

## ORIGINAL RESEARCH

### **Mucormycosis in COVID: A pandemic induced epidemic in World's diabetic capital**

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#### **ABSTRACT**

**Background:** Mucormycosis is a rare disease of immunocompromised adults largely restricted to the diabetic community with uncontrolled hyperglycaemia. In the second wave of Covid, in multiple cities over the Indian Peninsula, this much dreaded “*black fungus*” has afflicted many individuals who suffered from covid or were recovering from it.

**Aim:** To establish the risk factors, clinical presentation, diagnostic sensitivities, radiological survey of different types of mucormycosis in SARS Cov 2 patients.

**Methods:** Seventeen patients with covid infection admitted in tertiary care hospital with diagnosed mucormycosis between Nov 2020 to June 2021 via histopathological or culture confirmation. This is a cross-sectional observational study where detailed assessment of clinical profile, biochemical markers and sensitivities of diagnostic procedures was done. The data then collected and was made into a master chart and subjected to statistical analysis. Fischer exact test was used for statistical analysis.

**Result:** In total of 17 patients, mean blood glucose levels were compared at the onset of symptoms of covid and mucormycosis were statistically significant with ( $P=0.001$ ). Out of 17 patients, 11 were rhino-orbital mucormycosis, four had rhino-orbito-cerebral mucormycosis and 2 had pulmonary mucormycosis. HbA1c  $>8$  had significant correlation ( $P=0.009$ ) with rhino-orbital and rhino-orbito-cerebral mucormycosis while higher total dosage of steroids was associated with pulmonary mucormycosis ( $P=0.015$ ). Sensitivity of culture was 64.7% in our study while histopathology was considered gold standard.

**Conclusion:** Our study shows strong correlation between the long term as well as short term glycaemic control with the onset of rhino-orbital mucormycosis while dosage and duration of steroids with pulmonary mucormycosis.

**Key Words:** Mucormycosis, HbA1c, Culture positive, Histopathological diagnosis, COVID 19, Diabetics, KOH mount, Rhino-orbital, Rhino-orbito-cerebral mucormycosis

#### **INTRODUCTION**

Mucormycosis is one of the most rapidly progressing and fulminant forms of fungal infection. Hyperglycemia in diabetes mellitus stimulates fungal proliferation and also causes decrease in chemotaxis and phagocytic efficiency which permits the otherwise innocuous organisms to thrive in acid-rich environment.<sup>[1]</sup>

Chronic administration of corticosteroids impairs migration, ingestion and phagolysosome fusion in macrophages also leads to drug-induced diabetes. Prolonged (>3 weeks) high-dose systemic corticosteroids are risk factors for mucormycosis. [2]

COVID-19 caused by SARS-CoV-2 virus has been associated with a wide range of opportunistic bacterial and fungal infections. The primary reason that appears to be facilitating Mucor in Covid is an ideal environment of hypoxia, high blood glucose, metabolic acidosis and other risk factors including prolonged hospitalization with or without mechanical ventilators. [3]

The clinical approach to diagnosis has low sensitivity and specificity. [2] In this study, we throw more light on clinical and biochemical profile in Covid patients to identify susceptible individuals for effective screening, early diagnosis and immediate initiation of treatment of mucormycosis.

## METHODS AND MATERIAL

Seventeen histopathologically or culture proven confirmed cases of invasive mucormycosis diagnosed covid positive with active disease or recovered between November 2020 and June 2021 were cross sectionally observed and investigated at a tertiary care hospital. Their clinical presentation, laboratory investigations, radiologically appearance and treatment outcomes were analysed. Comprehensive workup at presentation included detailed history, comprehensive ocular examination, otorhinolaryngological and neurological examinations to assess the extent and severity of the disease.

Initial investigations included complete blood counts, renal function tests, liver function test, blood sugar, HbA1c, arterial blood gas analysis and covid biochemical profile. Diagnosis of mucormycosis was made on the basis of demonstration of broad aseptate hyphae with right angled branching on KOH preparation of specimens obtained from the nasal cavity and/or paranasal sinuses and confirmed by culture reports as well histopathological examination after debridement/ biopsy. CT scan and/or MRI of paranasal sinuses, orbit, brain and thorax wherever required were obtained to assess the extent and severity of disease.

