

## Mucormycosis in Covid; A Diagnostic and Therapeutic Challenge

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### Abstract

Mucormycosis was first reported as cause of human disease in 1885. Its an acute necrotizing fungal infection with fulminant course due to angioinvasion, being potentially deadly fungal infection with a mortality rate of 50%. It has been challenge for us to address in patients who had covid-19 infection. The rise in number in developing countries has been evident among those with uncontrolled diabetes and renal failure. Use of steroids early in the disease, continuous use of high flow oxygen, dry air in ICU, use of nasal prongs can cause dryness of nose and prolonged bedridden state thereby reducing nasal mucosal immunity are some of the attributable causes. This is a retrospective observational study of 71 post covid patients reported to our department with their confirmed histopathological reports of mucormycosis. About 68% of patients presented with "only sinus" type of mucormycosis. 20% presented with "rhino-orbital" and 12% with "rhino-orbital-cerebral" presentation. Palatal erosion was more common in sinus type. Involved facial tissues, including skin and muscle, any implicated skin on the nose, the maxillary and ethmoid sinuses, necrotic tissue in the infratemporal fossa, and orbital exenteration are all removed during surgery. Endoscopic debridement of disease with Intravenous Amphotericin B injection was the basis of treatment. The study indicates different management approach medically and surgically with great flexibility was the need of hour. Rapid Diagnostics, early antifungal therapy and prompt surgical intervention are essential.

**Keywords:** Black Fungus; COVID19; Uncontrolled Diabetes Mellitus; Mucormycosis; Amphotericin B; Posaconazole

### Abbreviations

MRI: Magnetic Resonance Imaging; CT: Computed Tomography; DM: Diabetes Mellitus; CAM: Covid Associated Mucormycosis; RFT: Renal Function Test; LFT: Liver Function Test; CRP: C-Reactive Protein

### Introduction

Mucormycosis was first reported as a cause of human disease in 1885. During the last two decades, there has been a dramatic increase in the occurrence of invasive fungal infections observed worldwide largely as a result of the increase in the size of the

population at risk. During this period of increased incidence, mucormycosis has not proven to be the exception. It is usually an acute necrotizing fungal infection with a fulminant course due to angioinvasion. Who would have thought that even as we struggle to fight off the Covid-19 threat, another one could emerge in its shadow. Mucormycosis, a serious potentially deadly fungal infection with a mortality rate of 50 percent would become another challenge for us to address immediately.

The rise in the number of patients in developing countries has been particularly evident among those with uncontrolled diabetes and renal failure. Use of steroids early in the disease, widespread use of Intravenous tocilizumab which acts like an Immunosuppressant, continuous use of high flow oxygen, dry air in ICU, use of nasal prongs can cause dryness of nose thereby reducing nasal mucosal immunity are some of the attributable causes.

Prolonged bedridden state can lead to accumulation of nasal secretion in sinus and further reduce nasal mucosal immunity. 2 (SARS-CoV2) has been wreaking havoc and causing a health crisis around the world for more than a year. The care of COVID-19 is still a priority, however numerous secondary Infections caused by bacteria and opportunistic fungi have appeared.

They include COVID-19-associated pulmonary aspergillosis and COVID-19-associated mucormycosis, two rare fungal illnesses (CAM) [1]. The ballooning of CAM during the second COVID-19 wave is cause for concern. In India, 47, 000 CAM cases were documented in just 3months [2]. The order Mucorales is the causative agent of the angioinvasive opportunistic infection known as mucormycosis, which has a global distribution [3]. Rhizopus, Mucor, and Rhizomucor, as well as Cunninghamella, Lichtheimia, and Apophysomyces, are the genera that cause human infection [4]. The typical sources of these omnipresent filaments include soil, manure, fruits, and decomposing materials. These spores of fungi can cause aggressive, life-threatening illness in immunocompromised hosts. Immunosuppressed people, particularly those with untreated Diabetes mellitus (DM), haematological malignancy, chronic malnutrition, chronic liver disorders, and recipients of hematopoietic stem cell transplants, are susceptible to infections brought on by these invasive Mucorales [5]. Clinically speaking, it can be divided into the following categories: rhino-orbital, paranasal sinus, rhino-cerebral, rhino-orbital-cerebral, oral,

pulmonary, gastrointestinal, cutaneous, and disseminated [6]. The rhino-cerebral manifestation is the most frequent, and palatal ulceration or necrosis and subsequent palatal manifestations are the most frequent oral manifestations (Figure 1).

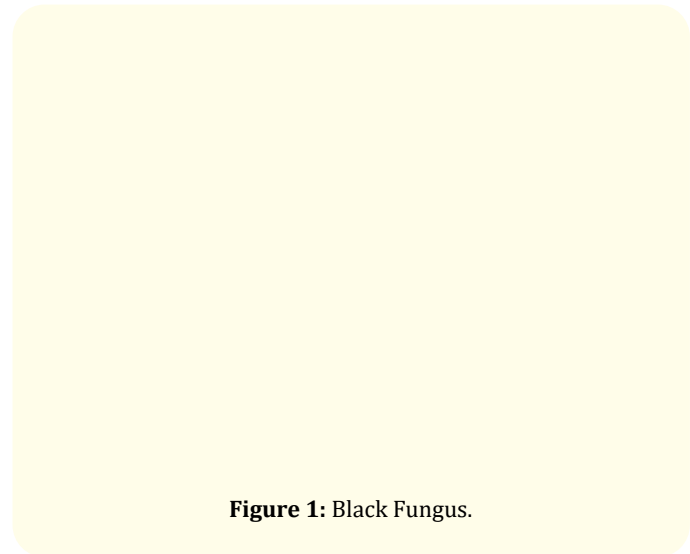


Figure 1: Black Fungus.

