symptom. Other common findings included ptosis, visual impairment, and ophthalmoplegia, which were more prevalent in patients with advanced disease affecting the orbital apex or optic nerve. Additionally, 70% of the patients experienced headaches, often resulting from sinusitis or orbital mass effects. Facial swelling and blood-tinged nasal discharge were also noted in six of the ten patients, with these symptoms being more frequent in those with significant sinus involvement.

While most of the patients in our case series presented with classic signs of rhino-orbital mucormycosis, a few exhibited atypical clinical features, which presented diagnostic challenges. These atypical presentations underscore the importance of maintaining a high index of suspicion for ROM, particularly in immunocompromised individuals, even when classic symptoms are absent. Case 2 describes a 75-year-old female initially who presented with vague, nonspecific symptoms, such as headache and syncope, without the prominent orbital involvement typically seen in ROM. Only two weeks later, when she presented with the classic signs of orbital apex syndrome (OAS), characterized by proptosis, ptosis, ophthalmoplegia, loss of corneal sensitivity, and facial numbness, that the diagnosis became clearer, as outlined in the literature.[24] The delay in recognizing orbital involvement complicated the timely diagnosis, ultimately contributing to an unfavorable outcome. Similarly, in Case 8, a 42-year-old female with AML presented with symptoms suggestive of acute central retinal artery occlusion (CRAO).[36] A dilated fundus examination revealed a swollen optic disc and a cherry red spot at the macula, which are hallmark signs of CRAO.[38] This complication, although rare in mucormycosis with an incidence of 16% to 20%,[39] added complexity to the diagnosis. Despite the presence of typical ROM symptoms, the CRAO presentation initially misled the clinicians. Literature supports the notion that sudden unilateral amaurosis can be an early manifestation of ROM.[40] The pathophysiology behind this presentation suggests that patients with rhino-orbital mucormycosis and CRAO may have a severe hypercoagulable and hyper-inflammatory state. This pro-thrombotic condition, combined with the extent of angio-invasive mucormycosis, likely contributes to the disease's severe clinical manifestations.[41] These atypical clinical features highlight the importance of heightened awareness for rhino-orbital mucormycosis, especially when symptoms deviate from the classic presentation. Early recognition and prompt intervention remain critical in improving outcomes, particularly in immunocompromised patients.

Table 2 summarizes the treatment approach and outcomes for each case with ROM, focusing on the role of orbital exenteration and timing of treatment initiation. The management of ROM in this case series primarily involved Amphotericin B therapy, complemented by surgical interventions such as debridement and orbital exenteration, in

Table 2 Overview of the Treatment Approach and Outcomes Highlighting the Role of Orbital Exenteration and Timing of Treatment Initiation

Case No.	Time for treatment initiation	Orbital Exenteration	Outcomes
Cases from our department			
1	Shortly after signs and symptoms appeared	Yes	Died
2	After two weeks following the admission	Yes	Died
Cases from published reports			
3 (2025)[31]	Delayed (symptoms present for 5 months)	No	Survived
4 (2023)[32]	Three days following signs and symptoms	No	Survived
5 (2021)[33]	20 days following signs and symptoms	Yes	Survived
6 (2024)[34]	Thick yellowish fluid oozing from the open wound 5 months before admission. With two weeks of ocular manifestations before admission	Yes	Survived

(*Continued*)

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Table 2 (Continued).

Case No.	Time for treatment initiation	Orbital Exenteration	Outcomes
7 (2016)[35]	Shortly after signs and symptoms appeared	Yes	Survived
8 (2024)[36]	Three days following signs and symptoms	Yes	Survived
9 (2024)[37]	Shortly after signs and symptoms appeared	No	Survived
10 (2024)[37]	Shortly after signs and symptoms appeared	No	Survived

accordance with standard treatment protocols. However, clinical outcomes showed considerable variability, influenced by factors such as the timing of diagnosis, the extent of surgical intervention, and the patient's underlying health conditions. The data clearly indicate that orbital exenteration plays a crucial role in patient survival. Among the patients who underwent orbital exenteration (cases 1, 2, 5, 6, 7, and 8), the majority survived, suggesting that a combination of surgical intervention, antifungal therapy, and debridement contributes to better outcomes in severe cases.[33–36] Nevertheless, despite the presence of orbital exenteration, our two patients (cases 1 and 2) unfortunately passed away. These outcomes underscore the importance of early intervention and timely initiation of antifungal treatment as critical factors influencing prognosis. Rapid initiation of treatment remains essential for improving survival chances.

