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Research Article

COVID-19 Associated Rhino-Orbital Mucormycosis During the Pandemic: Our Experience on Diagnostic Challenges to Management

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Abstract

Mucormycosis, also known as black fungus, is a rare but serious fungal infection that has been increasingly reported in patients with COVID-19. This infection typically affects the sinuses, but can also spread to the brain, lungs, and other parts of the body.

Risk factors for mucormycosis include uncontrolled diabetes, immunosuppression, and prolonged use of steroids. Patients with COVID-19 who have been hospitalized and on mechanical ventilation, as well as those who have received high doses of steroids, are particularly vulnerable to this infection.

Symptoms of mucormycosis include severe headache, facial pain or swelling, black discharge from the nose, and difficulty breathing. If left untreated, the infection can lead to blindness, brain damage, and even death.

Early diagnosis and prompt treatment are crucial for managing mucormycosis in patients with COVID-19. Treatment typically involves a combination of antifungal medications and surgical debridement of infected tissue.

It is important for healthcare providers to be aware of the potential for mucormycosis in patients with COVID-19, particularly those who have risk factors or are experiencing severe symptoms. Maintaining good glycemic control and avoiding unnecessary use of steroids in COVID-19 patients may also help to reduce the risk of mucormycosis.

Aim and Objective: 1. To provide a comprehensive overview of the clinical presentation, symptomatology, pathological, and radiological findings in cases of mucormycosis. 2. To examine the role of various risk factors in the development and progression of Post-COVID-19 mucormycosis and to use these findings to design a customized treatment strategy.

Methods: A prospective longitudinal study was conducted at our tertiary healthcare center in Maharashtra. Participants were selected based on the presence of clinical symptoms of mucormycosis and COVID-19 recovery. A comprehensive medical examination was performed, including otorhinolaryngologic (DNE, KOH, Fungal Culture), medical, and ophthalmological evaluations, as well as laboratory tests, biopsy, and imaging studies. The treatment strategy included administration of IV antifungals (Liposomal-Amphotericin B) and surgical procedures such as Modified Denker's approach, open maxillectomy, and orbital exenteration if needed. The patients were followed up for six months to monitor for recurrence.

Results: An initial diagnosis was made based on KOH mount and CT and MRI studies followed by fungal culture. All the patients were surgically treated. Out of 25 patients 12 patients underwent Endoscopic sinus surgery with modified Denker's approach, 4 patients underwent Total Maxillectomy with external facial degloving approach. One patient underwent surgical exenteration of the involved eye. All the patients were administered with Liposomal-Amphotericin-B 4 mg/Kg/body weight for a period of 14-21 days Patients were discharged after 21 days with Posaconazole and followed up after 3-weeks, 3-months and 6-months post-operatively and routine diagnostic nasal endoscopy is performed during all OPD visits and all the patients had significant improvement.

Conclusion: In India, particularly among the diabetic patients with steroid therapies for COVID-19 recovery during the second wave there was an exponential increase in invasive fungal diseases like Mucormycosis. Early diagnosis and prompt initiation of appropriate antifungal therapy is crucial in the management of post-COVID mucormycosis.

Keywords: Mucormycosis; Modified Denker's Approach; Rhino-Orbital-Cerebral Mucormycosis; Invasive Fungal Sinusitis; Post-Covid-19 Mucormycosis

Abbreviations

ROCM: Rhino-Orbital-Cerebral Mucormycosis; ESS: Endoscopic Sinus Surgery; LAMB Therapy: Liposomal Amphotericin-B Therapy; COVID-19: Corona Virus Disease-2019; RBS: Random Blood Sugar; Mg: Milligram; PNS: Paranasal Sinuses; CECT: Contrast Enhanced Computed Tomography; MRI: Magnetic Resonance Imaging