### Pathogenesis

Mucorales can enter a vulnerable host through the air they breathe, contaminated food they eat, or rubbed skin. These pathways result in respiratory, gastrointestinal, pulmonary, or infections of the skin or wounds. The angioinvasive property of mucormycosis, which causes vascular thromboses and ultimately tissue necrosis, is one of its distinguishing characteristics. Deferoxamine and ketoacidosis are known to increase the risk of developing mucormycosis, highlighting the significance of hyperglycemia, iron, and acidifying ketone bodies for mucorales pathogenicity. Angioinvasion has been linked to a connection between endothelium glucose regulator protein 78 (GRP78), which is expressed at the surface of endothelial cells, and a spore-coating protein family (CotH) on the surface of Rhizopus spp. This contact results in host cell damage and subsequent hematogenous spread of the fungus. <sup>6</sup> Fungal growth is accelerated by elevated blood glucose, iron, and ketone bodies (Figure 2).

### Aim

To assess challenges involved in diagnosis and treatment of Mucormycosis.

**Figure 2:** Diabetes, COVID-19, and mucormycosis: interactions with corticosteroids. Lymphopenia increases in the endothelial receptor glucose-regulated protein 78 (GRP-78) and spore coat protein homologs of endothelial receptor where COVID-19 is likely to produce hypoxia (Cot-H). Ketoacidosis, excessive corticosteroid use, pre-diabetes, and hyperglycemia are all risks in COVID-19 infection patients. Due to weakened immune systems, COVID-19 causes the production of a cytokine storm (interleukin 6), an increase in free intracellular iron, reactive oxygen species, and the invasion and overpowering of the defence by opportunistic fungi such Mucormycosis [7,8].

### Objective

- To assess type of Mucormycosis among patients reported at Centre.
- To describe various clinical presentations in patients.
- To find cause of different types of Mucormycosis.
- To assess different management protocols.

### Materials and Methods

This was a retrospective, observational study carried out in COVID-19 cases confirmed either by RealTime reverse transcriptase

Polymerase chain reaction or Rapid antigen test in our hospital. A total of 71 cases were included in this study and reported to the Department confirmed histopathological report of Mucormycosis. After obtaining the informed consent of every patient, information concerning demographics, oral symptoms, comorbidities, radiographic features, haematological investigations, therapy, surgical management, and prognosis was gathered. The study was accepted by the institutional ethics committee.

An early diagnosis with a prompt, well-coordinated, multidisciplinary approach has been vital to save the life of a patient.

The protocol followed by our institute was as follows

- **A Complete History:** illness with past history of covid 19 infection including RT PCR status was taken.
- **Nasal endoscopy:** Along with nasal swab was taken for fungal KOH and culture of every patient presenting with above symptoms. In case of crusts, endoscopic biopsy of the crusts was taken from that area and sent for histopathology (Figure 3).

**Figure 3:** Classical black nasal crust as seen on a OPD nasal endoscopy.

- **Histopathological and microbiological diagnosis:** Determined from the morphology using hematoxylin and eosin (H and E), periodic acid-Schiff, and Gomori's\*

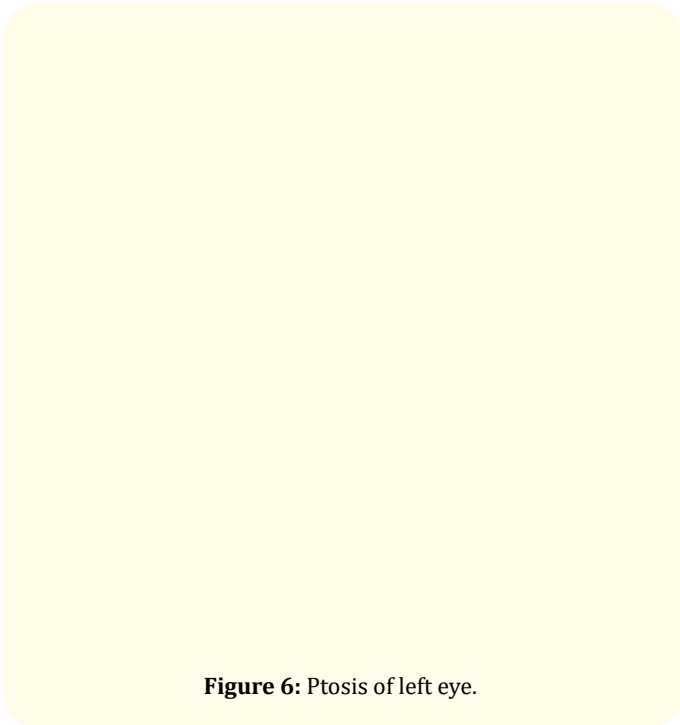
methenamine silver staining. The report was considered as positive when a fungal element, having large non septate branching hyphae, mycelia with surrounding tissue involvement, and/or a positive fungal culture report was seen. Mucor and Aspergillus' species were histologically differentiated based on their microscopic appearance (Figure 4).

**Figure 4:** Hematoxylin and Eosin (H and E) staining showing large Broad aseptate, Regular and Right-angle branching mycelia with surrounding tissue.

- **Radiological diagnosis:** MRI PNS/BRAIN/ORBIT (PLAIN with CONTRAST) was considered as the most effective radiological assessment. T2W fat suppressed coronal cuts helped in establishing the diagnosis, understanding the extent of the disease, involvement of orbit and intracranial extension (including cavernous sinus involvement) if any. CT PNS helped in surgical planning and anatomical variation. Considering the costs involved, we had to operate a few cases with only limited radiological assessment and imaging. CT chest was Done in certain patients with history of recent COVID having shortness of breath and to rule out pulmonary mucormycosis. In cases with no breathlessness or pulmonary complaints, a plain chest radiograph was considered sufficient (Figure 5).

