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Original Research Article

Analysis of ophthalmic manifestations of invasive rhino-orbito-cerebral mucormycosis in COVID-19 patients in a medical college

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ABSTRACT

Purpose: To analyze different ophthalmic manifestations of rhino-orbital mucormycosis (ROM) infection in COVID-19 patients.
Study Design: Prospective interventional clinical study.
Materials and Methods: 20 microbiologically confirmed ROCM cases with ophthalmic involvement hospitalized between May 2021 and July 2021 in our center were included in this study.
Results: Among 20 cases there were 9 female and 11 male with a mean age of 57.5 years. All 20 patients had uncontrolled type 2 diabetes with a mean diagnosis duration of 3.67 years. All patients had COVID-19-associated acute respiratory distress syndrome and received corticosteroids. The mean time interval between COVID-19 diagnosis and ROM diagnosis was 3.46 days. 4 patients (20%) had orbital apex syndrome, and 16 patients (80%) presented with orbital cellulitis. CT scan/MRI revealed sino-orbital involvement in all patients, and 3 of these had cerebral involvement at initial presentation. All 20 patients received intravenous amphotericin B and 7 patients received TRAMB and all 20 patients had undergone radical debridement of involved sinuses. Despite all measures, 3 (7.5%) of 20 patients with cerebral dissemination expired.
Conclusions: Severe COVID-19 is associated with a significant incidence of ROM with higher mortality rates due to immune dysregulation and the widespread use of steroids. An aggressive multidisciplinary approach can help to reduce mortality.

1. Introduction

Mucormycosis belongs to the order Mucorales of the class Zygomycetes, which are ubiquitous in nature, especially in soil and decaying vegetation.[1] These fungi develop rapidly and release large numbers of spores into the air. Mucormycosis is a rare acute invasive and life-threatening fungal infection that affects immunocompromised patients.[2,3] In susceptible patients, it is characterized by direct invasion with marked tissue necrosis of adjacent structures followed by rapid progression and angioinvasion from the nasal and sinus mucosa into the orbit and brain and formation of black eschar.[4,5] The risk of rhino-orbital-cerebral mucormycosis co-infections in patients with acute respiratory distress syndrome (ARDS), receiving broad-spectrum antibiotics, corticosteroids, and supported by invasive or non-invasive ventilation is even higher.[2,6,7] Coronavirus disease 2019 (COVID-19) has been declared a pandemic disease associated with substantial mortality and morbidity worldwide. The prevalence of co-infection was 63.64% among COVID-19 fatalities in a current study.[7]

2. Materials and Methods

This prospective, interventional clinical study was performed in the Department of Ophthalmology of

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Chhattisgarh Institute of Medical Sciences, Bilaspur, C.G. from May 2021 to July 2021. The study included 20 patients hospitalized with microbiologically confirmed ROM co-infection in severe COVID-19 patients with ophthalmic manifestations. Severe COVID-19 was defined as oxygen saturation < 93% in room air (PaO2/FiO2 < 300 mmHg), respiratory rate > 30 breaths/minute, and > 50% involvement of the lung parenchyma on chest computed tomography (CT).[4]

Patients' demographic data, clinical manifestations, underlying systemic conditions, laboratory and radiological investigations, medical treatment, and surgical interventions were recorded. The data recorded included age, gender, duration of the symptoms, history of DM, status of control of DM at presentation, any other immune deficiencies, clinical/radiologic involvement of the orbital apex, cavernous sinus, or the central nervous system (CNS), history of steroid use and that of immunomodulators, the CT severity scores (1–25) and the CORAD scores.

A detailed history, comprehensive ophthalmologic evaluation, otorhinolaryngological, and neurological examinations were assessed to determine the disease's extent and severity. Orbital apex syndrome was defined as the simultaneous dysfunction of the optic nerve and the cranial nerves, presenting with vision loss, ptosis, fixed and dilated pupil, and a complete internal and external ophthalmoplegia as a result of extensive orbital mucormycosis invasion to the optic canal region and the superior orbital fissure. Orbital cellulitis was defined as pain, proptosis, limitation of extraocular movements, and decreased visual acuity resulting from orbital involvement of mucormycosis.