In contrast, some patients who did not undergo orbital exenteration (cases 3, 4, 9, and 10) survived, indicating that survival is possible without radical procedure when treatment is started promptly.[31,32,37] For instance, Case 4, whose treatment was initiated just three days after symptom onset, and Case 9, whose antifungal therapy was initiated soon after diagnosis, both had favorable outcomes despite the absence of orbital exenteration.[32,37] A key observation from the data is that the time to treatment initiation appears to be a critical determinant of survival. Both patients who passed away experienced delays in treatment initiation, with therapy beginning only after significant disease progression. This highlights the importance of early antifungal therapy and surgical debridement in improving survival outcomes. Notably, the absence of orbital exenteration in some cases did not preclude survival, suggesting that with appropriate management, including timely antifungal therapy and regular debridement, survival can be achieved without the need for radical surgery.

An interesting finding was in case 7, where exclusive Amphotericin B treatment, without any surgical intervention, led to a positive outcome.[35] This raises the possibility that in certain cases, particularly when the disease is less advanced or diagnosed early, antifungal therapy alone may be sufficient. This challenges the assumption that surgical procedures are always necessary for successful outcomes.

Recent studies have documented numerous cases of ROM across diverse geographic regions with particular attention to COVID-19 associated presentations. In Romania, Jeican et al reported a case series of eight patients, highlighting distinctive histological and electron microscopy features of COVID-19-associated ROM. Their findings emphasized the potential role of nasal sinus dysbiosis and bacterial biofilms in disease progression.[42] Similarly a study by Sheba et al analyzed 24 cases from South India, focusing on the microbiological profile of ROM pathogens and their antifungal susceptibility testing.[43] While these studies primarily centered on ROM in the context of COVID-19, our report describes cases occurring in patients with immunocompromised states unrelated to SARS-CoV-2 infection, thereby expanding the understanding of ROM etiology beyond the pandemic-associated surge. Notably, our findings underscore the pivotal role of early and aggressive surgical management, particularly orbital exenteration, in influencing patient outcomes. We propose that timely surgical intervention may significantly improve survival, especially in cases with extensive orbital involvement, and should be considered an integral component of a multidisciplinary treatment strategy.

Overall, while orbital exenteration remains a key intervention in severe cases of ROM, early diagnosis and rapid initiation of antifungal therapy, along with surgical debridement, are the most significant factors influencing survival. Delayed treatment is strongly associated with poor outcomes, emphasizing the critical need for prompt and aggressive management in this life-threatening infection.

Discussion

We conducted a retrospective case series and literature review, incorporating two cases from our ophthalmology department at Ziv Medical Center and eight additional cases from published reports between 2021 and 2025.

The decision to perform orbital exenteration in ROM remains a topic of significant debate, particularly when evaluating its influence on patient survival. Several pivotal questions emerge when considering the necessity and outcomes of this radical procedure. If a patient recovers with medical therapy alone, without exenteration, it raises the question of whether early antifungal intervention was sufficient to control the disease. Conversely, when a patient survives after both medical treatment and exenteration, it remains uncertain whether the surgery itself was essential or if other factors, such as the patient's age or underlying comorbidities, contributed to the positive outcome. Additionally, for patients who die despite undergoing exenteration, the role of the procedure in influencing their prognosis remains unclear, whether due to the surgery's inability to halt disease progression or the presence of systemic factors such as advanced age or poorly controlled chronic illnesses, which may have rendered survival improbable. In cases where patients passed away without undergoing exenteration, one must consider whether earlier surgical intervention could have altered the outcome or whether delays in diagnosis played a more decisive role. A particularly important consideration involves the presence of pulmonary mucormycosis or mucormycosis in other distant locations, as detected by chest CT scans. Pulmonary involvement may serve as a prognostic indicator, influencing the decision to pursue orbital exenteration. Since mucormycosis frequently disseminates in immunocompromised patients, identifying systemic spread early could guide clinicians toward more aggressive surgical approaches or, conversely, prompt a reassessment of the feasibility and benefit of such an extensive procedure. These unresolved questions underscore the complexity of ROM management and the need for more robust, evidence-based guidelines to support clinical decisions.

Medical management remains the foundation of ROM treatment, with Amphotericin B serving as the first-line antifungal agent despite its nephrotoxic risks.[44] Historically, mucormycosis carried an almost universally fatal prognosis before the advent of amphotericin B.[44] Although antifungal therapy alone is rarely curative, it is an essential component when paired with surgical debridement to remove necrotic tissue.[18] For cases limited to the sino-nasal region, a straightforward approach of debridement and amphotericin B therapy (1 mg/kg/day to a total dose of 2–3 g) is typically sufficient.[45] However, once the orbit becomes involved, the therapeutic strategy becomes far more complex, with the decision to proceed to orbital exenteration requiring careful consideration. Orbital exenteration involves the removal of all orbital contents, including the globe and surrounding structures.[45] Traditionally, this procedure is regarded as critical for preventing the infection's spread to intracranial structures.[45] However, more recent studies question whether it is universally necessary.

