

**A CASE SERIES OF COVID-19 PATIENTS WITH MUCORMYCOSIS INFECTION-  
LESSONS LEARNED FROM SECOND WAVE**Anita Basavaraj<sup>1</sup>, Bilia K. Aipu<sup>2\*</sup> and Dharshan P.<sup>3</sup><sup>1</sup>Professor and Head of Department, Department of General Medicine, Government medical College and Hospital, Miraj, Maharashtra.<sup>2,3</sup>Senior Resident, Department of General Medicine, Government Medical College and Hospital, Miraj, Maharashtra.**\*Corresponding Author: Dr. Bilia K. Aipu**

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**ABSTRACT**

**Background:** The outbreak of coronavirus has spread rapidly on a global scale. Secondary infections especially mucormycosis cases have increased prevalence in covid 19 patients. **Aim:** We aimed to describe a case series of covid 19 patients with mucormycosis infection. **Materials & Methods:** 10 cases who were admitted and treated in our covid 19 hospital in the month of April-May 2021 were studied. Demographic information, clinical features, and treatment data were extracted from medical records. **Observations & Results:** Among the 10 patients, 6 were males and 4 were females. The patients were aged from 35 years to 80 years. All patients were diabetic. Among these 4 out of 10 had received corticosteroid treatment. 9 of the patients had presented with orbital cellulitis and 1 with facial puffiness. During the hospital stay, 5 developed cerebrovascular accident. Radiological study of all had shown sinusitis. 6 of these patients underwent mortality mainly due to cerebral extension.

**KEYWORDS:** Mucormycosis, Covid 19, Diabetes mellitus.**INTRODUCTION**

Since December 2019, the coronavirus disease 2019 (COVID-19) outbreak in Wuhan and spread rapidly all over the world. The outbreak of coronavirus disease (COVID-19) has spread rapidly on a global scale.<sup>[1]</sup> Despite great efforts, there is no definitive treatment of the disease. However, prevention and symptomatic management are the best options.

Secondary infections are a well-described phenomenon in influenza, SARS, MERS, and other respiratory viral illnesses. But super-infections and co-infections in COVID-19 pneumonia are still under exploration. Secondary infections are reportedly common in hospitalised, severely ill Covid-19 patients, encompassing between 10 and 30% of cases, fungal being 10 times more common. As the nature of the disease is still not completely unveiled, it can't be confirmed if it's a complication of the disease or its management.

Both Aspergillosis and Candida have been reported as the main fungal pathogens for co-infection in people with COVID-19.<sup>[2]</sup> Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported worldwide, in particular from India. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19

is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycaemia, steroid-induced hyperglycaemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalisation with or without mechanical ventilators.

Phycomycosis or zygomycosis was first described in 1885 by Paltauf and later coined as Mucormycosis in 1957 by Baker an American pathologist for an aggressive infection caused by Rhizopus. Mucormycosis is an uncommon but fatal fungal infection that usually affects patients with altered immunity. Mucormycosis is an angioinvasive disease caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia of Order- Mucorales, Class- Zygomycetes. The Rhizopus Oryzae is the most common type and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral (ROCM) form. Mode of contamination occurs through the inhalation of fungal spores which are present in soil, manure, fruits and starchy foods.

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of the year 2019–2020. In other words, India has the highest cases of mucormycosis in the world. Notwithstanding, India is already having the second largest population with diabetes mellitus (DM) and is the diabetes capital of the world. Importantly, DM has been the most common risk factor linked with mucormycosis in India, although haematological malignancies and organ transplant takes the lead in Europe and the USA.

Nevertheless, DM remains the leading risk factor associated with mucormycosis globally, with an overall mortality of 46%.<sup>[12]</sup> Indeed, the 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, and the most common species isolated was *Rhizopus* (48%). While long-term use of corticosteroids has often been associated with several opportunistic fungal infections including aspergillosis and mucormycosis, even a short course of corticosteroids has recently been reported to link with mucormycosis especially in people with DM. A cumulative prednisone dose of greater than 600 mg or a total methyl prednisone dose of 2–7 g given during the month before, predisposes immunocompromised people to mucormycosis. These findings need a relook in the context of COVID-19 pandemic where corticosteroids are often being used.

