Rhino Orbital Cerebral Mucormycosis with Central Retinal Artery Occlusion: Case Series and Review of Literature

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Abstract

Background: Mucormycosis is a rare, aggressive fungal infection. It frequently affects immunocompromised individuals, leading to devastating outcomes. This study explores 4 cases of mucormycosis-induced central retinal artery occlusion (CRAO). **Case Presentation:** This case series includes four patients aged 50-57 years with uncontrolled diabetes mellitus. They presented with a sudden onset of severe unilateral visual loss, orbital symptoms, and systemic involvement. Each patient underwent a combination of nasal endoscopy, biopsy, and neuroimaging. A variety of treatment modalities were used, including antifungal therapy, intravenous antibiotics, surgery, and intravitreal injections. Despite intensive medical and surgical management, two patients succumbed to the disease. One patient, despite refusing further surgical intervention, was able to control the spread of infection with long-term medical management but suffered significant vision loss. Another patient showed some improvement in orbital symptoms but remained visually impaired. **Conclusion:** Mucormycosis-induced CRAO in patients with diabetes mellitus represents a severe and challenging clinical scenario, often culminating in profound vision loss or death despite aggressive treatment. These findings highlight the critical importance of early recognition, prompt intervention, and meticulous long-term management in these high-risk patients.

Keywords: Diabetes Mellitus, Orbital, Rhino-orbital Mucormycosis, Central Retinal Artery Occlusion.

Introduction

Mucormycosis is a lethal, antiinvasive fungal disease, which primarily occurs in individuals who are metabolically or immunologically compromised. Nonetheless, the prevalence of mucormycosis among patients without predisposing medical conditions has also been reported.[1] Rhino-orbito-cerebral mucormycosis (ROCM) is the most common manifestation of the disease in large case series.[2] The causative organisms are members of the family Mucoralean, which belongs to the order Mucorales of the class Zygomycetes.[3] They are saprophytes commonly found in soil, decomposed vegetation, and in the healthy human respiratory and digestive tracts, and their distribution is worldwide. ROCM is a rapidly progressive disease, and any delay in appropriate treatment may lead to devastating consequences. It has been reported that despite the provision of intensive antifungal treatments and surgical interventions, the mortality rate associated with ROCM remains alarmingly high, ranging from 50 to 100%. This can be attributed to the nonspecific clinical symptoms in the early stages of the disease, often leading to late diagnosis

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and treatment.[3] The following case series describe the clinical characteristics and treatment of four patients with histopathologic ally confirmed rhino cerebral mucormycosis.

Objectives

- Analyze the clinical symptoms and progression of ROCM with CRAO in diabetic patients to aid in early diagnosis.
- Assess the effectiveness of antifungal therapy, antibiotics, surgery, and intravitreal injections in managing ROCM-induced CRAO to identify optimal treatment strategies.
- Analyze treatment responses and disease progression to recognize factors influencing success or failure in managing ROCM with CRAO.
- Highlight the importance of early detection and ongoing care in improving outcomes and preventing severe complications in high-risk patients.

Research Intention

The intention of this particular research is to mainly provide a proper comprehensive analysis of the rhino-orbital cerebral mucormycosis (ROCM) which is complicated by that of central retinal artery occlusion (CRAO) via a case series and literature review. The research specializes in the trajectory of the sickness from early signs and symptoms to consequences, which consist of the effectiveness of treatments including antifungal treatment, surgical interventions, and adjunctive measures like intravitreal injections. It also seeks to perceive patterns in disease development and response to treatment, contributing precious insights into the control of this life-threatening situation. Through precise case descriptions and a compare of present literature, the studies intend to highlight the importance of early diagnosis, intervention, and the need for treatment of ROCM.

Research Motivation

The motivation behind this particular research mainly rises from the stems from the urgent need to address the actual high mortality and morbidity which is associated with that of rhino-orbital cerebral mucormycosis (ROCM, particularly while compounded by way of way of important retinal artery occlusion (CRAO). Mucormycosis, an aggressive fungal contamination, poses massive annoying conditions, mainly in individuals with uncontrolled diabetes mellitus, a population increasingly more at risk of extreme infections.[4] The rarity of ROCM with CRAO, combined with its devastating impact on vision, underscores the need for a deeper knowledge of its control. Despite advances in medical and surgical treatments, patients often revel in profound vision loss or death, highlighting a gap in effective therapeutic techniques and early intervention practices. This research aimed to identify the need of higher diagnostic techniques to reduce the level of incidence of that of the severe complications and fatalities associated with this condition.

Groups that May Benefit

The research findings will mainly benefit some of the several key groups. Firstly, the healthcare professionals, including that of the ophthalmologists, infectious disease specialists, and endocrinologists, will be beneficial from precious insights into the management of mucormycosis with CRAO, leading to diagnostic and treatment. Secondly, patients with uncontrolled diabetes mellitus, who are at threat of growing excessive fungal infections, will gain from higher recognition and preventative measures. Thirdly, researchers and clinicians in the field of infectious and ophthalmology will be beneficial from interventions and refining treatment for ROCM cases. Lastly, public health care able to make use of the research to suggest for higher screening and also the early intervention to mitigate the various form of risks which are associated with mucormycosis and CRAO in high-risk populations.