In less aggressive or localized cases, conservative management with antifungal therapy and surgical debridement may achieve similar outcomes without the need for radical surgery.[46] The extent of orbital involvement, including optic nerve involvement, central retinal artery occlusion, or superior ophthalmic vein thrombosis, often dictates the surgical approach. Therefore, evaluating and reviewing orbital exenteration indications remains a key research priority.

Pulmonary involvement complicates the picture further. It is often associated with rapid disease progression and poor outcomes. It typically presents with non-specific symptoms, such as fever, dyspnea, cough, and chest pain.[47] Radiological findings include consolidation, cavitation, nodules, and, more rarely, with signs like the air-crescent or halo sign. The non-specific nature of the symptoms and imaging findings contribute to delayed diagnoses and consequently high mortality rate.[47] The prognosis for pulmonary mucormycosis remains poor, especially in patients with hematologic malignancies, with mortality rates of 76%, rising to 95% when infection disseminates beyond the lungs.[47–49] Our case series demonstrated that while orbital exenteration supports local control, it proves insufficient when pulmonary involvement is present, as illustrated by the two patients who passed away despite undergoing the procedure and showing suspected pulmonary spread. This highlights the importance of comprehensive radiological assessment, including high-resolution chest and abdominal CT scans, to identify distant infection and guide surgical decisions more effectively.

Several proposed algorithms and scoring systems aim to define indications for orbital exenteration. Hanover et al recommend exenteration for cases with extensive orbital involvement, including occlusion of the central retinal artery, superior ophthalmic vein thrombosis, OAS, or vision loss. It also suggests exenteration for patients with significant

central nervous system (CNS) involvement, such as cavernous sinus thrombosis or brain infarction.[50] Singh VP et al stress that factors such as the degree of retinal artery involvement, disease progression, overall patient health, and response to antifungal therapy must inform the decision.[51] Levinsen et al recommend exenteration for cases involving orbital apex syndrome or facial necrosis.[52] Blitzer et al reported that the orbital exenteration is required if orbital apex necrosis occurs.[53] The Sion Hospital Scoring System, introduced by Shah et al, offers a structured approach to evaluating clinical presentation, ophthalmoscopic findings, and radiological evidence to guide exenteration decisions.[45] However, despite its promising potential, the scoring system has limitations, including a small sample size and lack of external validation, limiting its broader applicability. Further multi-center research is essential to refine such tools and establish more universally accepted guidelines.[45]

Despite these recommendations, the optimal timing of orbital exenteration remains controversial. The decision is highly individualized, guided by the clinical context and close multidisciplinary collaboration among ophthalmologists, otolaryngologists, and infectious disease specialists to ensure early diagnosis, rapid correction of underlying conditions such as ketoacidosis, and aggressive antifungal and surgical intervention.[29] Various techniques are employed for orbital exenteration, with the choice depending on the severity of the disease and the patient's clinical condition. Lid-sparing exenteration preserves the eyelid, offering better cosmetic outcomes and promoting faster recovery, which facilitates earlier prosthetic fitting.[54] Additionally, extended enucleation and endoscopic orbital exenteration are viable alternatives, particularly when the nature of the infection and the extent of orbital involvement warrant more targeted approach.[55] Studies by Hargrove et al, Pelton et al, and Bergstrom et al consistently reinforce the importance of early recognition and prompt intervention in improving survival.[56–58]

While orbital exenteration remains a pivotal component of ROM management, particularly in advanced cases, its role must be evaluated alongside timely antifungal therapy, thorough surgical debridement, and an assessment of systemic disease spread. The decision to proceed with such a radical procedure is complex and should balance the potential for survival against the significant functional and psychological consequences for the patient. Orbital exenteration can have a profound impact on patients' quality of life, particularly affecting their social and emotional well-being. In a study performed in ten post-exenteration subjects, 50–60% felt deeply uncomfortable with their appearance.[59] These patients frequently endured unwelcomed comments and unpleasant stares, even from close friends and relatives, contributing to feeling of distress and social withdrawal.