Routine blood investigations were done, including complete blood counts, blood sugar, liver function tests and renal function tests. Diagnosis of mucormycosis was made microbiologically based on a demonstration of broad aseptate hyphae with right-angled branching on 20% potassium hydroxide (KOH) preparation of specimens obtained from the nasal cavity and/or paranasal sinuses and Sabouraud's Dextrose Agar culture reports. CT and/or magnetic resonance imaging (MRI) of paranasal sinuses, orbit, and brain were obtained to identify the disease's extent.

Diabetes was controlled with insulin therapy. All patients received systemic amphotericin B and seven patients received TRAMB. The systemic dose was 1.0 mg/kg/day, increasing a total dose of 2.5–3 g, and the retrobulbar dose was 1 ml of 3.5 mg/ml.

Three consecutive doses of TRAMB containing the same dose were given. The maximum duration of therapy for systemic antifungal was 6 weeks. Renal functions were monitored throughout the treatment. All patients underwent functional endoscopic sinus surgery with extensive debridement of involved sinuses and sinus lavage by amphotericin B, and specimens obtained were sent for histopathology and mycology. Repeat surgery was performed, when necessary, based on the clinical course of the patients.

The outcome of treatment was assessed in terms of favorable and unfavorable outcomes. A favorable outcome was defined as a complete resolution of the infection or stabilization without further progression on radiology at the end of follow-up. Treatment failure was defined as recurrence of disease & death due to the intracranial spread of the infection.

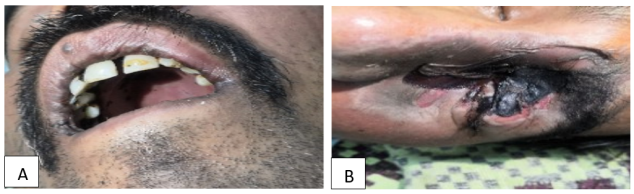

Fig. 1: A): Photograph of patient with left eye black eschar and necrosis of eyelid; **A):** Blackening of hard palate and gingival gum

The patient was diagnosed COVID-19 positive 3 months before the formation of black eschar and was on ventilator support for 15 days with use of systemic corticosteroids, he was diagnosed diabetic 15 days after testing COVID-19 positive. Patient was admitted in CIMS, Bilaspur in poor general condition, semiconscious, severe COVID respiratory distress, necrosed eyelids of left eye, exposure keratopathy, loss of vision and complete ophthalmoplegia. The patient died on the first day of admission. The authors obtained the patient's publication permission by the Patient Consent Form for Figure 1.

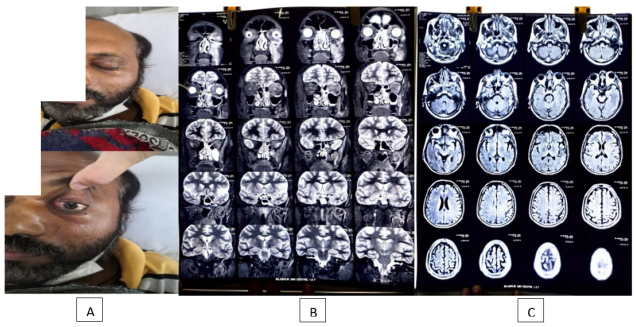

Fig. 2: A): Photograph of patient with left eye orbital apex syndrome; **B):** Patient presented with proptosis, lagophthalmos, conjunctival chemosis, complete ophthalmoplegia and loss of vision; **C):** Axial magnetic resonance imaging T2-weighted scan showing signs of ethmoid and sphenoid sinusitis with the involvement of left medial rectus muscle and retroorbital fat

Fundus examination of patients left eye showed signs of central retinal artery occlusion. The patient presented with left eye orbital apex syndrome after 1 week of testing

COVID-19 positive. The patient received oxygen support and systemic corticosteroids for first 3 days of admission. He was a known case of type II diabetes mellitus for 6 years on regular oral medication. He had to undergo left eye exenteration due to rapid progression of disease. The authors obtained the patient's publication permission by the Patient Consent Form for Figure 2.

