

## Study of Clinical Profile with Radiological and Histopathological Evaluation of Patients with Orbital Mucormycosis in COVID-19 Era

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### Abstract

**Introduction:** “Mucor” is a fungus normally found in the environment, mainly in soil. Mucormycosis occurs in patients with compromised immunity like uncontrolled DM, prolonged ICU stay, post organ transplant, patients on anti-cancer drugs, prolonged use of steroids (any dose for >3weeks or high dose >1week), HIV/AIDS, prolonged neutropenia, IV drug abusers, etc. Recently, abrupt rise is being reported in Mucormycosis cases with COVID-19 spread, leading to serious ocular complication like globe proptosis, blurred vision, loss of vision and eye and may be life threatening.

**Objective:** To study the clinical profile of patients with Orbital Mucormycosis with radiological and histopathological evaluation during covid-19 pandemic.

**Methodology:** We evaluated the clinical and imaging data of ten patients-seven males and three female, 20 to 65 years old diagnosed of Orbital Mucormycosis. All the patients included in the study had recent history of COVID-19 infection. On evaluating risk factors: 5-diabetes mellitus, 3-prolonged ICU stay, rest 2 were with concomitant immunocompromised state.

**Results:** All patients included in the study received - IV Dexamethasone for COVID-19 related disease and IV Amphotericin B for Orbital Mucormycosis. Besides that, eight patients received Inj. Remdesivir, and nine patients were on additional Ventilatory support. Within 4-5 weeks of the diagnosis, three patients could not survive, five patients showed satisfactory systemic outcome but with ocular complication of irreversible vision loss, while two patients showed favourable outcome in ocular as well as systemic ailments.

**Conclusion:** COVID 19 infection recently emerged as a risk factor for Orbital Mucormycosis.

**Keywords:** Orbital Mucormycosis; Radiological and histopathological evaluation; COVID-19 infection.

### Introduction

“Mucor”- a fungus normally found in the environment as commensal, mainly in soil. Mucormycosis usually occurs in patients with compromised immunity viz. uncontrolled DM, prolonged ICU stay, post-transplant, patients on anti-cancer drugs, prolonged use of steroids (any dose use for >3weeks or high dose >1week), HIV/AIDS, prolonged neutropenia, IV drug abusers, etc. This fungus is unique to cause severely devastating disease in patients with

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ill controlled diabetes mellitus and immunocompromised patients, and often lead to significant morbidity and mortality. The commonest clinical manifestation is Rhino-orbital cerebral Mucormycosis (ROCM)<sup>1</sup>. Recently, abrupt rise is being reported in Mucormycosis cases with COVID-19 spread, leading to serious ocular complication like globe proptosis, blurred vision, loss of vision and eye and may be life threatening.

A number of hospitals mostly in India, Pakistan and Egypt, have reported an increased rate of ROCM cases during the first wave of the pandemic<sup>2</sup>.

Clinical presentation of patients with ROCM:

- Fever, headache, nausea, and generalized weakness as initial complaints
- Nasal discharge (blackish/bloody, foul smelling) with or without epistaxis.
- Sinusitis and Nasal ulceration with black Eschar
- Periorbital or retro-orbital pain with swelling or redness, diplopia, blurred vision, painful proptosis
- Vitritis and/or Endophthalmitis, optic disc edema.
- Partial or complete loss of vision
- One sided facial pain, numbness or swelling, Palatal eschar
- Cranial nerve palsies with varying involvement of II, III, IV, V, VI, VII nerves
- Cavernous sinus thrombosis, Superior orbital fissure syndrome and Superior ophthalmic vein thrombosis
- Altered consciousness, unstable gait, and/or seizures

## Methodology

An observatory study conducted at Department of Ophthalmology, Shri Vasantrao Naik Govt. Medical college, Yavatmal, evaluated the clinical, imaging and histopathological data of 10 cases (20 to 65 years) with Mucormycosis of the craniofacial areas- ROCM (Rhino-orbito-cerebral Mucormycosis) out of which 7 were males and 3 were females. Written informed consents were obtained from all study patients in accordance with the declaration of Helsinki. Duration of study = The cases included were collected from 9th November 2020 - 9th January 2021. Selection of patients for study was done by confirmed diagnosis of Mucormycosis established by means of biopsy, culture, or autopsy, along with supportive findings on Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI). Also, all the patients included in the study had recent history of COVID-19 infection tested RTPCR positive. On evaluating risk factors: 5-diabetes mellitus, 3-prolonged ICU stay, rest 2 with concomitant immunocompromised states.

Ethical approval was not required as there was no active intervention done to the patients included in the study.