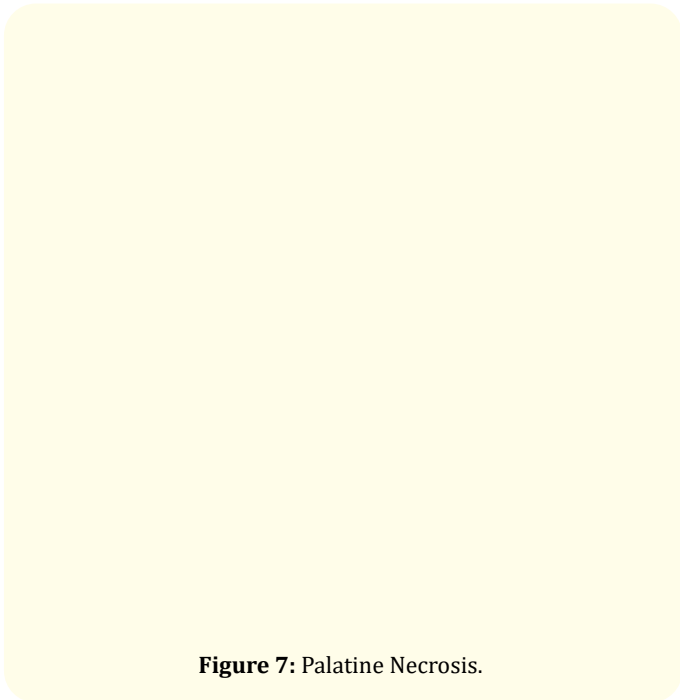
**Figure 5:** Contrast Enhanced MRI T2W fat suppressed coronal cuts.

- **Complete hemogram:** Blood sugar, RFT, LFT, serum electrolytes, CRP, APTT, PT INR, blood urea and creatinine were the routine hematological and biochemical investigations with complete cardiac evaluation was performed.
- **Clinical presentation:** Our hospital has treated around 71 patients including many high risk cases and late presentations. A panoramic view of the various clinical presentations of mucormycosis seen in our institute has been given below.
- **Early signs and symptoms:** Included headache and facial pain, Facial numbness, ophthalmoplegia, and visual loss.
- **Nasal complaints:** Included shortness of breath, nasal blockage, anosmia, hyposmia rhinorrhea, discolored mucosa, granulation, crusting, atrophic rhinitis, septal perforation, necrosed, lateral wall nose.
- **Orbital and eye involvement:** Presented with Epiphora, ophthalmoplegia, ptosis, diplopia,
- vision loss, chemosis, subperiosteal abscess, orbital apex syndrome, extensive inflammation (Figure 6).

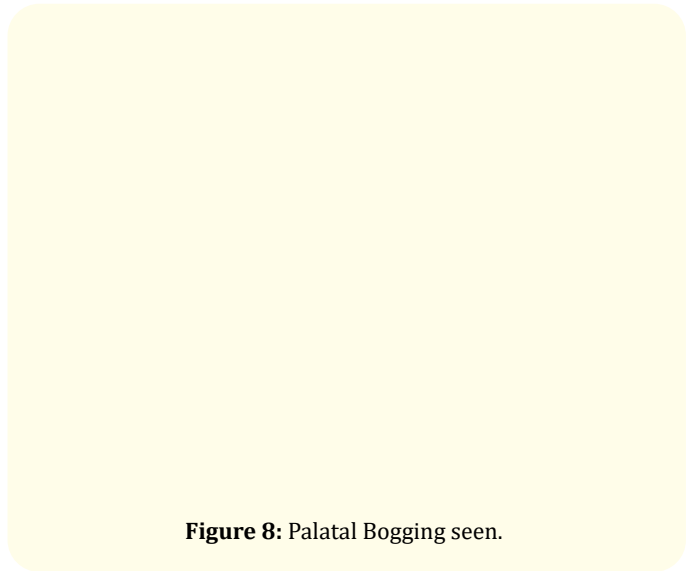


**Figure 6:** Ptosis of left eye.

- **Oral cavity involvement:** Consisted of loosening of teeth, palatal ulceration, unilateral palatal necrosis, central palatal necrosis, oroantral fistula (Figure 7,8).



**Figure 7:** Palatine Necrosis.

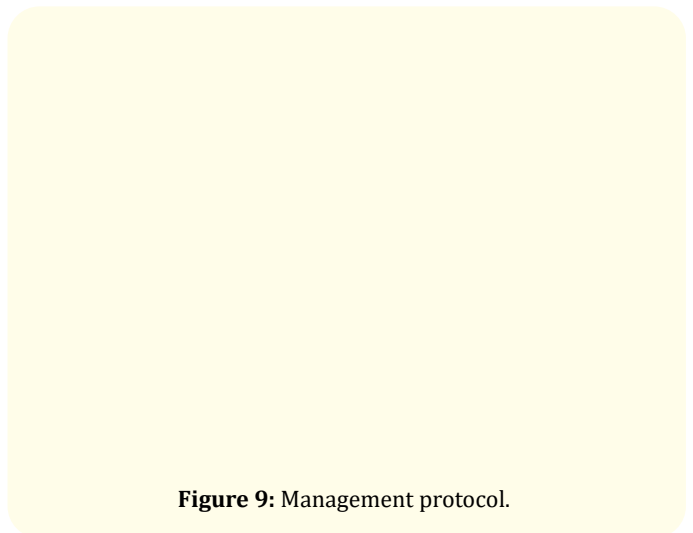


**Figure 8:** Palatal Bogging seen.

- **Central/Intracranial extension:** Altered mental state, facial nerve palsy, cavernous sinus thrombosis, III, IV, VI nerve palsy, temporal lobe abscess, encephalitis, central retinal artery thrombosis.

#### Treatment protocol

Both antifungal medications and surgical intervention together with control of any associated medical conditions are necessary for control of disease (Figure 9).



**Figure 9:** Management protocol.

**MEDICAL-** Liposomal Amphotericin B (L-AmB) is the main line of treatment only after a confirmed microbiological or histopathological diagnosis of mucormycosis.