Literature Review

According to Hussain *et al*.[5], Mucormycosis is a very much severe and often fatal form of fungal infection caused by molds belonging to the Mucorales family, exacerbated through situations which includes COVID-19, diabetes, and steroid use. The contamination, generally known as "black fungus," has visible a top notch upward pushes in prevalence, especially among immunocompromised individuals. This growth is hooked up to the COVID-19 pandemic, which weakens the immune system, making patients more susceptible to opportunistic infections. Effective treatment remains an assignment, with traditional medications like Amphotericin B (Am) displaying some promise but often observed by using manner of issues about protection and efficacy.[5] Liposomal formulations of Am have grown to be the standard because of their stepped forward safety profile. Newer antifungal dealers, which include monogenic and echinocandins, are being investigated for their capacity blessings. Despite these advancements, mucormycosis stays a crucial problem, underscoring the need for continued studies into effective treatment. The assessment highlights the urgent need for novel recuperation techniques to combat this deadly contamination.

According to Darwish *et al*.[6], Mucormycosis, which is a very rare but also a very severe fungal infection caused by mucoromycetes, has gained some level of attention due to its association with COVID-19 This evaluation explores its epidemiology, scientific manifestations, chance elements, analysis, and treatment. Mucormycosis, historically referred to as zygomycotic, encompasses infections from fungi in the Mucorales and Entomophthorales orders, with Rhizopus oryzae being an essential pathogen. These fungi thrive in decaying flora and soil, spreading via airborne spores or infected substances. The contamination's occurrence is underreported because of diagnostic traumatic situations. Major risk elements includes diabetes mellitus, hematological malignancies, and corticosteroid use, with geographical versions affecting incidence and chance. In areas like India and the Middle East, diabetes is a sizeable hazard, at the equal time as in Europe, hematological situations are greater common. COVID-19 sufferers,

mainly the ones on steroids, have verified extended mucormycosis times. Clinically, mucormycosis presents in numerous paperwork: rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated.[6] Effective control calls for set off surgical debridement, antifungal therapy, and addressing underlying situations. Treatment alternatives are restrained, with polyenes like amphotericin B as empirical remedy and posaconazole or azaconazole for refractory instances. The review mainly underscores the actual need for that of the heightened awareness as well as the timely intervention to improve outcomes for this aggressive infection

According to Sharma *et al*.[7], mucormycosis had mainly emerged as a, a very severe fungal infection, in that of various patients with a history of COVID-19. Conducted at a tertiary care center over four months, the research centered on 23 sufferers with invasive fungal sinusitis associated with previous or ongoing covid infection. The findings display that everyone sufferers had mucormycosis associated with COVID-19, normally affecting the ethmoid sinuses (a hundred%) and regularly extending to the orbit (43.47%). Diabetes mellitus emerge as present in 21 sufferers, with 12 having out of control diabetes, and all patients had used steroids at some stage in their COVID-19 remedy.[5] The look at highlights the exacerbation of mucormycosis within the context of COVID-19, underscoring the risks of uncontrolled diabetes and excessive steroid use. Mucormycosis, characterized through rapid tissue invasion and immoderate mortality expenses if untreated, is an extensive fear in COVID-19 patients, emphasizing the need for vigilance and proper management to mitigate this serious post-pandemic threat.

As per the view of Huang *et al*.[8], Gastrointestinal mucormycosis (GIM) is a very much rare but also a very severe fungal infection with a very poor prognosis, normally affecting immunocompromised individuals. This file highlights unusual instances of GIM in immunocompetent patients, demonstrating bizarre contamination web sites and a loss of obvious predisposing elements. The first case consists of a 16-three hundred and sixty-five days-vintage boy with gastrointestinal bleeding and perforation from a gastric ulcer, main to GIM prognosis thru pathological exam and next a success treatment. The 2d case skills a 33-12 months-vintage lady with gastric necrosis following a leg damage, diagnosed with GIM postoperatively and treated efficaciously with surgical treatment and antifungal remedy.[8] These times underscore that GIM can arise in sufferers without conventional hazard elements, emphasizing the want for heightened popularity and early prognosis. Timely surgical intervention and systemic antifungal treatment are crucial for enhancing evaluation. Insite of having the high mortality rate associated with that of GIM, both the patients in this report recovered well as a result of the prompt and aggressive management, highlighting the actual level of importance of early detection and intervention.

Methodology

Case Studies

Case 1

A 57-year-old female with underlying diabetic mellitus and end stage renal disease, presented with right facial swelling and numbness, drooping of the right upper eyelid, acute loss of vision within one week. (Figure 1a). She also had fever, vomiting and reduced oral intake. Visual acuity was non perception of light (NPL) over right eye with the presence of relative afferent defect. On examination, right eye showed complete ptosis with total ophthalmoplegia. Chemosis was present temporally and the pupil was fixed and dilated. Fundus examination revealed presence of central retinal artery occlusion. Computed tomography (CT) angiogram showed mucosal thickening of the right frontal, maxillary, sphenoid, and bilateral ethmoid air cells with cavernous sinus thrombosis (Figure 1b). Right Functional Endoscopic Sinus Surgery (FESS) done by the ENT team revealed presence of necrotic tissue in the right middle turbinate extending to the lateral wall. Fungal debris was seen in the maxillary, ethmoid, sphenoid and frontal sinuses (Figure 1c). Biopsy result confirmed zygomycotic with extensive hemorrhagic infarct (Figure 1d). The patient was administered with intravenous (IV) liposomal amphotericin B, Meropenem and Metronidazole. She was also given retrobulbar amphotericin B Injection. Despite intensive treatment, her condition deteriorated, and she unfortunately succumbed to death after two weeks hospitalization.