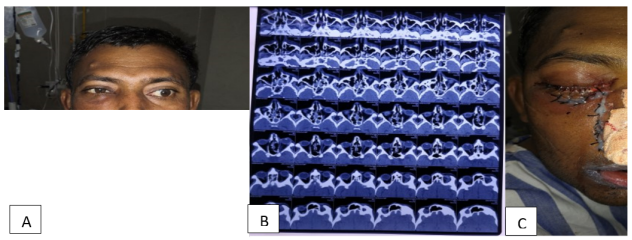

Fig. 3: A): Photograph of patient with right eye periorbital edema and chemosis; **B):** Axial magnetic resonance imaging T1-weighted scan showing signs of right maxillary, frontal, ethmoid and sphenoid sinusitis with the involvement of right inferior rectus muscle and extraconal fat; **C):** Post-operative picture of the patient who underwent right total maxillectomy, ethmoidectomy, uncinectomy, sphenoidectomy, debridement of inferior rectus muscle and removal of right orbital floor

Fundus examination of both eyes presented no abnormality. He was given three consecutive doses of TRAMB before operation. The authors obtained the patient's publication permission by the Patient Consent Form for Figure 3.

2.1. Statistical analysis

The data was arranged on an Excel spreadsheet. Relevant statistical analysis was done using SPSS 22. Continuous parametric data were reported using the mean (±SD) and nonparametric data were reported as the median. Chi-square test were performed to assess the effect of multiple factors that might have influenced the outcome and mortality. A p-value of <0.05 was assigned as statistically significant.

3. Result

The study included twenty patients. All patients developed ROCM following COVID-19 infection. There were nine (45%) females and eleven (55%) males. The mean age was 57.5 years (range: 45-70 years). All twenty-six (100%) patients had uncontrolled type 2 diabetes with a mean diagnosis duration of 3.67 years. All twenty-six (100%) patients had COVID-19-associated acute respiratory distress syndrome and were put under oxygen support and received corticosteroids in the past. Three (15%) patients had no perception of light in both eyes at time of presentation, 4 (20%) patients had <6/60 in both eyes, 2 (10%) patients had perception of light only, 4 (20%) patients had visual acuity <1/60, and the rest patients had good ambulatory visual acuity. Three (15%) patients had a chronic renal failure at the time of presentation; one developed acute renal failure during the course of treatment. The mean chest CT severity score was 15.95 ± 4.74 (median: 17). Three (15%) patients' coagulation status showed an increase in D-Dimer and received low molecular weight heparin (1 mg/kg body weight). The mean time interval between COVID-19 diagnosis and ROM diagnosis was 3.46 days (range: 10-60 days). All patients underwent sinus surgery within an average of 2.1 days of admission after being evaluated and investigated completely.

The left eye was involved in nine patients (45%), while the right eye was involved in eleven patients (55%) and only two patients had involvement of both the eyes (10%). MRI findings showed involvement of lateral rectus muscle in 7 (35%) patients, medial rectus muscle in 1 (5%) patient, inferior rectus muscle in 6 (30%), and involvement of extraconal fat in 13 (65%).

Fever was noted in 12 (60%). Headache and eye pain were noted in 18 (90%) and 20 (100%) patients respectively. 10 (50%) patients had proptosis while ptosis was noted in 5 (25%) and facial swelling and pain were noted in 10 (50%). Extraocular muscle limitation was noted in 4 (20%) patients.

Mouth lesions were seen in 5 (25%) and the classic black eschar on nasal endoscopy was noted in 100% of cases while one patient presented with black eschar over upper eyelid. On imaging, features of orbital cellulitis and orbital abscess were seen in 6 (30%). Other imaging features included paranasal sinus involvement (100%), orbital apex involvement in 4 (20%), CNS involvement in 3 (15%), and cavernous sinus involvement in one case.