5-10mg/kg/day (3weeks minimum duration) Should always be mixed with 5% Dextrose. Concentration for IV infusion is 0.5mg/ml to 2 mg/ml. Monitor S. Creat and Electrolyte alternate day for 2-6 weeks.

Another lipid formulation, Amphotericin B lipid complex (ABLCL) could be used in mucormycosis but without central nervous system (CNS) involvement. AmB Deoxycholate which is nephrotoxic is not advisable. Choice of antifungal agents typically consist of amphotericin B, voriconazole, and/or posaconazole and is managed by infectious disease specialists depending on the organism detected and patient's condition with therapeutic drug monitoring.

In stable disease-Posaconazole DR tablets-2 x 300mg on day 1, and 1 x 300mg/day from day 2 as maintenance therapy for a minimum of three weeks. In progressive disease-Posaconazole IV or DR tablets, Posaconazole oral suspension -4 x 200mg/day.

The combination therapy of liposomal amphotericin B and oral posaconazole is for 4 to 7days after resolution to allow for the onset of action of Posaconazole.

In case of intracranial involvement-Isavuconazole was administered with the loading dose is two capsules (equivalent to 200mg) every 8hours for first 48 hours Maintenance dose was once daily after starting 12 to 24hours after first loading dose.

### Surgical

Endoscopic debridement included resection of the middle turbinate, wide middle meatal antrostomy, ethmoidectomy, sphenoidotomy, and medial maxillectomy with or without modified Denker's procedure. Certain cases required Draf III procedure.

Orbital involvement was managed by a wide variety of surgical approaches including endoscopic evacuation of subperiosteal abscess, orbitotomy, orbital decompression, and orbital exenteration in case of orbital invasion with blindness. Neurosurgeon was consulted for operative intervention in the cases complicated by temporal/frontal lobe abscess or involvement of cavernous sinus. Palatal necrosis was managed either by infrastructure

maxillectomy or palatotomy according to extension of necrosis with post-debridement obturator insertion (Figure 10).

**Figure 10:** Surgical Management.

### Post operative care

Every patient underwent nasal endoscopy every 3rd day followed by nasal douching, nasal scabs if present were cleaned off and rebiopsy was taken in cases of recurrence. Blood investigations were done every 3rd day to assess blood sugar levels, serum creatinine, CRP and deranged electrolyte function. We were guided in every step by our physician colleagues in managing these complicated cases.

### Follow up

The patients were asked to keep a follow up every week for first two weeks, then every fortnight for the next month and then monthly visits for the next six months. All these patients underwent a diagnostic nasal endoscopy on every visit.

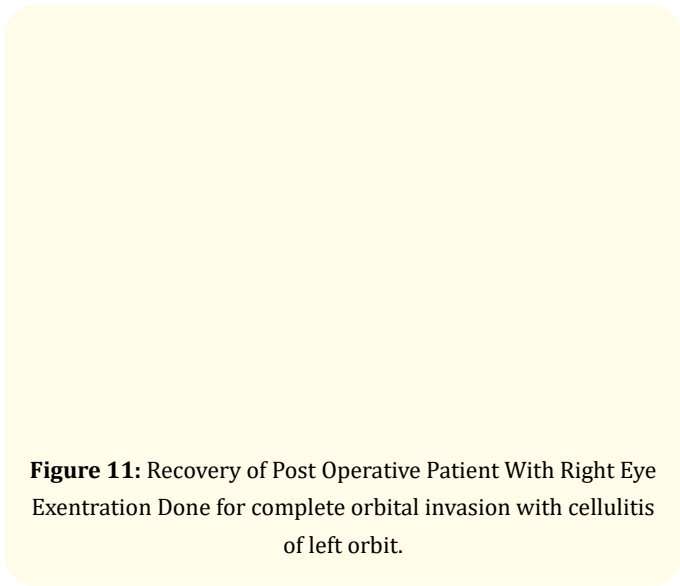
Patients who underwent palatal debridement were followed up with maxillofacial surgeon for further dental treatment and rehabilitation (Figure 11,12).

### Results and Discussion

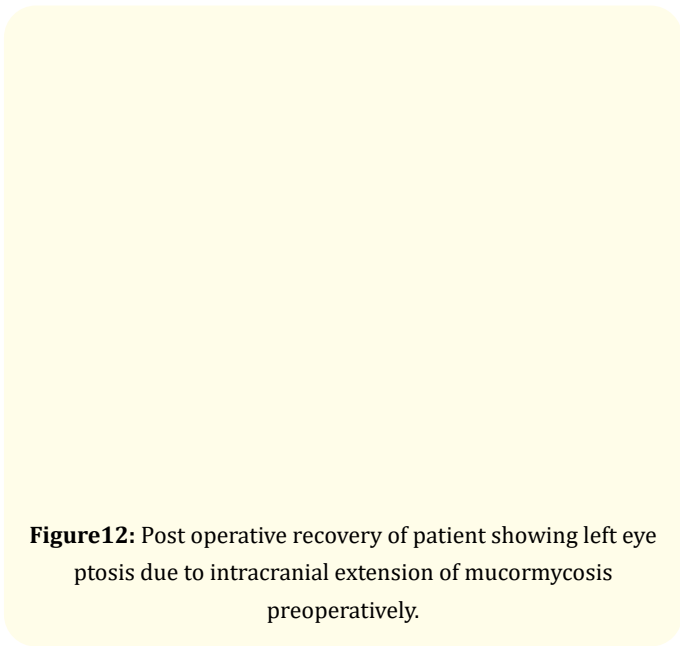
Out of 71 patients

#### Sex

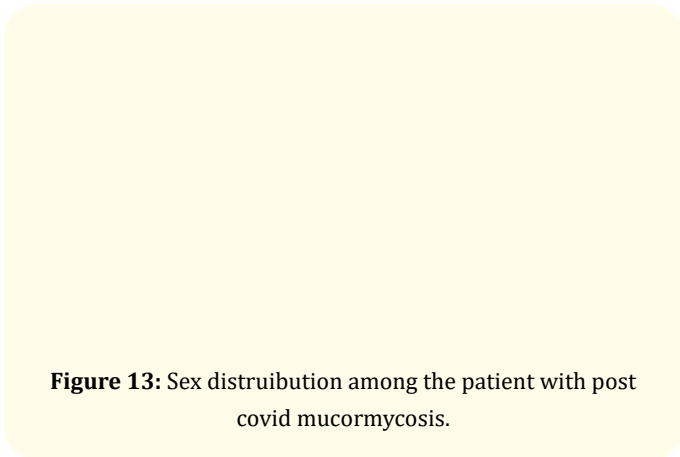
61% patients were male and 39% were female patients (Figure 13).