A significant limitation of the current case studies is the absence of certain advanced diagnostic modalities that could have enhanced our understanding of rhino-orbital mucormycosis (ROM). Notably, electron microscopy, which enables detailed visualization of the ultrastructural features of microorganisms was unavailable during the investigation.[60,61] This technique is invaluable for identifying fungal morphology and distinguishing it from other pathogens, thereby improving diagnostic accuracy.[60,61] Additionally, the use of MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization–Time of Flight) mass spectrometry, an emerging standard for rapid and precise microbial identification,[62] was not employed in this study. MALDI-TOF functions by ionizing microbial proteins and measuring their mass-to-charge ratios to generate a unique spectral fingerprint, which is then compared against a database for species identification.[63] It is increasingly used in clinical microbiology laboratories as a paradigm-shifting, rapid, cost-effective, and highly specific method for accurately identifying a broad range of pathogens including gram-positive and gram-negative bacteria, anaerobes, mycobacteria, yeasts, and molds often to the species level.[63] Its diagnostic performance is comparable to or better than traditional sequencing methods. MALDI-TOF is particularly valuable in detecting fungal species with limited therapeutic options or predictable antifungal resistance, and is especially important when species-level identification is necessary for clinical decision-making in the absence of susceptibility testing.[64] The lack of these advanced diagnostic tools limited our ability to fully characterize the fungal etiology and may have influenced clinical decisions regarding the duration and scope of antifungal therapy. These techniques are crucial for optimizing management and predicting the risk of recurrence, particularly in immunocompromised patients. We believe that future studies incorporating such diagnostics would offer a more comprehensive understanding of ROM and support more precise, evidence-based treatment protocols to improve patient outcomes.

Our study is a retrospective, non-consecutive case series, which introduces several inherent limitations. First, the non-consecutive nature may lead to selection bias, as only specific cases were included, potentially reducing the generalizability of the findings. Additionally, the retrospective design relies on pre-existing data, which may be

incomplete or inconsistently recorded, affecting data accuracy and depth. Compared to larger case-control studies or randomized controlled trials, our sample size is smaller, limiting the ability to detect less common outcomes. Despite these limitations, our findings offer valuable insights into this specific patient cohort, highlighting areas for future prospective studies to explore more comprehensively.

Variability in patient demographics and comorbidities may be seen as a limitation to comparability. However, this diversity was intentionally included to provide deeper insights into non-classic ROM cases. It highlights how a wide range of immunocompromised states, predisposing risk factors, and patient ages, as outlined in the case series, can significantly influence clinical decision-making for orbital exenteration. By selecting cases ranging from patients with minimal comorbidities to those with complex risk profiles, we aimed to broaden our understanding of orbital exenteration's role across diverse patient populations.

Further research and development of validated scoring systems are crucial to standardizing clinical decision-making and optimizing patient outcomes in this life-threatening disease.

Conclusion

ROM remains a devastating opportunistic infection with high mortality, particularly in immunocompromised patients. Our case series, in conjunction with the reviewed literature, underscores the pivotal importance of early recognition and prompt initiation of antifungal therapy in improving clinical outcomes. While orbital exenteration may offer survival benefits in advanced cases, timely medical treatment combined with less invasive surgical interventions can also lead to favorable results in selected patients. Clinical decisions should be individualized, based on disease severity, host factors, and radiological findings.

In contrast to the favorable outcomes often reported in the literature, both of our patients unfortunately succumbed to the disease, highlighting the grave consequences of delayed diagnosis and treatment. Although our literature review included eight cases with positive outcomes intentionally selected to emphasize the potential for survival with early intervention this case series contributes a more balanced perspective by addressing the underreporting of fatal outcomes. Presenting these two fatal cases alongside successful ones emphasizes the diagnostic and therapeutic challenges that can significantly affect prognosis. Together, these findings advocate for heightened clinical vigilance, timely imaging, and early surgical consideration as essential strategies to reduce mortality and improve management of ROM in similar high-risk settings.

Abbreviations

ROM, rhino-orbital mucormycosis; ROCM, rhino-orbital cerebral mucormycosis; OAS, orbital apex syndrome; AIDS, acquired immunodeficiency syndrome; MRI, magnetic resonance imaging; CT, computed tomography, FESS, functional endoscopic sinus surgery; IV, intravenous; CSF, cerebral spinal fluid; CNS, central nervous system; HbA1C, hemoglobin A1C; COVID-19, coronavirus disease 2019; AML, acute myeloid leukemia; CRAO, central rental artery occlusion; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate.

Ethical Approval Consent to Participate

Two cases from our Ophthalmologic Department were retrospectively reviewed, and as such, additional approval from our Ethics Committee (ZIV Medical Center, Safed) was not required.

Consent

Written informed consent for publication of medical details was obtained from the legal guardians of both patients included in this report.

Disclosure

The authors report no conflicts of interest in this work.

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