Out of all 20 ROCM patients the ethmoid (90%) and maxillary sinuses (82.4%) were the most commonly involved, followed by sphenoid (75%) and frontal (72.5%), which is in line with the literature.[8] In total, sixteen patients (80%) had multiple sinus involvement. Intracranial involvement was revealed in three patients at initial presentation, who died within 1 day of admission due to systemic dissemination of mucormycosis. Seven patients who received TRAMB showed good ophthalmic outcome with no further progression of mucormycosis.[9]

External ophthalmoplegia reversed in seven patients who received retrobulbar liposomal amphotericin B and were radiologically stable at the end of follow-up >6 months. Sinus debridement and systemic treatment with antifungals were performed in all patients. Following debridement, the sinus cavity was irrigated with 5 ml of amphotericin-B in a dose of 1 mg/ml. Induction treatment was initiated with intravenous liposomal amphotericin-B in a dose of 5 mg/kg/day under monitoring of renal functions for 2 weeks. Following this, patient was shifted to maintenance therapy with oral Posaconazole in a dose of 300 mg BD for day 1 followed by 300 mg OD for a period of 4–6 weeks. Four (20%) patient was unable to complete the 2

Table 1:

	Number of cases (N) %
Cases	20 (100)
Mean age (range)	57.5 (45-70)
Gender (F:M)	9 (45):11 (55)
Accompanying diseases	
Diabetes	20 (100)
Hypertension	12 (60)
Thyroid disease	3 (15)
Heart disease	2 (10)
Facial palsy	4 (15)
CKD	3 (15)
Locations of involvement	
Sino orbital	20 (100)
Rhino Orbital Cerebral	3 (15)
Rhino cerebral	0
History of	
Laboratory Confirmed COVID-19 positive	20 (100)
Hospitalization with oxygen	20 (100)
Steroid use for COVID treatment	20 (100)
Treatment	
Surgical debridement	20 (100)
Systemic Amphotericin B	20 (100)
Retrobulbar Amphotericin	7 (35)
Outcome	
Survival	17 (85)
Recurrence on follow up	4 (20)
Death	3 (15)
Orbital apex syndrome	4 (20)
Orbital cellulitis	6 (30)
Imaging manifestation (CT/MRI)	
Thickening of sinus mucosa	20 (100)
Intra-orbital involvement	13 (65)
Inflammation in periorbital muscle	14 (70)
Involvement of cavernous sinus	1 (5)
Signs of cerebral infarct	3 (15)

Table 2:

Signs/symptoms	Number of cases (N)	%
Breathing difficulty	3	15
Fever	12	60
Headache	18	90
Eye pain	20	100
Diminution of vision	20	100
Cranial nerve palsy	6	30
Blepharoptosis	5	25
Facial swelling and pain	10	50
Periorbital edema	18	90
Ocular purulent discharge	1	5
Proptosis	10	50
Fundus examination findings		
Central retinal artery occlusion	2	10
Optic atrophy	3	15
Macular atrophy	1	5
Myopic fundus	5	25
Choroiditis patch	4	20

weeks induction therapy with liposomal amphotericin-B in view of development of renal failure and were shifted to maintenance therapy early. The antifungals were stopped as soon as no progression on clinical examination or on radiology was noted. The mean follow-up duration was 5.62 ± 0.78 months (median 6). A favorable final outcome was seen in 13 (65%) cases. An unfavorable outcome was seen in 7 patients (35%). Of this mortality was seen in 3 (15%) and in the remaining 4 (20%) patients the disease remained unchanged on radiology at the end of follow-up even after repeat surgery.

4. Discussion

The presence of uncontrolled diabetes and comorbidity, orbital apex involvement, CNS involvement, the duration of steroid use during active phase of COVID-19 infection and the stage at which antifungal treatment was started were associated with determination of treatment outcome.