**Figure 11:** Recovery of Post Operative Patient With Right Eye Exentration Done for complete orbital invasion with cellulitis of left orbit.



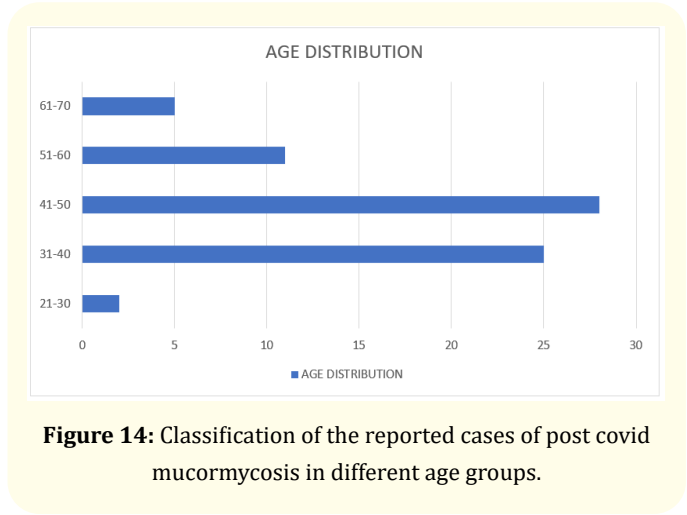
**Figure 12:** Post operative recovery of patient showing left eye ptosis due to intracranial extension of mucormycosis preoperatively.



**Figure 13:** Sex distribution among the patient with post covid mucormycosis.

**Age**

most common presentation was seen in age group of 41-50 years old (Figure 14).



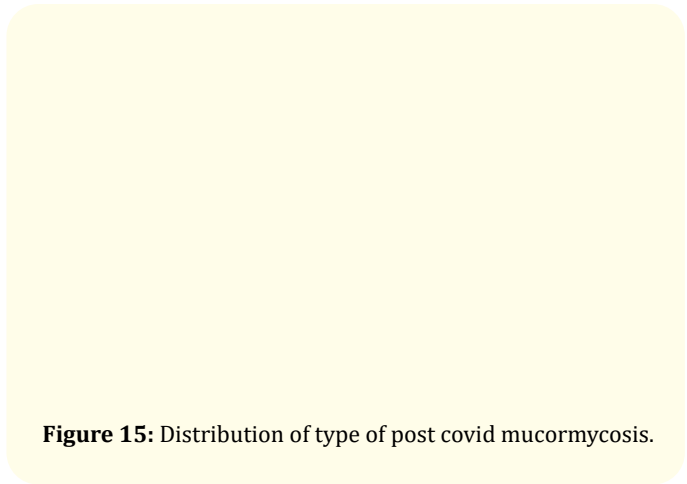
**Figure 14:** Classification of the reported cases of post covid mucormycosis in different age groups.

**Predisposing factors**

- 46% patients presented with pre-existing diabetes mellitus,
- 35% required nasal oxygen prongs during their covid icu admission.
- 35% patients had pre-existing hypertension,

**Type of mucormycosis**

About 68% of patients presented with “only sinus” type of mucormycosis. Palatal erosion was more common in sinus type. 20% presented with “rhino-orbital” and 12% with “rhino-orbital-cerebral” presentation (Figure 15).



**Figure 15:** Distribution of type of post covid mucormycosis.

49 recovered completely, 16 recovered with some sort of morbidity, 3 were lost to follow up with incomplete treatment, while 3 unfortunately had a sad demise. 14 required partial/total infrastructural maxillectomy with primary or secondary closure. 3 were administered retrobulbar Amphotericin B injection post-operatively. 2 patients with extensive eye involvement had to undergo orbital exenteration to save their lives. 2 patients were administered Isavuconazole tablets. 4 had to be shifted to the Critical Care Unit for close monitoring and management.

## Discussion

Mucormycosis is characterised by angioinvasion, which is followed by thrombosis and tissue necrosis. These Mucorales are aggressive due to their inborn thermotolerance, rapid development, fondness for endothelial cells, and capacity to obtain iron from the host [7].

Zygomycetes, a group of fungus that develop branching ribbon-like hyphae and reproduce sexually by forming zygospores, are responsible for a variety of illnesses that are referred to as mucormycosis. The pathogen can be widely found in fruits, dirt, and faeces. It can also be cultured from the throat, nasal passages, and oral cavity of healthy people who are disease-free. Zygomycetes' subtype Mucorales causes a specific pattern of clinical infection. The fungi are typically non-pathogenic and only become so when the host resistance is extremely low. In the maxillofacial region, mucormycosis can enter through an extraction wound in the mouth or an ulcer in the mucosa, especially if the patient is immunocompromised [8].

The minute spores are airborne and land on human nose and oral mucosa. These spores will be stopped in most immunologically capable hosts by a phagocytic reaction. If this reaction is unsuccessful, germination will occur and hyphae will form. In immunocompromised patients, polymorphonuclear leukocytes are less successful in removing hyphae, therefore the infection establishes in these circumstances. The condition worsens when the hyphae spread into the walls and lumens of the arteries, where they cause thrombosis, ischemia, and infarction as well as dry gangrene of the affected tissues. Sepsis is caused by hematogenous spread to other organs, such as the lung, brain, and others [9].