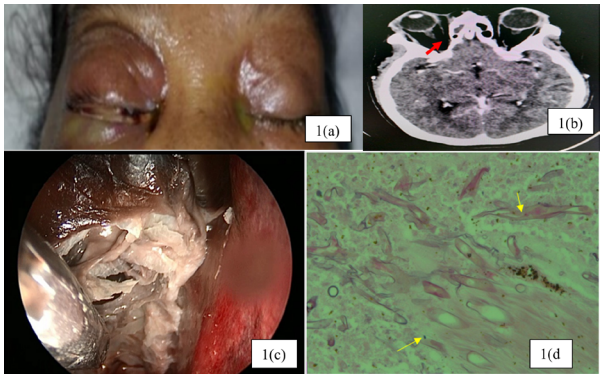

Figure 1(a): Right Eye Proptosis with Upper and Lower Lid Swelling. Figure 1(b): Axial CT Scan of Brain Showed Mucosal Thickening of the Right Frontal, Maxillary, Sphenoid and Bilateral Ethmoid Air Cells with Right Ophthalmic Artery Thrombosis. Figure 1(c): Black eschar with Necrotic Tissue Seen in Right Nasal Sinus through Endoscopy. Figure 1(d): Right Nasal Tissue Showing Broad Aseptate Hyphae Highlighted by Periodic Acid–Schiff Staining (yellow arrow).

Case 2

A 56-year-old man with underlying diabetic mellitus and end-stage renal disease presented with right periorbital swelling, toothache, and persistent fever. He was critically ill, intubated and admitted to ICU, treated for sepsis with prompt initiation of intravenous antibiotics. Oral

examination revealed blackish eschar on his soft palate. Ophthalmic examination revealed right eye upper lid swelling, and proptosis with lagophthalmos. Fundus examination showed presence of right central retinal artery occlusion. His preliminary diagnosis was orbital cellulitis secondary to oropharyngeal abscess. Biopsy of palatal tissue yielded zygomycotic. CT brain showed multifocal areas of hypodensity at the right frontal, internal capsule, and right pons with infarction due to septic emboli. He was aggressively treated with IV Amphotericin B, IV Meropenem and IV Metronidazole. In view of his generalized poor systemic condition, he was deemed not fit for surgery. He succumbed to death after 2 weeks of hospitalization.

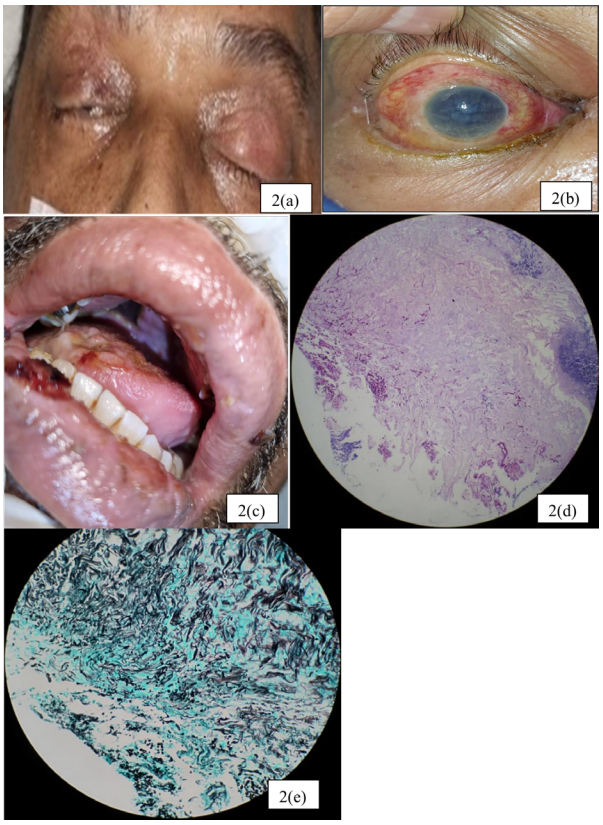

Figure 2(a): Right Eye Ptosis with Lid Swelling. Figure 2(b): Right Eye Injected Conjunctival with Hazy Cornea. Figure 2(c): Blackish Eschar Seen on Soft Palate. Figure 2(d): Right Middle Turbinate Tissue Showing Broad Paupiette Ribbon Like Hyphae with Wide Angle (90 degree) Branching at Focal Area Highlighted by Periodic Acidic Shift Stain (black arrow). Figure 2(e): Fungal Elements Highlighted by Gomora Methenamine Stains within the Muscularized Vessels Wall.