Severely ill COVID-19 patients have higher pro-inflammatory cytokines, including interleukin (IL-1, IL-2, IL-6), tumor necrosis factor-α, increase in IL-4 and IL-10 levels of anti-inflammatory cytokines, less CD4 interferon-γ expression, and fewer CD4 and CD8 cells. [7, 5] Besides the disease's immunological features, most people affected by severe COVID-19 are old and have other predisposing conditions such as type 2 diabetes mellitus. In addition to these, the patients frequently receive broad-spectrum antibiotics and corticosteroids. Also, they are supported by invasive or non-invasive ventilation due to severe ARDS. As a result, critically ill COVID-19 patients are candidates for very high-risk ROM. Although there is no direct relationship between COVID-19 and mucormycosis, the findings mentioned above suggest the existence of an indirect association. While immune suppression with steroids may be required in moderate to severe COVID-19, the use of steroids and the worsening glycemic control provide an opportunity for mucor to become invasive. [10–16] Mucor produces keto-reductase as a virulence factor enabling them to grow in the acidic and glucose-rich environment generated in ketoacidosis states. [10,12–14]

In all of the patients in the present study, the presence of diabetes mellitus, history of use of steroids for COVID-19-related ARDS, and the fact that 80% of the patients were treated in the ICU under oxygenation illustrate the above-mentioned association between COVID-19 and mucormycosis.

Moorthy et al[16] reported the association of COVID-19 infection with uncontrolled DM and usage of corticosteroids. Similarly, Sen et al[17] reported a series of 6 diabetic patients with concurrent mucormycosis and

COVID-19 infection. Sarkar et al[18] reported a series of 10 diabetic patients with ROCM post-COVID-19. All their patients had uncontrolled blood sugar values and were treated with steroids during active COVID-19 infection. Current literature suggests that usage of systemic steroids in patients, who otherwise may have controlled diabetes, or may not be diabetics at all, can precipitate mucormycosis.[19–23] Mekonnen et al[24] reported a case of invasive fungal rhinosinusitis with orbital involvement in a patient with COVID-19 with uncontrolled DM and HbA1c of 14%.

Moorthy et al[16] reported 18 patients with ROCM with COVID-19 infection. Loss of vision was noted in 67% of patients and 39% underwent orbital exenteration. Mortality was seen in 33%. Ravani et al[25] published a series of 31 patients with ROCM following COVID-19 and suggested that the presence of cerebral involvement and a HbA1c value of ≥8 was found to be significant in the prediction of mortality in this subset. Our findings are in accordance to this observation.

As a result, the overall survival rate of our patients was 85%; only three of our patients died due to intracranial extension of mucormycosis in COVID-19 patients. In a previous review, including ROM in non-COVID-19 patients, the overall survival rate was 59.5%.[18]

TRAMB should be considered an adjunctive non-surgical treatment modality to prevent exenteration and halt orbital progression.[9] The administration of TRAMB may cause a post-injection pro-inflammatory state mediated by increased cytokine expression and increased edema or conjunctival chemosis with development of an orbital compartment syndrome. None of our patient experienced this form of reaction. Close monitoring of the patient's orbital examination including visual acuity, development of conjunctival chemosis and intraocular pressure (IOP) testing was critical.

This study's limitation is that our results may not reflect the exact survival rate of ROM in COVID-19 patients and it has a small sample size.

5. Conclusion

In conclusion, this study's outcomes show that ROM incidence has dramatically increased with higher mortality rates in severe COVID-19 patients. These results suggest that the prognosis of preexisting ROM may be worse after severe SARS-CoV-2 infection. SARS-CoV-2-related immune dysregulation, the widespread use of steroids/broad-spectrum antibiotics, and ventilatory support seem to be the main factors that make patients susceptible. An aggressive multidisciplinary approach to ROM can help reduce mortality. Early diagnosis, control of the systemic predisposing factors, prompt initiation of systemic and retrobulbar antifungal therapy in patients having intraocular involvement, and radical debridement of involved sinuses are crucial to improving outcomes.

6. Source of Funding

None.

7. Conflict of Interest

None.

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