## Diagnosis of Rocm

Reaching an early definite diagnosis of Mucormycosis is challenging, whereas the delay in diagnosing the condition and initiating the treatment will further aggravate the morbidity and mortality. High index of suspicion is thus imperative for early diagnosis.

## Radiological diagnosis:

CECT Nose and PNS: Erosion and thinning of bones, masticatory muscle enlargement, mucosal thickening in the sinuses, changes in fat planes. With involvement of the cavernous sinus, CECT scan shows lack of enhancement in the cavernous sinus area, which points towards cavernous sinus thrombosis due to deep fungal invasion. Other radiographic findings are- soft tissue thickening along the paranasal sinuses, with opacification and fluid levels in the sinuses, may also show bony destruction. MRI Brain, Orbit and Face: Evidence of optic neuritis, orbital apex syndrome, superior orbital fissure compression syndrome, Intracranial extension of inflammation and necrosis, Cavernous venous sinus thrombosis, Infratemporal fossa involvement. MRI demonstrates variability in T1 and T2 intensity with focal areas of lack of enhancement in areas of devitalized sinus mucosa and eschar.

Because above mentioned are often nonspecific-findings, it can be difficult to distinguish Mucormycosis from other similar inflammatory sino-orbital conditions. However, once the diagnosis of Mucormycosis has been confirmed on histopathology or culture reports, CT and MRI can be very helpful to delineate the extent of damage and thus guide on modality of management (surgical debridement).

## Histopathological diagnosis:

The signs, symptoms, and radiographic findings of Mucormycosis are nonspecific; thus, direct histopathological examination of scraping/biopsy sample of involved tissue or paranasal sinus secretions obtained endoscopically are diagnostic. It shows haemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils (in non-neutropenic hosts), and perineural invasion.

The fungal invasion may be patchy, so multiple biopsies are required for definitive diagnosis.

Biopsy need to be repeated if initial report was negative, yet the patient had signs/symptoms of progressive orbital involvement and imaging also revealed sinus involvement (high suspicion).

Histopathology with special stains—such as Grocott Gomori methenamine silver nitrate (GMS), periodic acid–Schiff (PAS), or calcofluor white stain shows –pathognomonic

broad ribbon-like hyphae (at least 6–16µm wide, irregular, non-septate, and branching hyphae at right-angle).

Evidence of angio-invasion (vessel occlusion) and tissue ischaemia are also suggestive of severe inflammation due to invasive fungal infection.

Fungal culture- Routine culture media at 30°C and 37°C in standard conditions. Typical findings on culture media-cotton like white to greyish black colonies.

### Treatment of Rocm

Management of rhino-orbital cerebral Mucormycosis is a medical as well as surgical emergency. A three-pronged approach is undertaken- control of immunosuppressive state with simultaneous early administration of IV antifungals, and extensive surgical debridement based on the amount of damage.

### Control of underlying risk factors

Strict glycaemic control, treating co-morbid illness or infection, judicious use of systemic steroids. Review the ongoing Covid-19 treatment for immunomodulators and steroid to be used optimally. Regular monitoring by simple tests like pupillary reaction, ocular motility, sinus tenderness and palatal examination for progression to orbital/ intracranial involvement. Use of clean distilled water for humidifiers during oxygen therapy to critically ill patients.

### Medical Treatment

Antifungal treatment with Amphotericin B/ Posaconazole- Inj. Amphotericin B = 1.0-1.5 mg/kg/day or Inj. Liposomal amphotericin B = 5-10mg/kg/day (intra cranial involvement-10 mg/kg /day), Tab. Posaconazole 200 mg QID or, Posaconazole delayed-release tablets (300 mg every 12 hours on first day, then 300 mg once daily) taken with food. Continue treatment till resolution of initially indicative findings on imaging and reconstitution of host immune system. Amphotericin monitoring chart to be maintained daily for dosage monitoring based on urea, creatinine and serum electrolytes.

### Surgical treatment

Urgent surgical debridement to be considered in all patients of diagnosed Mucormycosis to minimize its progression and mortality. Surgical debridement can be done endoscopically or through an open approach to remove all necrotic tissue.

### Indications for surgical treatment

- When Nasal and sinus involvement is present without bony erosion- Endoscopic sinus debridement surgery.
- When bony erosion involves Maxilla - Maxillectomy (partial/ total).

- Maxilla + Minimal zygoma involvement – Maxillectomy (partial/ total) with Zygoma debridement.
- Maxilla+ Zygoma+ Orbit involvement – Maxillectomy (partial/ total), Zygoma debridement, Debridement of Orbital floor/walls with debridement of necrosed tissue of localised orbital disease.
- Orbital Exenteration - 1) Vision loss 2) Total ophthalmoplegia 3) Necrosis of orbital tissues
- (NOTE: vision loss is not always the indication of exenteration)
- Regular periodic debridement is to be done until clinical improvement is established.
- When Frontal bone and skull base involved – 1) Anterior table: Debridement; 2) Posterior table: Cranialization; Debridement of osteomyelitic skull bones.