All patients received intravenous liposomal amphotericin B as soon as a diagnosis of mucormycosis was confirmed; it was given in dose of 5.0 mg/kg/day. Renal functions and electrolytes were monitored during therapy. Diabetes was controlled with insulin therapy.

Transnasal endoscopic radical debridement of involved sinuses was done in most patients and specimen obtained was sent for histopathology and culture.

All collected data was entered into a masterchart and studied. For statistical correlation, HbA1c and steroid dosage was graded according to the severity (Table 1) and recommended dose (Table 2). Important derivations from the masterchart are included in the result.

**Table 1: Interpretation of HbA1c levels in this study**

HbA1c	Inference
<6.5	Excellent Control/ Non-Diabetics
6.5-8	Good Control
8-10	Poor Control
>10	Grossly Uncontrolled

Treatment was carried out as per National Covid treatment guidelines and antifungals were instated as per laid out protocols and latest advancements. Steroid treatment was carried out as follows according to AIIMS National Guidelines for Sars Cov 2.

**Table 2: Standard steroid dosage in AIIMS Delhi guidelines for COVID management and reference values**

Standard Dose	Inj Methylprednisolone- 1-2mg/kg BW in 2 divided doses over 5-10days (or equivalent dose of dexamethasone)
Low Dose	Any dose below the recommended dose
High Dose	2x-3x of recommended dose
Very High Dose	>3x of recommended dose

(<https://covid.aiims.edu/clinical-guidance-for-management-of-adult-covid-19-patients/>)

**INCLUSION CRITERIA:**

1. RTPCR positive adults >18yrs age
2. Asymptomatic patients with Covid Nucleocapsid antibody positivity (total)
3. Culture positive from Nasal biopsy, Ocular exenteration
4. Sputum culture positive for pulmonary mucormycosis
5. Histopathologically proven biopsy

**EXCLUSION CRITERIA:**

1. KOH mount positive for aseptate hyphae but culture/ histopathologically unproven samples
2. RTPCR/ Antibody negative individuals
3. Patients positive for other fungal infections

**RESULT**

Results were analysed by Statistical software, *Vassarstats*: Website for statistical computation 1998-2021

A total of 17 patients of mucormycosis were included in this study. Mean age of patients of 55.1+ 16.2yrs, with range of 22-79yrs.

**Table 3: Age wise distribution of patients**

Age	Male	Female	Total
18-30yrs	1(5%)	0	1(5%)
30-50yrs	1(5%)	4(23%)	5 (30%)
>50yrs	7(41%)	4(23%)	11 (65%)

Mean duration of onset of symptoms of mucormycosis since the diagnosis of Covid infection was 9.7 days. Regarding vaccination status of patients only 2 (12.5%) patients received both the doses of the vaccine while 10 (62.5%) had not received any dose of vaccination.

All patients (100%) had Diabetes Mellitus, with 5 (31.3%) were newly diagnosed while 4 (25%) patients were diabetic for more than 10yrs and one had Type 1 diabetes. Mean blood sugar levels on clinical presentation of covid was 224.70mg/dl while blood sugar levels at the time of diagnosis of mucormycosis was 443.52 mg/dl. There was significant increase in mean blood sugar levels [ $P$  (<0.01) ( $t=-7.62$ ), Fischer Exact Test] during symptom onset of mucormycosis. Only 1 patient had diabetic ketoacidosis at the time of diagnosis. A total of 14 patients were tested for their HbA1c and mean value is 11.07 while median value is 11.6.

**Table 4: HbA1c distribution in patients**

HbA1c	No of patients	Glycaemic Control
<6.5	0	Non diabetic/ Excellent Control
6.5-7.9	2 (14.2%)	Good Control

8-9.9	2 (14.2%)	Poor Control
>10	10 (71.4%)	Grossly Uncontrolled
Total	14 patients tested	

**Table 5: HbA1c with reference to different types of mucormycosis:**

HbA1c levels	Pulmonary	Rhino-orbital	Rhino-orbital cerebral	Total
6.5- 7.9	2	0	0	2
8-9.9	0	2	1	3
>10.0	0	7	3	10
	2	9	4	17

It was seen that 9 out of 11 rhino-orbital mucormycosis cases and all the cases of rhino-orbital-cerebral cases had HbA1c levels >8. The results were highly significant ( $P<0.01$ , two tailed, Fischer Exact Probability Test).