Case 3

A 50-year-old female with uncontrolled diabetic mellitus presented with sudden onset of right eye blurring of vision, periorbital pain, headache, and vomiting. She had elevated blood glucose level (30mmol/L) with high serum ketone 4.8 and was treated for diabetic ketoacidosis. Her visual acuity was hand movement (HM) over right eye with presence of relative afferent pupillary defect (RAPD). Ophthalmologic examination revealed right eye complete ptosis, total ophthalmoplegia, and paresthesia over right forehead. Fundus examination revealed right central retina artery occlusion. Diagnostic nasal endoscopy showed adherent blackish eschar covering the whole right inferior and middle turbinate. CT brain and paranasal sinuses revealed mucormycosis involving right inferior and middle nasal meaty with bony erosion of the right inferior nasal turbinate, along with evidence indicative of right cavernous sinus thrombosis. Biopsy result yielded Rhizopus species. She underwent right nasal cavity tissue debridement, posterior ethmoidectomy, sphenoidotomy, medial maxillectomy and wide local excision of right soft palate by Orto laryngeal team. She was treated with IV amphotericin B, IV Rocephin and IV Flagyl. At third day of admission, she developed signs of right endophthalmitis and focal cerebritis. Urgent vitreous tap was performed for the right eye with injection of intravitreal vancomycin, ceftazidime and amphotericin B. Culture results were negative.

Against medical advice, she opted for discharge but returned a year later with the infection spreading to her left eye and worsening right sinusitis. CT scans confirmed the extensive spread of the fungal infection, bilateral cavernous sinus thrombosis, and thrombosis in her left carotid artery. Despite refusing further surgical intervention, she was managed with a rigorous medical regimen, including intravenous Amphotericin B, antibiotics, and continued long-term oral antifungal medication. Subsequent follow-up revealed that her right eye remained blind, with complete ptosis and total ophthalmoplegia. Left eye symptoms resolved with best corrected visual acuity of 6/24.

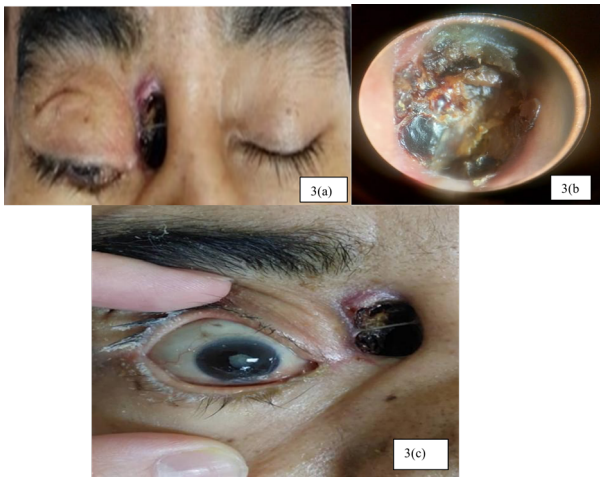

Figure 3(a): Right eye Ptosis with Proptosis. Figure 3(b): Blackish Sinus Near Right Nasal Bone. Figure 3 (c): Necrotic Patch Seen in the Sinus.

Case 4

A 65-year-old woman with diabetes mellitus presented with an acute loss of vision in her right eye lasting for

three weeks, which was associated with a headache. Her visual acuity was no-perception of light in the right eye, with presence of a relative afferent pupillary defect. Ophthalmologic examination revealed proptosis, total ptosis, and total ophthalmoplegia. Fundus examination revealed central retinal artery occlusion (CRAO) and virtutis. B-scan ultrasound showed loculations with the presence of scleritis. Magnetic resonance imaging (MRI) brain and orbit revealed extensive pansinusitis and cavernous sinus thrombosis, right orbital apex syndrome, and erosion of the inferior orbital wall. FESS was performed by the ENT team, which revealed invasive fungal sinusitis. A biopsy showed scattered broad branching fungal hyphae with blood vessel invasion and extensive necrosis suggestive of mucormycosis. Urgent vitreous tap with injection of intravitreal vancomycin, ceftazidime and amphotericin B was performed, cultures were negative. She was treated with oral Posaconazole and intravenous antibiotics. Furthermore, she received a total of twelve intravitreal injections of vancomycin, Fortum, and amphotericin B over two weeks. Subsequently, she showed signs of improvement with reduction of proptosis and ptosis. The patient was stable systemically thereafter till the last follow-up at 3 months. Despite aggressive interventions, her vision did not improve.