Introduction

During the second wave of the COVID-19 pandemic in India, there has been a significant increase in cases of rhino orbital mucormycosis, a rare but severe fungal infection of the sinuses. This is likely due to a combination of factors, including hyperglycemia (high blood sugar) and the use of steroids in the treatment of COVID-19. Hyperglycemia, a common complication of diabetes, can make it more difficult for the body to fight off infections. Additionally, steroids can suppress the immune system and create an environment that is more favorable for fungal growth in the nose and sinuses. It is crucial for healthcare providers to be aware of the risk factors for rhino orbital mucormycosis and to take steps to prevent and treat it as soon as possible [1]. The term "mucormycosis," formerly known as "zygomycosis," describes a number of illnesses brought on by an infection with fungi from the order Mucorales. Of this group, Rhizopus species are the most harmful organisms. The other genera with species known to cause mucormycosis are Mucor, Cunninghamella, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, Rhizomucor, and others. Cerebro-rhino-orbital mucormycosis is most common and most aggressive form of Mucormycosis [2]. Uncontrolled metabolic conditions especially Diabetes Mellitus in ketoacidosis and neutropenia are major risk factors and core determinant of worldwide incidence of Mucormycosis. Mucormycosis is a rare but serious complication that can occur in diabetic patients receiving steroidal therapy for COVID-19. Steroids, which are often used to reduce inflammation and swelling in the lungs, can also suppress the immune system and make individuals more susceptible to fungal infections. In patients with diabetes, high blood sugar levels can also create an environment that is favorable for the growth of mucormycosis [3]. Symptoms of mucormycosis can include black or dark-colored lesions on the skin, fever, headache, and changes in vision. If left untreated, the infection can spread to other parts of the body and be fatal. Individuals with diabetes who are receiving steroidal therapy for COVID-19 should be closely monitored for signs of mucormycosis, and prompt treatment with antifungal medication should be initiated if the infection is suspected. It is also important for diabetic patients to closely monitor and control their blood sugar levels [4-6].

Owing to Covid-19: Mucormycosis/mucormycosis due to COVID-19

Impact of Covid-19 in the pathogenesis of mucormycosis

In 2003, it was determined that patients with SARS-1 had a fungal infection at a rate of 14.8-27%, while those who were critically ill had a rate of 27-33%. The SARS2 virus, the virus that causes COVID-19, is a devastating pandemic that spreads from person to person and has caused a sizable amount of mortality and morbidity. Studies have shown that almost 5% of patients suffering from COVID-19 were positive for fungal infection. Aspergillus flavus, Candida glabrata, and Candida albicans could all be seen in the fungal culture specimens. The most prevalent fungi found in COVID-19 patients are Aspergillus and Candida. The other unusual fungal infections that affect the lungs in COVID-19 patients are Mucor and Cryptococcus [7].

Lymphopenia and immune-mediated alterations are the basis of the fungal infections in COVID-19. The quantity of granulocytes

and monocytes if aberrant, COVID-19 harms the lung tissues, making them more susceptible to fungal infections. 94% of the patients in a research, people with mucormycosis with COVID-19 had diabetes. The COVID-19 virus alters the metabolism of iron. Iron concentrations within cells may rise as a result of diabetic ketoacidosis inducing the formation of ferritin [8].

41 COVID-19 and mucormycosis case reports were examined by John., *et al*. There have been 29 cases reported from India. 33 of the 41 instances that were reported had diabetes, and 36 of the 41 were being treated for COVID-19 with steroids. 16 patients were diagnosed with mucormycosis and COVID-19. Therefore, COVID-19 alone may be a risk factor for mucormycosis in some patients who were not diabetics or were on steroids [9].

There are several proposed hypotheses that suggest that COVID-19 infection may increase the risk of mucormycosis. One theory is that the viral infection itself can cause changes in the body's immune response, which can create an environment that is favorable for the growth of Mucorales fungi. Additionally, the use of certain medications, such as corticosteroids, which are commonly used to treat COVID-19, may also increase the risk of mucormycosis by suppressing the immune system. Furthermore, the disease severity and the prolonged hospital stay of COVID-19 patients may also increase the risk of mucormycosis by providing a conducive environment for fungal growth [7].