Among comorbidities, 6 patients were hypertensives and 3 were hypothyroid.

## CLINICAL PROFILE

**Table 6: Symptomology of patients**

Symptoms	Percentage
Periorbital/ Facial Swelling	88.2%
Fever, Cough, shortness of Breath	58.8%
Vision Loss	52.9%
Tooth Ache	29.5%
Headache	17.6%
Focal Neurological Deficits	11.7%
Nasal discharge	11.7%

A total of 10 patients had right eye involvement (58.8%) for no clear reason. Majority of patients (94.1%) had ptosis and 82.3% had proptosis on presentation. Nearly 60% patients had ophthalmoplegia while 64.7% had non-reactive pupils and 50% patients had no perception of light. Black eschar was not a common finding seen only in 3 patients.

## HAEMATOLOGICAL AND BIOCHEMICAL PROFILE

In this study, 40% individuals were anemic, leukocytosis and lymphopenia ( $ALC < 1000$ ) was seen in 13/17 (76.4%) and 10/17 (58.8%) individuals respectively. Abnormal high monocyte count was found in 9/17 individuals. LMR values were abnormally low in 6/17 (35.2%). The NLR was higher (18.39 +/- 11.48) in patient who did not survive but the results were not significant ( $t = -1.54$ ,  $p = 0.14$ ). Kidney function tests were deranged in 3 individuals out of which 1 was known case of CKD. Liver function tests were normal in all subjects.

## DIAGNOSIS

Out of 17 patients, 11 patients were diagnosed to be rhino-orbital mucormycosis, 4 were rhino-orbital-cerebral mucormycosis and 2 were pulmonary mucormycosis. HRCT thorax was available in only 8 patients, 5 patients had severe CTSI with CORADS 6.

Mucormycosis was detected in 100% of patients who were radiologically screened. Majority (92.8%) individuals had sinusitis while 28.5% of which had bilateral involvement. Maxillary sinus and Ethmoid sinus were involved in 100% of these individuals. Sphenoid sinus was the next most common paranasal sinus involved. A minority of patients subsequently developed ischaemic infarcts of the brain and one patient even developed cerebral venous thrombosis.

A total of 11 patients (64.7%) were found to have blackish eschar on nasal sinus endoscopy while 4 patients had absolutely normal study. Only 9 patients (52.9%) had aseptate hyphae on a KOH mount for nasal biopsy sample. Out of all patients, 11/17 (64.7%) had culture positive results for mucor. Histopathology report was confirmatory for all individuals who were tested.

The sensitivity of culture test in already confirmed cases of mucormycosis was more compared to KOH mount i.e 64.7 vs 58.8% respectively. They both missed 6 and 7 cases respectively of mucormycosis, which were detected by histopathological examination, which remains the gold standard for diagnosis in the study.

However, when sensitivity of KOH was compared with culture, it came out to be 63.6% and specificity was 50%, with PPV of 70% and NPV of 92.8%.

**Table 7: Distribution of patients according to dose of steroids given.**

Dosage	Pulmonary	Rhino-orbital	Rhino-orbital cerebral
Low Dose	0	3	1
Standard Dose	0	3	1
High Dose	0	0	0
Very High Dose	2	2	1
Total	2	8	3

Both the cases of pulmonary Mucormycosis had history of very high dose steroid (total dose) with mean dose of 3.4g methyl prednisolone for a duration ranging from 9 to 25 days. However, 3 cases of (42.8%) of rhino-orbital mucormycosis and 1 case (33.3%) rhino-orbital-cerebral mucormycosis respectively were associated with intake of high dose steroids for which the association was highly significant ( $P$  0.01, two tailed, Fischer Exact Probability Test).

Thirteen patients (74.6%) had received higher end antibiotics while eleven (64.7%) required oxygen support. Total 9 patients (52.9%) had received Remdesivir while almost all received Amphotericin B after diagnosis. Surgery was performed on only 11 individuals as 3 were unstable, 1 was reluctant and 2 patients left against medical advise. Mean duration from diagnosis to surgical intervention in our hospital was 7.54 days.