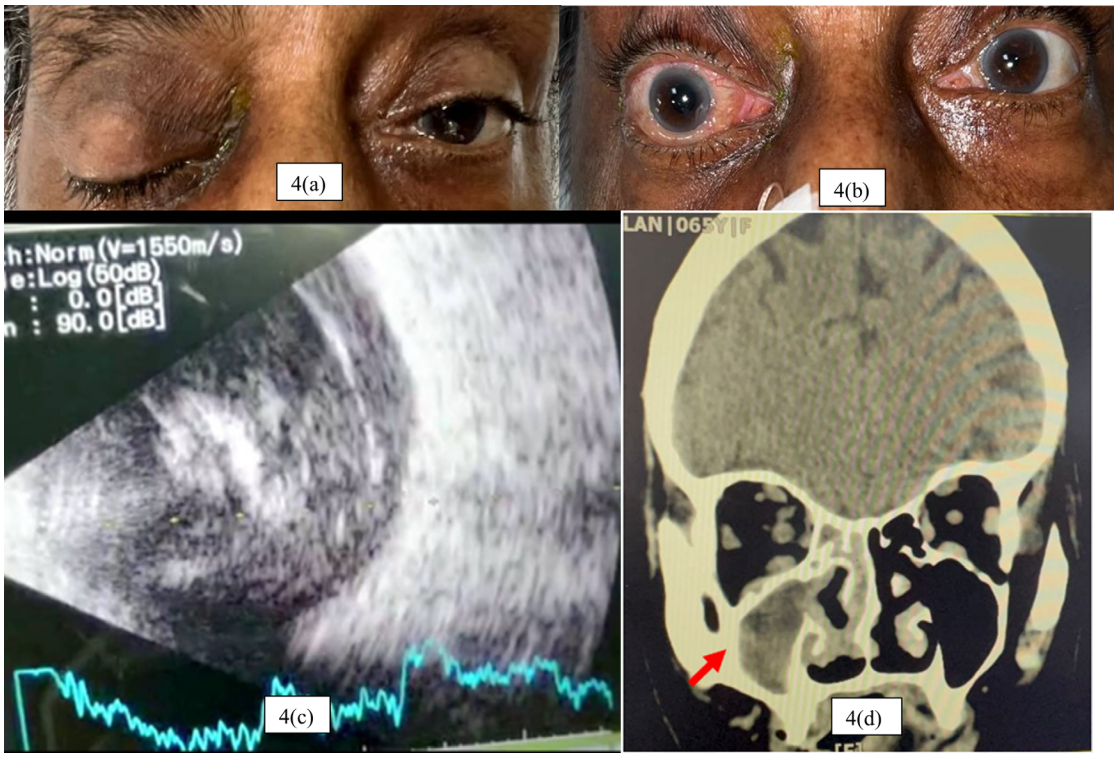

Figure 4 (a): Right Eye Ptosis with Lid Swelling. Figure 4 (b): Right Eye Conjunctival Injected with Chemosis. Figure 4 (C): B Scan Ultrasonography Showing Vitreous Loculations and scleritis. Figure 4 (d): Magnetic Resonance Imaging (MRI) Brain Coronal View Shows Extensive Pansinusitis and Erosion of the Inferior Orbital Wall.

Table 1: Clinical Profile, Treatment and Outcome in Rhino Cerebral Orbital Mucormycosis.

No of Patient	Age/Gender	Clinical Symptom	Comorbid	Imaging Finding	Treatment	Surgery	Outcome
1	57/female	Facial swelling and numbness, fever, ptosis, total loss of vision, total ophthalmoplegia CRAO	DM ESRD	Sinusitis including frontal, maxillary, sphenoid, bilateral ethmoid, cavernous sinus thrombosis	Liposomal amphotericin B, I Meropenem I Metronidazole Retrobulbar amphoteric B injection	Ethmoid-sphenoid-Maxillectomy	Deceased (14days)
2	52/male	Periorbital swelling, toothache, fever, proptosis CRAO	DM ESRD	Multifocal septic emboli at right frontal, internal capsule, pons	IV Amphotericin B, I Meropenem IV Metronidazole	No	Deceased (14days)
3	50/female	Periorbital pain, headache, vomiting loss of vision, ptosis, total ophthalmoplegia, CRAO, endophthalmitis	DM	Right inferior, middle nasal turbinate, cavernous sinus thrombosis	IV amphotericin B, IV Ceftriaxone, IV Metronidazole IVT vancomycin, ceftazidime an amphotericin B	Ethmoid, sphenoid-maxillectomy local excision of soft palate	Resolution (alive 14months)
4	65/female	Facial pain, headache, proptosis, total loss of vision, total ptosis, total ophthalmoplegia, CRAO, endophthalmitis	DM	Extensive pansinusitis, cavernous sinus thrombosis orbital apex syndrome, erosion of the inferior orbital wall	oral Posaconazole, IV Ceftriaxone, IV Metronidazole IVT vancomycin, ceftazidime, amphotericin B	Ethmoid-sphenoid-Maxillectomy	Resolution (alive 10months)

DM: diabetic mellitus ESRD: end stage renal disease, IVT: intravitreal

Selection and Characteristics of Cases

The four cases which are selected for this report mainly involve patients with that of the underlying diabetes mellitus who mainly presented with some of the symptom's indicative of severe fungal infections, specifically with that of the mucormycosis, a progressing and existence-threatening situation. The patients, ranging in age from 50 to 65 years, all had underlying diabetic situations, with moreover affected by end stage renal disorder. These comorbidities drastically compromised their immune structures, making them distinctly at risk of opportunistic infections like mucormycosis.[9] The instances had been determined on based totally at the severity of infection, the rapid progression of symptoms. Despite aggressive medical treatments, the outcomes are varied, highlighting the challenges in managing such severe fungal infections in immunocompromised individuals.

Case Summaries

Case 1: A 57-year-old woman with diabetes mellitus and end-stage renal disease presented with right facial swelling, numbness, and acute vision loss in the right eye, along with systemic symptoms and signs which include fever and vomiting. Ophthalmic exam determined complete ptosis, preferred ophthalmoplegia, and a set, dilated scholar inside the proper eye. Fundus examination showed critical retinal artery occlusion (CRAO). A CT angiogram observed sinus mucosal thickening and cavernous sinus thrombosis.[10] Functional Endoscopic Sinus Surgery (FESS) exposed necrotic tissue and fungal debris in a couple of sinuses, and biopsy confirmed zygomycotic. Despite intravenous antifungal and antibiotic treatments, her condition deteriorated, and she succumbed to the infection after weeks.