Delivery of oxygen and mucormycosis: A Relationship

Inadequate or poor-quality oxygen delivery may increase the risk of mucormycosis. One reason for this is the increased use of industrial oxygen in the treatment of COVID-19, which may not meet the same quality and hygiene standards as medical oxygen. Industrial oxygen is produced in large quantities and is not intended for medical use, while medical oxygen is specifically produced to meet the needs of patients in a clinical setting. The use of industrial oxygen in a medical setting can increase the risk of contamination and may not provide the same level of purity as medical oxygen. This may lead to an increased risk of mucormycosis, as the fungus thrives in an environment with low oxygen concentrations [10].

Staging of rhino-orbital mucormycosis [11]

The proposed staging system for rhino-orbital mucormycosis is a widely used method that follows the progression of the infection from the nasal mucosa to the paranasal sinuses, orbit, and brain. The system takes into account the severity of the infection in each of these anatomical locations and is used to guide diagnostic and treatment decisions. However, it is important to note that this system is not officially recognized or standardized. As the critical care teams are starting to receive an increasing number of ROCM patients in the setting of COVID-19, this staging system can help triage patients and customize their care. The next step in the research would be to validate this system, propose the preferred management for each stage, and then correlate the outcomes [11].

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischemia, eschar	Diagnostic nasal endoscopy; Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: > Two ipsilateral sinuses and/or palate/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy; Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anesthesia	Signs in Stage 1 and 2 + conjunctival chemoses, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis. V1 and V2 nerve anesthesia, and features of III, IV and VI nerve palsy indicating orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy; Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy; Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Figure a: Use the Home tab to apply 0 to the text that you want to appear here. 1 Proposed Staging of ROCM.

Management approach for various stages of ROCM

The management of Rhinosinusitis-associated Osteomyelitis of the Cranium (ROCM) is a challenging task for healthcare professionals, as the treatment options range from systemic antifungal therapy to extreme surgical interventions. In the early stages of the disease, immediate initiation of intravenous liposomal Amphotericin B is considered the gold standard treatment. Liposomal Amphotericin B, at a dosage of 5-10mg/kg, has been shown to be highly effective in preventing the progression of ROCM, with minimal toxicity and better preservation of renal function [3-5,11].

It is important to note that alternative antifungal agents, such as Amphotericin B Deoxycholate (ABDC) or Amphotericin B Lipid Complex (ABLC), are not as effective and may lead to higher toxicity. In cases where renal function is impaired, alternative antifungal agents such as Isavuconazole and Posaconazole may be considered. Isavuconazole is administered intravenously at a dosage of 200mg thrice a day on day 1-2, and 200mg once a day from day 3. Posaconazole is administered intravenously at a dosage of 300mg twice a day on day 1, and 300mg once a day from day 2 [12,13].

In conclusion, ROCM is a complex disease that requires a multidisciplinary approach for its management. Immediate initiation of intravenous liposomal Amphotericin B is considered the gold standard treatment in the early stages of the disease, with alternative antifungal agents considered for cases with impaired renal function. Further research is needed to establish the optimal treatment protocols and to improve the outcomes of ROCM patients [13].

Materials and Methods

- **Study Title:** COVID-19 Associated Rhino-Orbital Mucormycosis during the Pandemic: Our Experience on Diagnostic challenges to Management.
- **Type of Study:** Descriptive Longitudinal Study.
- **Duration of study:** 12 Months.
- **Study period:** 1st December 2020 to 31st December 2022.
- **Sample Size:** 24.
- **Study group:** The study subjects comprised patients diagnosed from Mucormycosis recovered from Coronavirus disease (SARS-COV-2 Infection).
- **Study Setting:** All the patients diagnosed of Rhino-Orbital Mucormycosis and recovered form COVID-19 infection, attending ENT O.P.D of Dr. B.V.P R.M.C, Loni B.K.