Early diagnosis and aggressive treatment have been advocated by some authors in the management of invasive fungal disease. The routine administration of amphotericin B particularly in its liposomal form has been found to reduce mortality in mucormycosis. Some authors advocate aggressive surgical debridement with orbital exenteration for mucormycosis, whereas others have demonstrated survival with a more conservative approach without exenteration. Nonetheless, there remains a lack of consensus regarding the indications for exenteration, with the decision to perform this procedure resting primarily on the judgment of the treating physicians.

There has been a steep rise in case reports/series of mucormycosis in people with COVID-19, especially in India. Similarly, several case reports are being reported from other parts of the globe. Several anecdotal cases are being reported in grey literature such as the print and electronic media. These findings are unprecedented and carry immense public health importance, especially because the fatality rate with mucormycosis is pretty high. Especially the intracranial involvement of mucormycosis increases the fatality rate to as high as 90%<sup>[3]</sup> Moreover, the rapidity of dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 h in the diagnosis could be fatal, the reason

50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series.<sup>[4]</sup>

This prompted us to study a case series of 10 patients with mucormycosis in people with COVID-19, to know its temporal associations concerning comorbidities, association with drugs being used in COVID-19, and overall characteristics of patients with its outcome.

## METHOD

10 patients admitted to our hospital during April-May as suspected or confirmed mucormycosis cases were randomly selected. Their detailed history COVID 19 status clinical features laboratory investigations, radiological findings treatment, and outcome were studied retrospectively. Among the 10 patients, 2 were COVID19 RTPCR negative but clinically had bilateral pneumonia hence included in the study. COVID 19 patients were diagnosed based on criteria of WHO interim guidance. Mucormycosis was diagnosed based on clinical features, KOH mount /histopathology positive or radiological findings.

## Procedure

Medical records of all 10 patients who were treated in our hospital was studied. Demographic information, clinical features, and treatment were extracted from medical records. Data were recorded into a computerised database

## Laboratory and Radiological information

Throat swabs were tested for COVID-19 by RTPCR according to the recommended protocol. The laboratory tests include routine blood investigations and blood sugar level, urine ketone level. CT brain with PNS of all patients had been done. KOH mount for fungal elements was sent for all patients.

## RESULT

### Demographic characteristics

Among the 10 patients, 6 were males and 4 were females. The patients were aged between 35-80 years. 3 were at age of 20-40 years, 4 were between 41-60 years and 3 were above 60 years.

### Predisposing factors

All 10 patients were diabetic, 1 is a newly diagnosed case (PT no. 6). Among 10 patients, 5 patients were in DKA, 3 had uncontrolled DM, other 2 had controlled DM. 2 patients had hypertension, 1 patient was a known case of ischemic heart disease.

### Mucormycosis and covid 19

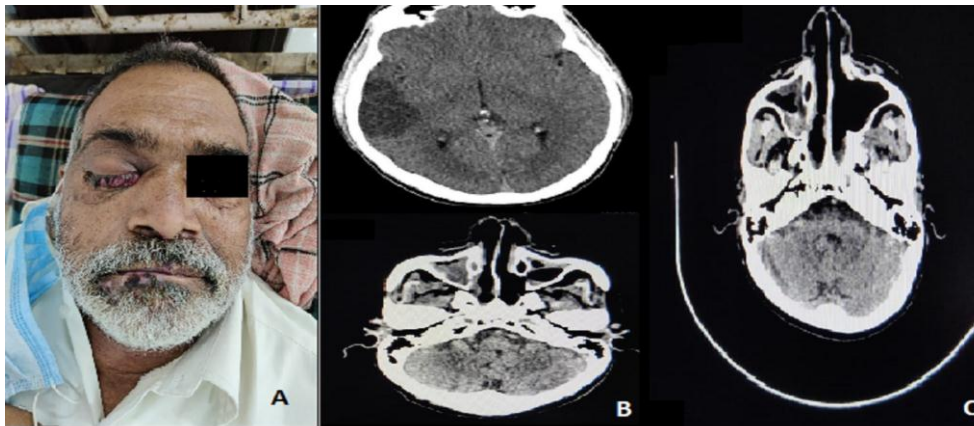
Among 10 patients 8 were Real time-PCR(RTPCR) proven covid 19, 2 were RTPCR negative (PT no 1&2) but CT chest showed bilateral pneumonia which was typical of covid 19 infection and was treated accordingly. 2 were post covid patients, rest had active covid 19 infection. None of these were vaccinated. Except 2 all had given o2 via mask before development of

mucormycosis. 4 out of 10 had received steroids for treatment of covid.