### CLINICAL OUTCOME OF THE PATIENT

Out of 17 patients, nine (52.7%) patients succumbed to the disease and 8 were discharged on Tb. Posaconazole. Out of 11 cases of ROM ,five died (45.5%) while two (50%) died of Rhino-orbitocerebral disease. There was 100% mortality in pulmonary mucormycosis.

### DISCUSSION

Although mucormycosis is an extremely rare in healthy individuals but several immunocompromised conditions predispose it. This includes uncontrolled DM with or without DKA, hematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine therapy, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma. [3] A 2019 nationwide multi-center study of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19, Prakash et al. found that 18% had DKA and 57% of patients had uncontrolled DM [4]

In another study conducted of total 38 patients who were diagnosed as having mucormycosis in a tertiary care hospital in 2010. The mean age of the patients was 40.43 years, with 72% male. Rhino-orbital mucormycosis (61.5%) was the most common presentation followed by cutaneous manifestations (31%), gastrointestinal symptoms (5%), and pulmonary (2.5%).

Diabetes mellitus (56%) was the significant risk factor in rhino-orbito-cerebral presentation (OR = 7.55, P = 0.001). [5]

Singh *et al.* in his study proved DM remains the leading risk factor associated with mucormycosis globally, with an overall mortality of 46%. Indeed, presence of DM was an independent risk factor (Odds ratio [OR] 2.69; 95% Confidence Interval 1.77–3.54; P < 0.001) in a large 2018 meta-analysis of 851 cases of rarely occurring mucormycosis. [3]

Another study which identified 43 patients; 41 cases with documented mucormycosis (proven in 38, probable in 3) and 2 putative cases. We identified five patients with rhino-orbital disease, and one patient with rhino-orbital-cerebral disease, which was not included as there was no culture or histopathology documentation, given the fact that COVID-19 rarely can mimic rhino-orbital disease due to ophthalmic vein thrombosis. Of the 35 patients with information on glycemic status, 33 had DM, with a mean HbA1C of 10, and 22 had uncontrolled DM before admission; three patients had new-onset DM. Of the eighteen patients with DM and report of blood glucose and acid status, 8 were in diabetic ketoacidosis (DKA) at the time of presentation. [6]

This finding was consistent in our study where mean age was 55.1+- 16.2yrs although male to female ratio was almost equal. There was no sex association in patients of mucormycosis. Majority of patients (88.2%, 14/17) were diagnosed cases of covid while three of them were tested for covid antibodies which showed significant titres. Four patients had received a single dose of Covid vaccine while only two had received both the doses despite of which they were all admitted for Covid pneumonia and were ventilation dependent. All patients in our study were type 2 diabetic which is consistent with all previous studies. Duration of diabetes was variable in our study as five of our patients were newly diagnosed diabetics while their HbA1c was tested to be of uncontrolled diabetics. Significant association between HbA1c >8 was seen in our study with rhino-orbital and rhino-orbito-cerebral form of mucormycosis.

Although HbA1c is not routinely done laboratory work up for diabetics in a covid facility but our recommendation would be to test all diabetics for three monthly glycaemic control. Those with HbA1c > 8 should be put under surveillance for mucor symptoms and made to be screened for early intervention. This would also lead to prevention of localised spread and early surgical intervention could reduce mortality. IV steroids being the pillar of management of Covid ARDS further deranges the already uncontrolled glycaemia of these patients. These patients should be under strict blood glucose monitoring. Pulmonary mucormycosis has strong association with total dose of steroids being administered to these patients, especially in ICU setting. Indiscriminate use of steroids to fight cytokine storm should be curbed and unnecessary prolongation of steroid therapy beyond the recommendation duration should be avoided. DKA was present in only one patient in our study despite very high blood sugar levels at admission as well as after steroid therapy.

Unlike CAPA, invasive mucormycosis has been observed even in patients with mild to moderate SARS- CoV-2 infections. The strongest predisposing factor appears to be hyperglycemia in undiagnosed or uncontrolled diabetics. Hyperglycemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is the ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron becomes readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further enhancing their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycemia, the diabetic COVID 19

patient receiving corticosteroids or other immunosuppressants is exceptionally vulnerable to the development of mucormycosis. [7]

In our study, periorbital and facial puffiness was seen in majority of patients. Dental pain was the initial complaint in three individuals while only headache was the initial complaint in three patients. Contrary to expectations, eschar was a rare initial presentation and should not be looked for while screening patients. Vision loss was observed in 8 patients while on examination, 11 patients had complete ophthalmoplegia. It took a mean of 9.7 days from the diagnosis of covid infection to the onset of mucormycosis symptoms in our study.