The study conducted a comprehensive otorhinolaryngologic evaluation of patients presenting with suspected mucormycosis in the setting of COVID-19. A biopsy sample was collected from the nasal cavity for KOH examination. The oral cavity, oropharynx, nasal cavity, and nasopharynx were evaluated using a portable fiberoptic laryngoscope. Patients with a high degree of suspicion for mucormycosis were initiated on IV LAMB therapy. Further imaging, including CECT PNS and Orbits, was performed and contrast enhanced MRI was done in selected cases to evaluate for extensive orbital involvement and intracranial extension. Upon completion of a thorough evaluation and workup, surgical debridement was promptly scheduled within two days of admission.

Ethical clearance is obtained from the ethical committee of Dr.B.V.P Rural Medical College Loni

Inclusion criteria

- All patients recovered from COVID-19 infection and presenting with symptoms of Rhino-Orbital Mucormycosis in ENT OPD.
- Endoscopic and radiological evidence of mucormycosis.

Exclusion criteria

- Growth in the nasal cavity, benign or malignant
- Pregnant or lactating female patients
- Non-Consenting patients

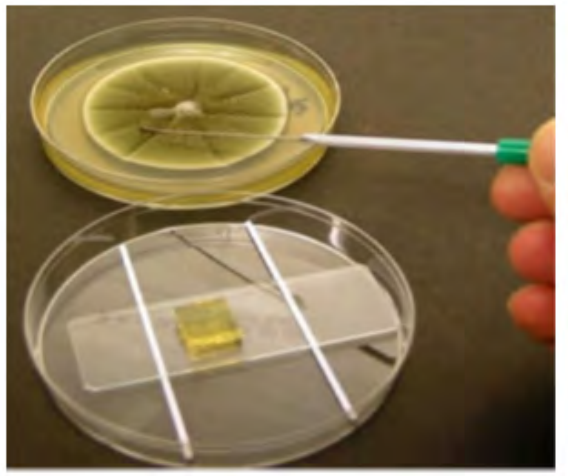

Figure 1: KOH Mounting test for Mucormycosis.

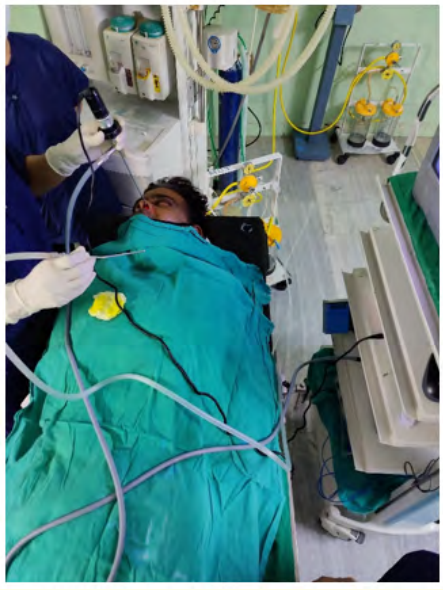

Figure 2: Performing DNE in a suspected patient of Mucormycosis (RCOM).

Figure 3: Presence of blackish eschar over dorsum of Nose.

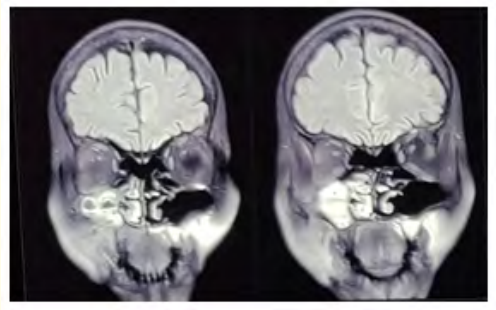

Figure 4: T1 weighted MRI PNS-Orbit depicting Mucor involvement of Rt. PNS and Orbit.

Figure 5: A 65-yr old mucormycosis patient with palatal necrosis and left orbital involvement.

Results and Discussion

This case series reports on 25 patients who were diagnosed with mucormycosis after or concurrently with a confirmed SARS-CoV-2 infection. Only patients with adequate clinical or radiographic findings were included, and none of them had received a SARS-CoV-2 vaccine. All patients had symptoms when infected with COVID-19 and had varying levels of oxygen saturation, ranging from 80% to 96%. The summary of the included patients' characteristics and outcomes is presented below in the following table 1.