Case 2: A 56-year-old man with diabetes mellitus and end-stage renal disease was critically ill, presenting with right periorbital swelling, toothache, and fever. He modified into handled in the ICU for sepsis and identified with orbital cellulitis secondary to oropharyngeal abscess. Ophthalmic and oral examinations found out eschar at the gentle palate, proptosis, and CRAO. CT mind scans indicated more than one hypodense regions because of septic emboli. Biopsy showed zygomycotic. Given his terrible systemic situation, he changed into deemed undeserving for surgical procedure and modified into handled aggressively with intravenous antifungal and antibiotic remedy. Despite those efforts, he died after two weeks of hospitalization.

Case 3: A 50-year-old woman with uncontrolled diabetes mellitus presented with sudden right eye vision loss, periorbital pain and signs and signs of diabetic ketoacidosis. Ophthalmic examination revealed ptosis, ophthalmoplegia, and CRAO. Diagnostic nasal endoscopy showed vast mucormycosis with bony erosion.[11] Biopsy showed Rhizopus species. She underwent substantial surgical debridement and modified into handled with intravenous antifungals and antibiotics. Despite this, she advanced right endophthalmitis and cerebritis. After selecting discharge in competition to clinical advice, she back a 12 months later with worsening signs, which includes bilateral cavernous sinus thrombosis. Her proper eye remained blind, however her left eye spoke back in part to treatment.

Case 4: A 65-year-old woman suffering from diabetes mellitus presented with a proper three-week history of acute vision loss in the right eye, accompanied by headache Ophthalmic examination found out proptosis, well-known ptosis, and CRAO with virtutis. MRI showed sizeable pansinusitis, cavernous sinus thrombosis, and orbital apex syndrome. FESS showed invasive fungal sinusitis, and biopsy found out mucormycosis. The affected person obtained intensive remedy, along with more than one intravitreal injections and intravenous antifungals. While systemic signs and symptoms stabilized and proptosis reduced, her vision did no longer get higher.

Enlightenment from the Cases

These cases highlight the intensive and life-threatening nature of mucormycosis, especially in patients suffering with diabetes mellitus and other immunocompromise conditions. The rapid progression of the infection in all four cases underscores the need for prompt prognosis and early intervention. Despite aggressive antifungal and antibiotic treatment, the outcomes were usually poor with patient succumbing to the contamination and others experiencing irreversible vision loss or other organs involvement.[12]

Comparison of Cases

Clinical Presentation: All four patients presented with various symptoms included periorbital swelling, vision loss, as well as signs of systemic infection. The severity of ophthalmic involvement numerous, with all cases displaying signs and symptoms of CRAO, ptosis, and proptosis. Systemic signs and symptoms and symptoms which includes fever and vomiting were additionally not unusual, indicating widespread infection.

Diagnostic Findings: CT and MRI scans in these cases consistently showed signs of sinusitis, cavernous sinus thrombosis and brain involvement. Biopsies showed mucormycosis, with fungal factors seen on special staining strategies.[13] The imaging findings had been important in guiding surgical intervention and determining the severity of the infection.

Treatment and Outcomes: Treatment for all four cases concerned the usage of intravenous antifungal, with amphotericin B being the mainstay treatment. Surgical intervention through FESS were done in three cases, aiming to remove necrotic tissue and reduce the fungal load. However, in Case 2, the patients was criticallly ill and not fit for surgery, and this correlated with a rapid decline and deadly outcome. Despite these aggressive interventions, the mortality rate was 50%, and patients who survived suffered from morbidity, including irreversible blindness and chronic systemic infections.

Factors Affecting Outcomes: Several factors seemed to affect results in those cases. The presence of end stage renal disease and uncontrolled diabetes mellitus leads

to poorer consequences, as seen in Cases 1 and 2.[14] Surgical debridement plays an important role. Patients who underwent surgical treatments survive longer. The timing of intervention is critical, with delays in treatment likely contributing to devastating consequences. The resistance of the fungal infection to treatment and the underlying compromised immune states of the patients in addition complicated the conditions.

Results

Clinical Profiles and Presentations

This study includes four cases of rhino cerebral orbital mucormycosis, a severe and threatening fungal infections, all imparting with massive orbital and cerebral involvement. Each affected individual had underlying comorbidities, poorly controlled diabetes mellitus (DM) and end stage renal disease (ESRD).

Table 2: Clinical Profiles of the Cases.

Case No	Age/Gender	Clinical Symptoms	Comorbidities	Imaging Findings
1	57/Female	Facial swelling and numbness, fever, ptosis, total loss of vision, total ophthalmoplegia, CRAO	DM, ESRD	Sinusitis (frontal, maxillary, sphenoid, bilateral ethmoid), cavernous sinus thrombosis
2	52/Male	Periorbital swelling, toothache, fever, proptosis, CRAO	DM, ESRD	Multifocal septic emboli at right frontal, internal capsule, pons
3	50/Female	Periorbital pain, headache, vomiting, loss of vision, ptosis, total ophthalmoplegia, CRAO, endophthalmitis	DM	Right inferior, middle nasal turbinate, cavernous sinus thrombosis
4	65/Female	Facial pain, headache, proptosis, total loss of vision, total ptosis, total ophthalmoplegia, CRAO, endophthalmitis	DM	Extensive pansinusitis, cavernous sinus thrombosis, orbital apex syndrome, erosion of the inferior orbital wall

Imaging Findings

All patients exhibited extensive sinusitis, with involvement of multiple sinuses including the frontal, maxillary, sphenoid, and ethmoid sinuses. In 3 cases, cavernous sinus thrombosis become referred to, at the equal time as one case additionally exhibited multifocal septic emboli extending into the pons.[15] These findings underscore the competitive nature of mucormycosis, which rapidly spreads to adjacent tissues and essential structures.