### Clinical manifestations

The most common presenting symptom was orbital swelling except 1 who had presented with facial

puffiness, numbness at cheek. 5 had right eye swelling, 3 had left orbital swelling, 1 had bilateral eye swelling. 1 patient had presented with right nasal mass and epistaxis. During the course in the hospital, 5 had developed cerebrovascular accident.



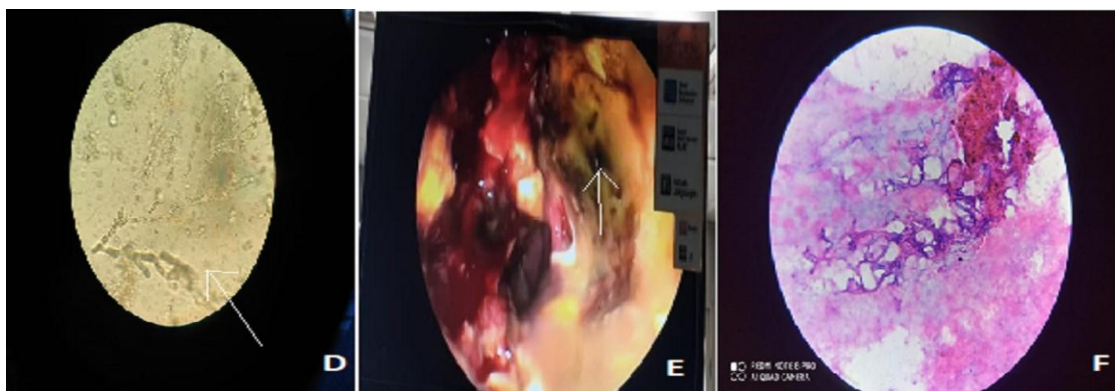
**Figure 1:** A- patient presenting directly with orbital cellulitis, B- CT brain with PNS of pt no.4 showing right maxillary sinusitis with right temporooccipital infarct, C- CT PNS of PT no 6 showing maxillary sinusitis.

### Radiological findings

CT brain with PNS of all patients had shown sinusitis. 7 had pansinusitis rest has maxillary sinusitis. Those who developed CVA CT brain showed acute infarcts. MRI was done for 5 patients which showed pansinusitis.

### KOH mount

Among 10 patients 6 had KOH mount positive and 4 had negative. Out of 4, KOH negative 1 patient underwent surgical debridement and histopathology was suggestive of mucormycosis.



**Figure 2:** D- KOH mount of patient 1 showing fungal elements, E- Endoscopic picture of FESS done in patient no. 6 showing black necrotic tissues[Eschar], F- HPE of specimen from patient no 6 showing mucormycosis.

### Treatment

Among 10, 4 underwent surgical debridement (PT no 5,6,8&9). 7 were given inj amphotericin B at standard doses, and in rest of the patients amphotericin B was not given due to deranged RFT. Histopathological examination of surgical biopsy specimens of 4 patients showed mucormycosis.

Oxygen therapy was given for 8 patients as 2 patients were maintaining saturation in room air. 6 patients were put on mechanical ventilation rest received oxygen by mask. All had received empirical antibiotic therapy. 6 patients were admitted to ICU, rest 4 in ward.

### Outcome

Among 10 patients, 6 did not survive and the rest 4 got discharged (pt no 5,6,8&9). The cause of death in 5 patients was due to cerebral extension of mucormycosis and 1 is due to sepsis.(pt no2)

### DISCUSSION

A case series of 10 mucormycosis patients with covid 19 were included in our study. This study showed that males are more affected than females with mucormycosis. This is comparable to a study conducted by A.K Singh et.al which revealed Mucormycosis was predominantly seen in males (78.9%), both in people who were active (59.4%) or recovered (40.6%) from COVID-19.

All age groups are affected with mucormycosis. All patients are known cases of diabetes mellitus which strongly suggested the relationship between diabetes mellitus and mucormycosis. The majority had uncontrolled blood sugar levels. A 2019 nationwide multi-centre 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<sup>[5]</sup> Presence of DM significantly increases the odds of contracting Rhinooculocerebral[ROCM] by 7.5-fold (Odds ratio 7.55, P = 0.001) as shown in a prospective Indian study, before COVID-19 pandemic.<sup>[6]</sup> In a recent systematic review conducted until April 9, 2021, by John et al.<sup>[7]</sup> that reported the findings of 41 confirmed mucormycosis cases in people with COVID-19, DM was reported in 93% of cases, while 88% were receiving corticosteroids. Collectively these findings suggest strong relation between diabetes mellitus and mucormycosis.