Oral mucormycosis can have one of two possible causes. One results from disseminated infection, with inhalation (via the nose) as the point of entry, and the other from direct wound contamination with dispersion to other viscera as a frequent consequence.

When it comes through the nose and PNS, the infection may result in palatal ulceration that eventually necrosis, and the majority of the time, the affected area appears black. Clinical manifestations of an infection that has spread due to direct wound contamination can occur anywhere in the oral cavity, including the mandible. Cavernous sinus thrombosis, a major consequence of maxillary infections, is a key distinction between infection involving the maxilla and mandible [10].

Diabetes mellitus has a tendency to alter the body's typical immune response to infections in a number of ways. Fungal growth is accelerated by hyperglycemia, which also reduces phagocytic and chemotactic effectiveness, allowing ordinarily harmless species to flourish in an acidic environment. When *Rhizopus oryzae* produces the enzyme ketoreductase, which enables them to consume the patient's ketone bodies, there is an increased risk of mucormycosis in diabetics with ketoacidosis [8]. It is known that diabetic ketoacidosis momentarily impairs transferrin's capacity to bind iron, and that this change disables a crucial host defensive mechanism and promotes the growth of *Rhizopus oryzae* [11].

Systemic glucocorticoids are a double-edged sword since they can save lives when used to address COVID-19 problems but can also cause opportunistic fungal infections that can be fatal. According to findings in the literature, Diabetes Mellitus is a separate risk factor for mucormycosis. This connection has been attributed to Diabetes Mellitus effects such as decreased chemotaxis, phagocytosis, and neutrophil dysfunction. It is also hypothesised that by attaching to ACE 2 receptors on pancreatic cells, SARS CoV 2 causes insulin resistance via impairing cells of the pancreas. SARS-COV-2-induced cytokine storm amplifies this [12-16].

The most frequent type of infection seen in people with uncontrolled diabetes mellitus is rhinomaxillary form [17]. Clinical symptoms include low-grade fever, lethargy, headache, facial pain, and edoema. The condition generally begins in the nasal mucosa or palate and progresses to the paranasal sinuses by nearby vessels such the angular, lacrimal, and ethmoidal vessels. Furthermore,



mucormycosis may directly extend to the retro-orbital area [18]. Fungal hyphae can travel to other organs like the brain or lungs if they get into the bloodstream, which can be dangerous [19].

Squamous cell cancer, chronic granulomatous infections such tuberculosis, tertiary syphilis, midline fatal granuloma, and other deep fungal infections should also be considered in the clinical differential diagnosis of the lesion. A magnetic resonance imaging scan or a CT with contrast can show bone erosion or disintegration and help determine the severity of the illness [20].

According to histopathology, the lesion exhibits broad aseptate fungal hyphae with right-angle branching. The aspergillosis with septate, narrower, and more acutely angled *Aspergillus* species hyphae is one of the histopathological differential diagnoses. Early diagnosis allows for the combination of surgical debridement of the diseased region and systemic amphotericin B treatment to cure mucormycosis [21].

In our study, the majority patients were between the 2nd and 7th decades of life with a maximum a number of cases above the age of 40 years. Similar studies have also reported analogous findings. The maximum number of patients included in the present study were males (n = 43). This might be due to the fact that most of the COVID19 affected patients globally are males. Mucormycosis has not shown any gender predilection both in COVID19 and nonCOVID19 era; however, it has been suggested that oestrogen might protect females from systemic fungal infections [22].

All cases in this study were reported to the Department of ENT after Magnetic resonance imaging, functional endoscopic sinus surgery, and confirmed histopathological report of Mucormycosis. This finding is in accordance with Mehta S., *et al.* [23]. suggestive of maxilla being the most commonly involved structure. Rhinoorbitocerebral mucormycosis usually affects the maxillary sinus with the involvement of maxillary teeth, orbits, and ethmoidal sinuses. According to Sanghvi., *et al.* [24]. contrastenhanced magnetic resonance imaging (MRI) is the best mode of choice for the demonstration. Black turbinate is the classical imaging sign but there was no positive correlation seen between the type of Mucormycosis with an altered the signal density of nasal cavity, maxilla, mandible and maxillary sinus.

Risk stratification for disease severity, thorough pre-diagnosis work in the clinical and laboratory settings, and prompt commencement of therapeutic intervention are the fundamental tenets of Medical therapy. Together with rigorous surgical debridement of necrotic lesions, efficient antifungal therapy (monotherapy or combination therapy) is recommended. Early diagnosis and treatment can reduce the need for extensive surgery, prevent progressive tissue invasion and the resulting deformity, and increase survival. a multifaceted strategy that addresses underlying risk factors and uses active antifungal medications early. [25-29].

In the majority of the instances discussed in this study, liposomal lamphotericin was utilised to treat mucormycosis in COVID 19 patients. Similarly, the combination of amphotericin B, patients with COVID-19 have also received treatment for mucormycosis with micafungin and isavuconazole. Posaconazole and liposomal amphotericin B have also been used together for mucormycosis treatment in COVID-19 patients [30]. According to the European Confederation of Medical Mycology, moderate to high doses of Isavuconazole or posaconazole can be used as a last resort treatment for mucormycosis in patients in general [31].