Series	Co-Morbidities	RBS	COVID-19 Symptoms	Onset after COVID-19 recovery	Symptoms	Mucormycosis	Surgical Approach	Outcome
Case 1	DM-II Bronchial asthma HTN	320 mg/dL	Fever;	3 W	No neurologic symptoms were reported	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Stable

Case 2	DM-II	300 mg/dL	Fever; cough;	10 D	Slurred speech; perioral numbness	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 3	DM-II, HTN	450 mg/dL	Fever; cough;	2 W	Slurred speech; seizure; periorbital numbness	Rhino-Orbital	Total maxillectomy with facial degloving	Improved
Case 4	DM-II	350 mg/dL	Fever; cough; diarrhea;	4 W	Numbness in the affected side of the face; lethargy	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 5	HTN	400 mg/dL	Fever; cough; breathlessness	3 M	Slurred speech; periorbital numbness	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 6	DM-II, HTN	320 mg/dL	Fever; breathlessness;	14 D	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 7	HTN	300 mg/dL	Fever; cough; breathlessness diarrhea	24 D	Slurred speech; perioral numbness	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach (four handed technique)	Improved
Case 8	DM-II	450 mg/dL	Fever; cough; breathlessness, diarrhea	4 W	Slurred speech; seizure; periorbital numbness	Rhino-Orbital	Total maxillectomy with facial degloving	Improved
Case 9	DM-II, HTN	300 mg/dL	Fever; breathlessness;	34 D	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved

Case 10	Bronchial asthma	160 mg/dL	Fever; breathlessness;	4 W	No neurologic symptoms were reported	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 11	DM-II	400 mg/dL	Fever breathlessness;	7 W	Slurred speech; periorbital numbness	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 12	HTN, DM-II	320 mg/dL	Fever; cough	4 W	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 13	HTN	144 mg/dL	Fever; cough	24 D	No neurologic symptoms were reported	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 14	DM-II	400 mg/dL	Fever; cough; diarrhea	15 D	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	B/L Total maxillectomy with facial degloving	Improved
Case 15	DM-II	320 mg/dL	Fever; cough; shortness of breath	3 W	No neurologic symptoms were reported	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 16	DM-II	240 mg/dL	Fever; breathlessness	3 M	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 17	DM-II	350 mg/dL	Fever; cough; breathlessness, diarrhea	4 W	No neurologic symptoms were reported	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved

Case 18	HTN, DM-II	400 mg/dL	Fever; cough; breathlessness	4 W	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	Total maxillectomy with facial degloving	Improved
Case 19	DM-II	320 mg/dL	Fever; breathlessnes;	4 D	No neurologic symptoms were reported	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 20	HTN, DM-II, Bronchial asthma H/o CABG	300 mg/dL	Fever; cough; breathlessness, diarrhea	4 D	Slurred speech; seizure; periorbital numbness	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 21	DM-II, HTN	450 mg/dL	Fever; cough; breathlessness, diarrhea	2 W	Numbness in the affected side of the face; lethargy	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 22	HTN, DM-II	300 mg/dL	Fever; cough;	2 W	Persistent Headache, Loss of vision, Blurring of Vision, Slurred Speech	Rhino-Orbital	Endoscopic sinus surgery with modified Denker's approach	Improved
Case 23	DM-II, HTN	320 mg/dL	Fever; cough;	2 W	Slurred speech; perioral numbness	Rhino-Cerebral	Endoscopic sinus surgery with modified Denker's approach	Stable
Case 24	DM-II, HTN	321 mg/dL	Fever; cough; diarrhea;	4 W	Slurred speech; seizure; periorbital numbness	Rhino-Cerebral	Endoscopic sinus surgery with modified Denker's approach	Stable
Case 25	Bronchial asthma, HTN, DM-II	322 mg/dL	Fever; cough; breathlessness, diarrhea	4 D	Persistent Headache, Loss of vision, Loss of vision, Slurred Speech	Rhino-Orbital and Cerebral	Endoscopic sinus surgery with modified Denker's approach and Surgical ecentration of the involved eye	Stable

Table 1: Case series of 25 post covid-19 patients with mucormycosis and outcomes.