### Results

All patients included in the study received IV Dexamethasone for COVID-19 related disease and IV Amphotericin-B for Orbital Mucormycosis. Besides that, 8 patients received Inj. Remdesivir, and 9 patients were on additional ventilatory support. Within 4-5 weeks of the diagnosis, 3 patients could not survive (2 died of severe acute respiratory distress syndrome leading to septic shock and 1 died of advanced Mucormycosis and cerebral involvement) accounts to 30% (3/10) mortality rate. Out of the remaining 7 cases, 5 cases showed satisfactory systemic outcome but left with ocular complication of irreversible vision loss due to optic nerve damage despite best available treatment, which accounts to 50% (5/10) ocular morbidity. Only 2 patients showed favourable outcome (ocular and systemic both).

### Discussion

Study by White et al. conducted by screening of 135 cases diagnosed with COVID-19 infection and reported an incidence of 26.7% of invasive fungal infections and these cases had higher mortality (53% with vs 31% without), which was significantly reduced by appropriate timely therapy<sup>3</sup>.

A case study by Hanley et al. on a 22-year-old male with COVID-19 Pneumonia and a middle cerebral artery infarct in whom Disseminated Mucormycosis involving the brain was incidentally discovered during postmortem study<sup>4</sup>.

A case of a 33-year-old female reported by Werthman Ehrenreich, presented with left-sided complete ptosis, severe proptosis and altered sensorium coexisting with diabetic ketoacidosis and COVID-19 infection. On investigating the case, Facial imaging showed significant maxillary and ethmoidal sinus mucosal thickening, MRI brain showed multiple areas of infarction and ischemia suspicious of invasive fungal disease. On nasal biopsy, Mucor was demonstrated that confirmed the diagnosis<sup>5</sup>.

A case report on a 55-year-old male patient, evaluated after discharging from COVID-19 infection ward with long standing uncontrolled DM, who received IV steroids and ventilator support for the management of COVID-19 related respiratory infection. This report emphasizes on the radiological diagnosis of ROCM and focusses on importance of follow-up imaging in post COVID-19 infection cases with a strong suspicion of opportunistic infections in immunocompromised hosts<sup>6</sup>.

A case study on a middle-aged woman with DM type 2, presented with left-sided facial pain, complete blepharoptosis and total ophthalmoplegia of the left eye with reduced visual acuity. She tested positive for COVID-19. On imaging, CT paranasal sinus revealed left-sided pansinusitis and MRI brain showed acute infarction in the left parieto-occipital region without angioinvasion. On Endoscopic sinus procedure, diagnosis of Mucormycosis confirmed after histopathological examination of sinus aspirates. Thus, this study highlights on rapid progression of invasive fungal infection like mucormycosis to orbital apex syndrome with brain infarction in a patient with COVID-19 infection<sup>7</sup>.

A case report presented by Bobby S. Corn on 2 fatal cases of ROCM associated with COVID-19 infection where both patients had risk factors like pre-existing diabetes mellitus type 2, were treated with high dose corticosteroids, and also developed ketoacidosis. Both patients showed rapid extension of invasive fungal infection into the intracranial cavity. Hence, the study postulated that corticosteroids, mechanical ventilation and Sars-CoV-2 induced immunosuppression are emerging risk factors for opportunistic fungal infection that occurs in COVID-19 cases. Therefore, the ophthalmologist's role is particularly important in the early diagnosis of Mucormycosis associated with COVID-19<sup>8</sup>.

A case study of 60-year-old man with history of poorly controlled type 1 DM, Asthma, Hypertension, Hyperlipidemia, and recent travel, also tested positive for SARS-CoV2, developed ARDS over time and this case reported acute invasive fungal rhinosinusitis with orbital involvement in the patient with COVID-19 which faced numerous challenges in early diagnosis and prompt therapy.

Owing to the robust inflammation and concurrent immunosuppression evidently seen in COVID-19 and use of immunosuppressive drugs, it is believed that the dysregulated immune response helps to provide a hospitable environment for the development of opportunistic fungal co-infections<sup>10</sup>.

## Conclusion

COVID 19 infection recently emerged as a risk factor for Orbital Mucormycosis. The extensive use of steroids, other

immunomodulators like monoclonal antibodies, and broad-spectrum antibiotics for the widespread management of COVID-19, increases the chances of new onset opportunistic fungal infection or exacerbate a pre-existing one. Rhino-orbital cerebral Mucormycosis is an angio-invasive disorder with high morbidity and mortality despite treatment.

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