Patients with progressive ocular involvement should have orbital exenteration, as well as pterygopalatine fossa and inferior orbital fissure debridement. to lessen the fungus load and stop the disease from spreading further to the skull. In chosen patients, functional endoscopic surgery has been consistently used as a successful therapy option for treating mild and early rhinocerebral mycosis [32]. While orbital exenteration can save lives, it is not always necessary and must be considered on a case-by-case basis [33]. The course of the illness, involvement, and response to anti-fungal medication are taken into consideration while deciding whether to exenterate the orbit. For best results, surgical treatment must always be combined with systemic antifungal medications (polyenes, azoles, etc.). When essential tissue cannot be fully removed around vital structures, anti-fungal medicines [34]. The nasal cavity and sinuses are the only areas that exhibit solitary pterygopalatine fossa involvement symptoms. In these circumstances, endoscopically guided with antifungal medication, mucormycosis is manageable. The sphenopalatine foramen occasionally becomes implicated as well, and in these cases, it needs

to be debrided or removed. When nasopalatine and descending palatine arteries invade the pterygopalatine fossa, mucormycosis can progress to the larger palatine canal, leading to black necrosis of the palate or erosion of the hard palate. Internal maxillary artery involvement and the nasal cavity and sinuses are the only areas that exhibit solitary pterygopalatine fossa involvement symptoms. Mucormycosis in these situations can be controlled with anti-fungal medication and endoscopically guided debridement.

The maxilla and palate may completely necrotize as a result of its tributaries [35]. The surgical procedure could be as basic as radical maxillectomy and palatal debridement, in addition to alveoloplasty. In the main closure process, the palatal flap's vitality is crucial. A maxillofacial surgeon's surgical options include hard palate debridement, marginal maxillectomy, Hemimaxillectomy, complete and radical maxillectomy, as well as maxillary sinus debridement using the Caldwell-Luc method. The crestal incision, vestibular gloving incision, lateral rhinotomy with subciliar or supra orbital, and Weber Ferguson methods can all be used to get access for surgery [36].

In our study most of the patients required endoscopic debridement with intact cosmetic appearance and no facial disfigurement was seen., though in extreme cases of invasion Inspection and possible debridement of the infratemporal fossa, hard palate, and maxillary sinus should all be performed. The tissue flaps can be seen following the removal of the affected tissue. be closed with local pediceled flaps like the Galealfrontalis-pericranial nasolabial flap, the temporalis muscle flap, the sub-mental flap, or the facial artery island flap, as well as primary closure and obturators. The anterolateral thigh flap, the fibula osteocutaneous flap, the latissimus dorsi free flap, the radial forearm free flap, the scapula osteocutaneous free flap, the transverse rectus abdominis musculocutaneous flap, the vascularized iliac osteocutaneous flap, and chimeric flaps can all be used to reconstruct large defects. In patients with hemodynamic instability, cellulitis, aggregated infections, partial resection, and when the recipient's arteries are compromised, immediate repair is not advised [37].

Central nervous system and cavernous sinus with the invasion of the orbital apex, cavernous sinus and central nervous system (CNS) involvement might arise. From the frontal sinus, sphenoid sinus, and Seldom occurs a cribriform plate to the CNS. Seizures,

a unilateral headache, loss of consciousness, and unilateral neurological symptoms on the opposite side are all indications that the CNS and cavernous sinus are involved. Even if it is linked to some sort of neurological deficiency, advanced disorders often recommend craniotomies and partial or complete lobectomies [38].

The results discussed above suggest that a variety of factors may contribute to the development of mucormycosis in COVID 19 individuals. Hence, a multidisciplinary team must handle focusing on co-morbidity control, prudent use of steroids, zinc supplements, and other medications, along with adequately designed personalised treatment methods.

## Conclusion

Mucormycosis is a deadly fungal infection that primarily affects immunocompromised patients and is linked to rising mortality. It is characterised by host tissue necrosis and infarction. It is widely considered that the increased use of corticosteroids for the treatment of viral problems, combined with uncontrolled diabetes, has contributed to the rise in Mucormycosis cases. Thus, it is imperative to maintain euglycemia and rationalise the delivery of corticosteroids to such individuals. The diagnosis of Mucormycosis is crucial since different fungal diseases can show similarly despite receiving different treatments. To protect against potentially fatal infections, prompt treatment with anti-fungal medications such as amphotericin B and precise surgical intervention is essential. Deadly complications and morbidities that alter life. Every efforts must be made to ensure that high-risk populations receive anti-fungal medication as soon as possible.

Fear amongst the patients about this unknown "Epidemic in Pandemic" or "Black Fungus" was a major factor of their distress. Immediate diagnosis of mucormycosis just after recovery of Covid 19 was a psychological set back. Further it was also a big drain on the finances with the cost of medicines, investigations, admission to critical care and surgery immediately after covid hospitalization especially in developing countries like India where most of them are not medically insured and have to pay out of their own pocket.

## Acknowledgements and Final Remarks

We could only manage all this with our excellent team of ENT consultants, anaesthetists, physicians, skull-base and

neurosurgeons, residents who worked round the clock, nurses, counsellors and ward staff. A lot of backroom work was also required for procurement of Ampho B injections as well as fulfilling government regulations. So a good office team was paramount for this extensive work which eased the tensions and troubles of the patients' relatives. With our various financial aids and charities, our institute was able to help these patients financially as much as possible. Psychological counseling and education was provided by our doctors and counselors. All in all, it was a memorable task to fulfill in a short span of time and with God's grace, we could pull it off as best as we could.

### Conflict of Interest

The authors have no funding, financial relationships, or conflicts of interest to disclose.