Gupta *et al.* studied 11 patients where there were nine male and two female patients with mean age of 46.8 years. Uncontrolled diabetes mellitus was noted in all patients. One patient had history of renal transplantation. The common presenting features were-ophthalmoplegia (73%), diminution of vision, (64%) proptosis (36%) and periorbital swelling (27%). [8]

CT scan/MRI revealed sino-orbital involvement in eight cases and rhino-orbital-cerebral involvement in three cases. Ethmoid sinus (100%) was the commonest paranasal sinus involved. KOH preparation and histopathology revealed broad aseptate filamentous fungi branching at right angles with tissue invasion. Culture on sabouraud's dextrose agar showed growth of mucor species. All patients received intravenous amphotericin B and had undergone radical debridement of involved sinuses.

Sen *et al.* recently reported a series of six cases of COVID-19 disease with rhino-orbital mucormycosis. One patient in this series had concurrent COVID-19 and mucormycosis at admission, while five other patients developed mucormycosis during treatment with systemic steroids for COVID-19. They have reported a cluster of 10 cases of clinically diagnosed orbital mucormycosis with concurrent COVID-19 illness at their institute over 2 months. [9]

In our study, the most common form was Rhino-orbital mucormycosis (64.7%, 11/17), rhino-orbito-cerebral (23.5%, 4/17) and only two cases of pulmonary mucormycosis. All cases were diagnosed mucormycosis on either microscopic histopathological examination or culture growth on Sabouraud's dextrose agar. All patients who were radiologically tested on CT scan had Maxillary and Ethmoid paranasal sinus involvement followed by sphenoid sinus. Two patients in our study developed cortical infarct while one developed cerebral venous thrombosis in the course of our study. Sinus endoscopy was used as screening method in our study for symptomatic patients in our study, also aided in taking biopsy. Blind biopsy increases chances of false negative result. In our study culture was found to be more sensitive technique than KOH mount which was only 63% sensitive. Histological examination was considered gold standard. For all those patients who for any reason cannot be taken up for debridement immediately should be screened with sinus endoscopy and biopsy sample should be sent for both KOH mount and culture. These investigations are fairly sensitive and can aid early initiation of antifungal treatment for those who are either unstable for surgery at present or on mechanical ventilation.

Thirteen patients in all had received higher end antibiotics in the course of their treatment which again predispose a patient to opportunistic fungal infections. We recommend tapered use of higher end antibiotics and treatment be guided by serum procalcitonin levels. In our study all patients except 1 received either liposomal or deoxycholate form of Amp B depending on their renal status.

Mucormycosis is frequently a life-threatening infection. A review of published mucormycosis cases found an overall all-cause mortality rate of 54%. The mortality rate varied depending on underlying patient condition, type of fungus, and body site affected (for example, the mortality rate was 46% among people with sinus infections, 76% for pulmonary infections, and 96% for disseminated mucormycosis). [10] In our study, roughly half (8/17) of our patients were discharged from the hospital on oral antifungals while

52.9%(9/17)succumbed to the disease . Mortality rate of rhinoorbital disease was 45.4%, 50% for rhinoorbitocerebral ,and 100 percent for pulmonary mucormycosis .

## CONCLUSION

In our study, Diabetes Mellitus with or without ketoacidosis has been established the single most important risk factor for the development of any form of mucormycosis. Those who have HbA1c above 8, are at a higher risk for development of locally invasive disease in the form of Rhino-orbital and rhino-orbital-cerebral disease while duration of stay, duration and dose of steroids, prior history of use of broad spectrum higher antibiotics is significant for developing pulmonary mucormycosis. Our recommendation would be to, maintain strict glycaemic control in covid inpatients especially those receiving steroids and it's timely tapering. Keep steroid use duration as short as possible with avoidance of higher doses unnecessarily. Also for early screening of covid patients with diabetes with their HbA1c levels and those patients with symptoms. Procedures such as sinus endoscopy can be used for screening symptomatic patients to identify disease at an early stage to prevent local spread and start appropriate therapy with debridement and IV antifungals at the earliest.

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