Treatment Modalities

The treatment regimens for these patients were aggressive antifungal treatment, massive-spectrum antibiotics, and surgical interventions aimed toward debridement and controlling the contamination. The treatments are summarized below.

Tables 3: Specific Treatments for the Cases.

Case No.	Treatment	Surgery	Outcome
1	Liposomal Amphotericin B, IV Meropenem, IV Metronidazole, Retrobulbar Amphotericin B injection	Ethmoid-sphenoid-maxillectomy	Deceased (14 days)
2	IV Amphotericin B, IV Meropenem, IV Metronidazole	None	Deceased (14 days)
3	IV Amphotericin B, IV Ceftriaxone, IV Metronidazole, IV Vancomycin, Ceftazidime, Amphotericin B	Ethmoid-sphenoid-maxillectomy, local excision of soft palate	Resolution (alive 14 months)
4	Oral Posaconazole, IV Ceftriaxone, IV Metronidazole, IV Vancomycin, Ceftazidime, Amphotericin B	Ethmoid-sphenoid-maxillectomy	Resolution (alive 10 months)

Outcomes

The consequences on this case were varied, with two patients surviving after extensive treatment and surgical intervention, at the same time as two patients succumbed to the contamination after 14 days of hospitalization. Notably, each surviving patients underwent competitive surgical debridement further to systemic antifungal remedy, which might also have done an essential role of their recovery.

Case 1: 57-Year-Old Female

This patient presented with acial swelling, ptosis, and complete ptosis of eye. Imaging reveled sinusitis more than one sinuses and cavernous sinus thrombosis.[16] Despite receiving liposomal amphotericin B, meropenem, metronidazole, and a retrobulbar amphotericin B injection, the patients deteriorated and surpassed away 14 days after admission. The surgical intervention, ethmoid-sphenoid-maxillectomy, which turned into inadequate to halt the sickness development.

Case 2: 52-Year-Old Male

This patient has history of DM and ESRD, presented with periorbital swelling and proptosis. Imaging confirmed multifocal septic emboli and involvement of the frontal sinuses. Treatment included IV amphotericin B, meropenem, and metronidazole. Unfortunately, no surgical intervention was carried out, and the patient died 14 days later, emphasizing the need for early and aggressive surgical manipulate in such cases.

Case 3: 50-Year-Old Female

This patient, who presented with periorbital pain, sign of endophthalmitis, underwent an ethmoid-sphenoid-maxillectomy and excision of the smooth palate. Imaging revealed cavernous sinus thrombosis. The treatment included IV amphotericin B, ceftriaxone, metronidazole, vancomycin, and ceftazidime. Following this treatment, the patient survived. This case highlighting the potential recovery ith timely and aggressive treatment.

Case four: 65-Year-Old Female

The very last case concerned a 65-old lady with facial pain, total loss of vision, and imaging findings of pansinusitis, cavernous sinus thrombosis, and orbital apex syndrome. She received oral posaconazole, IV ceftriaxone, metronidazole, vancomycin, ceftazidime, and amphotericin B. The surgical

method involved ethmoid-sphenoid-maxillectomy. The patient remained alive 10 months after the treatment, underscoring the effectiveness of combining surgical debridement with systemic antifungal treatment.

Comparative Analysis

The data revealed relationship between early surgical intervention and improved outcomes. Both patients who underwent surgical debridement with antifungal therapy survived, while two patients were unfit of surgical treatments succumbed to the infection.[17] This finding supportsh the crucial role of timing surgical treatment in dealing with rhino cerebral orbital mucormycosis.

Discussion

Mucormycosis, a rare fungal infection, has a global incidence of 0.005-1.7 cases per million population. [18] A significant upsurge of cases was noted at our institution between September and October 2022, marking a concerning rise.

Risk factors for ROCM include uncontrolled diabetes, hematological malignancies, immunodeficiency, severe burns, renal disease, malnutrition, post-organ donation immunosuppression, and deferoxamine medication. [19] The four cases studied shared predisposing factors: uncontrolled diabetes and end-stage renal disease, which compromise the immune response, increasing susceptibility to fungal infections. Diabetes mellitus is the most common predisposing factor for mucormycosis, especially when it is complicated by ketoacidosis.[20,21] By impairing host phagocytosis and the mobilization of polymorphonuclear leukocytes, diabetes alters the immunological ability to resist mucormycosis, increases blood glucose and acidosis levels, increased free serum iron availability at low pH favoring fungal growth. These fungi have an affinity for the internal elastic lamina of blood vessels, leading to angioinvasion, thrombosis and hemorrhagic necrosis facilitating the spread of paranasal sinus disease to the orbit and brain.[22]

This case series underscores orbital mucormycosis's complexity, which can manifest in various forms, often leading to delayed diagnosis. Case 1 to 4 exhibited different symptoms like facial swelling, numbness, acute vision loss, toothache, periorbital pain, and headaches, all associated with sinusitis. The non-specific initial symptoms were often misattributed for other conditions, causing a delay in starting appropriate antifungal therapy.