In our study, we looked at 25 patients who had developed symptoms of mucormycosis after recovering from COVID-19. The majority of patients were between the ages of 45 and 80, with an average age of 62.5 and a standard deviation of 15 years. The time between COVID-19 recovery and the onset of mucormycosis symptoms was measured and found to be an average of 21.52 days, with a standard deviation of 14.04 days. All patients were receiving humidified oxygen by mask during their active COVID-19 infection and had a fever. Out of the 25 patients, 9 reported experiencing breathlessness, 10 reported a cough with expectoration, and 4 had severe diarrhea. Patients were treated symptomatically.

Para-Nasal Sinus Involvement	No of cases
Maxillary	20
Ethmoids	25
Sphenoid	5
Frontal	3

Table 2: Incidence of Sinuses affected.

Among 25 patients with mucormycosis 20 patients had maxillary sinus involvement and all the patients had ethmoidal involvement and three patients had frontal involvement.

Co-Morbidities	Status and Cases
Type-2 Diabetes mellitus	Controlled -16
	Uncontrolled-5
Hypertension	15
Bronchial Asthma	5

Table 3: Associated Co-Morbidities.

Twenty-one patients enrolled in the study were diagnosed of Type-2 diabetes mellitus with 5 patients having uncontrolled diabetes. Fifteen patients had Hypertension and Five patients had bronchial asthma.

Out of 25 patients diagnosed with Post COVID-19 Mucormycosis 20 patients had slurring of speech, 9 patients had blurring of vision, 4 patients had peri oral numbness, 1 patient had loss of vision and 5 patients had few episodes of seizures.

An initial diagnosis was made based on KOH mount and CT and MRI studies followed by fungal culture. All the patients were surgically treated. Out of 25 patients 12 patients underwent Endoscopic sinus surgery with modified Denker's approach, 4 patients underwent Total Maxillectomy with external facial degloving approach. One patient underwent surgical exenteration of the involved eye. All the patients were administered with Liposomal-Amphoterecin-B 4 mg/Kg/body weight for a period of 21-days with routine monitoring of Renal function tests, Blood sugar level and Serum electrolyte levels with routine suction clearence and surgical debridement and post-operative MRI. Patients were discharged after 21 days with posaconazole and followed up after 3-weeks, 3-months and 6-months post-operatively and routine diagnostic nasal endoscopy is performed during all OPD visits and all the patients had significant improvement.

Figure 6: Left Partial Maxillectomy; Sub-Labial Approach.

Figure 7: Left total Maxillectomy by facial degloving and surgical exenteration of left eye (invaded by mucor).

Discussion

The combination of several factors, including underlying health conditions like diabetes, previous lung problems, Immunosuppressants, the danger of getting infections in the hospital, and the impact COVID-19 has on the body's immune response, can make someone more susceptible to developing secondary infections. These additional infections can have a serious effect on their health and increase the likelihood of death. Secondary infections during or after a COVID-19 infection can occur due to a weakened immune system and can be serious and potentially life-threatening. People with preexisting conditions, such as diabetes and respiratory issues, and those taking immunosuppressive therapy or in a hospital setting are more at risk. It's important to take measures to prevent and treat secondary infections to reduce their impact on health outcomes [14]. In a recent study, a sample of 806 patients was analyzed for the occurrence of secondary bacterial or fungal infections during hospital admission. The results indicated that 8% of the patients developed secondary infections. The widespread use of broad-spectrum antibiotics was observed, with 72% of the patients in the sample receiving these drugs, despite the absence of definitive evidence of infection. The overuse of broad-spectrum antibiotics has the potential to contribute to the development of antibiotic resistance, making it challenging to treat infections in the future. As healthcare providers, it is our responsibility to use antibiotics appropriately, only when there is clear evidence of infection [15]. In India, the current guidelines for the treatment of COVID-19 patients recommend the administration of intravenous methylprednisolone. For moderate cases, the recommended dose is 0.5-1 mg/kg/day for three days, while for severe cases, it is 1-2 mg/kg/day. The National Institute of Health has also recommended the use of dexamethasone, with a dose of 6 mg per day for a maximum of 10 days, for patients who require ventilation or supplemental oxygen. However, it is not recommended for milder cases. It is important to note that the guidelines also acknowledge the potential risk of developing secondary infections while undergoing treatment for COVID-19. This highlights the significance of considering this factor when choosing appropriate treatments for COVID-19 patients [16-18].