Out of 10,8 patients were COVID 19 patients and received O<sub>2</sub> therapy via mask as well as steroids for COVID 19 treatment. This suggests an association between the use of corticosteroids and mucormycosis. There appear to be some triggers that may precipitate mucormycosis in people with COVID-19 with corticosteroids: Uncontrolled hyperglycaemia and precipitation of DKA are often observed due to corticosteroid intake. Low pH due to acidosis is a fertile medium for mucor spores to germinate. Moreover,

steroid use reduces the phagocytic activity of WBC (both first line and second line defence mechanism), causes impairment of bronchi alveolar macrophages migration, ingestion, and phagolysosome fusion, making a diabetic patient exceptionally vulnerable to mucormycosis.

9 of them had orbital cellulitis as presentation and 5 developed cerebrovascular accident. (PT no1,3,4,7 &10) This suggests that Rhinooculocerebral mucormycosis is the most common type of mucormycosis. In a data of 465 cases of mucormycosis without COVID-19 in India, Patel et al.<sup>[26]</sup> has shown that rhino-orbital presentation was the most common (67.7%), followed by pulmonary (13.3%) and cutaneous type (10.5%). All had radiological evidence of sinusitis as 1<sup>st</sup> sign in mucormycosis. 5 patients showed cerebral infarct.

Among 10 patients 7 had received amphotericin injection. Amphotericin B injection was not given to 3 patients due to deranged RFT (3,7&10). Only 4 patients underwent surgical debridement (PT no5,6,8&9). Rest of the patients presented in late stage with cerebral extension and their general condition was not fit for surgical debridement.

The histopathological study of surgically debrided specimens was suggestive of mucormycosis. The outcome of mucormycosis was very poor. 6 out of 10 underwent mortality mainly due to cerebral extension of mucormycosis. One of the patient died due to sepsis (pt no2)

**Table no. 1: Demographic, clinical Features and Outcome of mucormycosis patients.**

Details	Pt 1	Pt2	Pt3	Pt4	Pt5	Pt6	Pt7	Pt8	Pt9	Pt10
Age	52	46	80	72	37	36	55	50	63	35
Sex	F	M	M	M	F	M	F	M	M	F
Orb.cellulitis	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Cva	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes
Covid 19	Neg	Neg	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Vaccination	No	No	No	No	No	No	No	No	No	No
Diabetes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Steroid treat	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Ct pns-sinusitis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ct brain-infarct	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes
Koh/hpe report	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Pos	Pos	Pos
Inj amphotericin	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
Surgical debridement	No	No	No	No	Yes	Yes	No	Yes	Yes	No
Outcome	Death	Death	Death	Death	Dis	Dis	Death	Dis	Dis	Death

PT-patient, ORB-orbital, HPE-histopathological examination, INJ-injection, F-female, M-male, NEG-negative, POS-positive

## CONCLUSION

Our study indicates that all age group are affected with mucormycosis. It is common among diabetes patients. The incidence is more among COVID 19 patients especially those received oxygen therapy and corticosteroids for COVID 19 treatment. Rhinoorbitocerebral mucormycosis is the most common

type of mucormycosis and it is a highly fatal disease. But early surgical intervention and treatment with injection Amphotericin B is life saving.

## Lessons learnt from the past

This study was conducted during the initial periods of second wave when mucormycosis has just arrived. As time passed by every treating doctors become alert about mucormycosis. As a result mucormycosis is being detected at early stage, surgical debridement is being done, amphotericin B injection was given, hence

mortality rate has decreased drastically. Also treating doctors started using steroids very vigilantly, sterility of water for oxygen therapy has been maintained, as a result the incidence of mucormycosis patients has decreased a lot now a days. Let us move forward considering the lessons from the past.

#### **Limitation of the study**

Small sample size.

#### **Funding**

No funding was needed.

#### **Authors contributions**

All authors contributed to the study at a different level.

#### **Abbreviations**

CVA-cerebrovascular accident, CT-computed tomography, DKA-diabetic ketoacidosis, HPE=histopathological examination, ICU-intensive care unit, ROCM-rhinoorbitocerebral mucormycosis, WHO-world health organization

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8. Consent "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".