Central retinal artery occlusion (CRAO) is a relatively rare manifestation associated with rhino-orbital-cerebral mucormycosis (ROCM), with an incidence of 16%-20%. [23] It usually presents at an advanced stage and may also be associated with cavernous sinus thrombosis and intracranial spread. Cavernous sinus thrombosis in orbital mucormycosis has been reported in several case studies. [24] This leads to ptosis, proptosis, conjunctival chemosis and total ophthalmoplegia. All patients in our case series presented with this rare but serious complication, indicating aggressive invasion of the central retinal artery by antiinvasive fungal pathogens originating from the orbit. Remarkably, the patients experienced simultaneous onset of CRAO and cavernous sinus thrombosis, causing severe visual impairment.

Mucor endophthalmitis, a potentially devastating condition of ROCM leading to vision loss, is caused by vascular invasion of the retina by antiinvasive fungi, leading to thrombosis and vitreous involvement.[25] Histopathological examination, more sensitive than cultures, is essential for diagnosis.[26] In a study on pulmonary mucormycosis sputum, bronchopulmonary lavage showed no growth in 17 of 18 cases confirmed at surgery or autopsy.[27] Similarly, our cases revealed no fungal growth, making genus identification impossible. Despite its rarity, it is crucial to highlight two instances of mucor endophthalmitis in our case series.

The treatment approach requires a combination of aggressive antifungal therapy, extensive surgical debridement, and control of underlying comorbidities.[28] As per 2019 international guidelines for the diagnosis and treatment of mucormycosis, Liposomal amphotericin B (L-AMB), owing to its superior ability to penetrate the brain and less nephrotoxicity, is recommended as the first-line monotherapy among the range of antifungal drugs. Azoles like azaconazole and posaconazole oral suspensions are also used in first-line treatment. In addition, the efficacy of topical treatments as an adjunct to systemic intravenous medications has been recognized. Safi et al reported a case of ROCM associated with focal anterior cerebritis that was effectively treated with retrobulbar injection of deoxycholate amphotericin B and concomitant systemic antifungal therapy. In our case series, treatment regimens were adapted based on resource availability and patients' clinical conditions. Three patients received intravenous amphotericin B as part of their treatment protocol. Intriguingly, one patient was managed with oral posaconazole, while another was treated with a transcutaneous retrobulbar injection of amphotericin B.

Surgical debridement aims to remove infected tissue, restore vascular supply, and improve drug penetration at the site of infection.[29] The cases presented here involved various surgical procedures such as nasal cavity tissue debridement, ethmoidectomy, and maxillectomy. However, despite these surgical interventions, the outcomes were not uniformly successful, highlighting the challenges associated with disease control and eradication.

Orbital exenteration may be life-saving in the presence of active fungal invasion of the orbit and should be considered for an actively infected orbit with a blind, immobile eye. It has been considered helpful even after intracranial spread has occurred.[30] The decision to perform orbital exenteration in cases of orbital mucormycosis is critical and has significant impact on patient outcomes. Although it may halt the disease progression and prevent further morbidity, its timing remains a challenge. A comprehensive literature review by Hargrove et al. highlighted the lack of a standardized protocol for orbital exenteration in

cases of mucormycosis. The decision-making process must consider several factors, including the extent of the infection, the patient's overall clinical status, and the feasibility of surgical intervention. In our case series, all the patients were critically ill and were unfit for surgery. This poses a unique dilemma, as the benefits of surgery must be carefully weighed against the potential risks associated with anesthesia and perioperative complications. In addition, the aggressive nature of orbital mucormycosis requires a prompt and decisive approach to management, leaving limited time for interventions that may improve the patient's clinical status before resorting to exenteration.

Treatment outcomes differed among the cases. Cases 1 and 2 deteriorated despite aggressive therapy and ultimately succumbed to the infection after 2weeks. Case 3 refused surgery, and was discharged with antifungal medications, but later showed signs of fungal spread. Case 4, though blind, showed no infection spread and stabilized with long-term antifungal therapy. Even with medical and surgical intervention, rhino-cerebral-orbital mucormycosis is still associated with immense morbidity if the patient survives.

Despite an understanding of its pathogenesis, mucormycosis is often diagnosed late due to inadequate initial intranasal examination, leading to poor prognosis despite rigorous treatment. While the mortality rate ranges from 15% to 31% in India,[19] our series reveals a concerning 50% mortality rate.

Conclusion

Rhino-orbital-cerebral mucormycosis is a fulminant fungal infection commonly diagnosed in patients with uncontrolled diabetes. Early diagnosis with radiological and histopathological evaluation is required to identify patients at risk of rhino-orbital-cerebral mucormycosis. The essential elements for successfully managing this fatal infection are controlling the predisposing factors, early detection with a high index of suspicion in patients with contributing factors, anti-fungal drugs, and surgical debridement of the involved tissues.

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