COVID-19 has unique pathophysiological characteristics that can increase the risk of secondary fungal infections. One of these is its tendency to cause widespread pulmonary disease, which can lead to alveolo-interstitial pathology and increase the risk of invasive fungal infections. Additionally, the immune dysregulation seen in COVID-19, characterized by decreased numbers of T lymphocytes, CD4+T, and CD8+T cells, may impact innate immunity, further contributing to the susceptibility to secondary infections [12,19].

In our study, the participants consisted of 59.2% males and 40.8% females. This gender distribution is consistent with the findings of Lav Pathak., *et al*. [20] and Satish., *et al*. [21] in their critical review analysis and case series, respectively.

In our study, nearly three-quarters of the patients had diabetes as a serious contributing factor. This result aligns with the findings from several independent case reports, case series, and review analyses conducted in India [20,22].

In our study, a high proportion of patients, 99%, received steroid therapy (Methyl Prednisolone, Dexamethasone) during their COVID-19 treatment. This finding is consistent with previous reports by Pathak., *et al*. Sarkar et al., and Sen., *et al*. [20,23,24].

In a study conducted by White., *et al*. on 135 adults diagnosed with COVID-19, and found that almost one-third of them (26.7%) developed invasive fungal infections, with aspergillosis being the most prevalent (14.1%) and candida the most common yeast (12.6%). The study showed that the mortality rate was significantly higher (53%) among patients with invasive fungal diseases, compared to those without (31%). However, the study also indicated that the appropriate therapy reduced this risk significantly. The research identified that corticosteroid therapy and a prior history of chronic pulmonary disease were contributing factors to a higher risk of developing invasive fungal diseases [12,18,25].

The surgical approach in our study was specifically designed to address the spread of mucormycosis and involved a range of techniques to effectively debride the infected tissue. Endoscopic sinus surgery with Modified Denker's approach, Open maxillectomy with orbital clearance were among the methods employed in this process. The majority of cases were treated using the Modified Denker's approach, which involved drilling the medial and lateral walls of the maxilla, creating a window in the posterior wall of the maxillary sinus, which is used to remove the necrosed tissue

from the pterygopalatine fossa and infratemporal fossa. We have also employed routine endoscopic techniques, such as Functional Endoscopic Sinus Surgery, to clear the disease from the remaining sinuses. To ensure preservation of important structures, the lamina papyracea and floor of the orbit were removed, along with the periorbital fat, while carefully protecting the optic nerve/bulb and the orbital muscles. During the treatment process, patients were empirically administered IV LAMB therapy until the results of the fungal culture reports were available. On average, patients received IV Amphotericin for 14-21 days, before being shifted to oral Posaconazole, which was continued for a duration of 3-6 months.

Conclusion

- The results of this study demonstrate the importance of early detection and aggressive treatment in patients diagnosed with post-COVID mucormycosis.
- The use of modified Denkers or open maxillectomy along with antifungal therapy is crucial in the successful management of these cases.
- The results of this study demonstrate the need for better education and awareness about post-COVID mucormycosis and its potential impact on patient outcomes.
- The findings of this study emphasize the need for a multidisciplinary approach to the care of patients with post-COVID mucormycosis, particularly in those with a history of steroid use.
- The findings of this study emphasize the need for a multidisciplinary approach to the care of patients with post-COVID mucormycosis, particularly in those with a history of steroid use.

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