### Bibliography

- Narayanan Shivakumar., *et al.* "Coronavirus Disease 2019-Associated Mucormycosis: Risk Factors and Mechanisms of Disease". *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 74.7 (2022): 1279-1283.
- Muthu Valliappan., *et al.* "Epidemiology and Pathophysiology of COVID-19-Associated Mucormycosis: India Versus the Rest of the World". *Mycopathologia* 186.6 (2021): 739-754.
- Sivapathasundharam B. "Shafer's Textbook of Oral Pathology". 8th edition. New Delhi, India: Elsevier (2012): 435-436.
- Roden, Maureen M., *et al.* "Epidemiology and outcome of zygomycosis: a review of 929 reported cases". *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 41.5 (2005): 634-653.
- Rodriguez-Morales, Alfonso J., *et al.* "COVID-19 associated mucormycosis: the urgent need to reconsider the indiscriminate use of immunosuppressive drugs". *Therapeutic Advances in Infectious Disease* 8 (2021): 20499361211027065.
- Baldin Clara and Ashraf S Ibrahim. "Molecular mechanisms of mucormycosis-The bitter and the sweet". *PLoS Pathogens* 13.8 (2017): e1006408.
- Kamat Mamata., *et al.* "COVID-19-associated mucormycosis of head-and-neck region: A systematic review". *Journal of Clinical and Translational Research* 8.1 (2022): 31-42.
- Marx RE and Stern D. "Inflammatory, Reactive and Infectious Diseases in Oral and Maxillofacial Pathology". Carol Stream III, USA. Quintessence Publishing (2003): 104-106.
- Kajs-Wyllie M. "Hyperbaric oxygen therapy for rhinocerebral fungal infection". *The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses* 27.3 (1995): 174-181.
- Lador Nilly., *et al.* "A trifuungal infection of the mandible: case report and literature review". *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* 101.4 (2006): 451-456.
- Artis WM., *et al.* "A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability". *Diabetes* 31.12 (1982): 1109-1114.
- Petrikkos George and Constantinos Tsioutis. "Recent Advances in the Pathogenesis of Mucormycoses". *Clinical Therapeutics* 40.6 (2018): 894-902.
- Alekseyev, Kirill., *et al.* "Rhinocerebral Mucormycosis and COVID-19 Pneumonia". *Journal of Medical Cases* 12.3 (2021): 85-89.
- Apicella Matteo., *et al.* "COVID-19 in people with diabetes: understanding the reasons for worse outcomes". *The Lancet. Diabetes and Endocrinology* 8.9 (2020): 782-792.
- Lin Xiling., *et al.* "Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025". *Scientific Reports* 10.1 (2020): 14790.
- Montefusco Laura., *et al.* "Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection". *Nature Metabolism* 3.6 (2021): 774-785.
- Castrejón-Pérez Ana Daniela., *et al.* "Cutaneous mucormycosis". *Anais Brasileiros de Dermatologia* 92.3 (2017): 304-311.
- Spellberg Brad., *et al.* "Novel perspectives on mucormycosis: pathophysiology, presentation, and management". *Clinical Microbiology Reviews* 18.3 (2005): 556-569.
- Kim J., *et al.* "A fatal outcome from rhinocerebral mucormycosis after dental extractions: a case report". *Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons* 59.6 (2001): 693-697.

20. Doni Bharati R., *et al.* "Sequence of oral manifestations in rhino-maxillary mucormycosis". *Indian Journal of Dental Research: Official Publication of Indian Society for Dental Research* 22.2 (2011): 331-335.
21. Burkets Textbook of Oral Medicine Diagnosis and Treatment 10<sup>th</sup> edition. Elsevier; Canada (2003): 79.
22. Roden Maureen M., *et al.* "Epidemiology and outcome of zygomycosis: a review of 929 reported cases". *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 41.5 (2005): 634-653.
23. Mehta Salil and Abha Pandey. "Rhino-Orbital Mucormycosis Associated With COVID-19". *Cureus* 12.9 (2020): e10726.
24. Sanghvi D and H Kale. "Imaging of COVID-19-associated craniofacial mucormycosis: a black and white review of the "black fungus". *Clinical Radiology* 76.11 (2021): 812-819.
25. Skiada A., *et al.* "Challenges in the diagnosis and treatment of mucormycosis". *Medical Mycology* 56.1 (2018): 93-101.
26. Peixoto Driele., *et al.* "Isavuconazole treatment of a patient with disseminated mucormycosis". *Journal of Clinical Microbiology* 52.3 (2014): 1016-1019.
27. Ervens J., *et al.* "Successful isavuconazole salvage therapy in a patient with invasive mucormycosis". *Infection* 42,2 (2014): 429-432.
28. Graves Bianca., *et al.* "Isavuconazole as salvage therapy for mucormycosis". *Medical Mycology Case Reports* 11 (2016): 36-39.
29. Mekonnen Zesemayat K., *et al.* "Acute Invasive Rhino-Orbital Mucormycosis in a Patient With COVID-19-Associated Acute Respiratory Distress Syndrome". *Ophthalmic Plastic and Reconstructive Surgery* 37.2 (2021): e40-e80.
30. Dallalzadeh Liane O., *et al.* "Secondary infection with rhino-orbital cerebral mucormycosis associated with COVID-19". *Orbit (Amsterdam, Netherlands)* 41.5 (2022): 616-619.
31. Cornely, Oliver A., *et al.* "Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium". *The Lancet. Infectious Diseases* 19.12 (2019): e405-e421.
32. Alobod I., *et al.* "Treatment of rhinocerebral mucormycosis by combination of endoscopic sinus debridement and amphotericin B". *American Journal of Rhinology* 15.5 (2001): 327-331.
33. Rapidis AD. "Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: perspectives from a maxillofacial surgeon". *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 15.5 (2009): 98-102.
34. Ferguson BJ. "Mucormycosis of the nose and paranasal sinuses". *Otolaryngologic clinics of North America* 33.2 (2000): 349-365.
35. Kyrmizakis Dionysios E., *et al.* "Palate ulcer due to mucormycosis". *The Journal of Laryngology and Otology* 116.2 (2002): 146-147.
36. Hosseini Seid Mousa Sadr and Peyman Borghei. "Rhinocerebral mucormycosis: pathways of spread". *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* 262.11 (2005): 932-938.
37. Palacios Julio Juarez., *et al.* "Reconstruction of Head and Neck Mucormycosis: A Literature Review and Own Experience in Immediate Reconstruction". *Journal of Reconstructive Microsurgery Open* 04 (2019): e65-e72.
38. Abu El-Naaj Imad., *et al.* "The surgical management of rhinocerebral mucormycosis". *Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery* 41.4 (2013): 291-295.