

## Original Research Article

# Mucormycosis: a rare but rising fungal infection in COVID-19 patients at tertiary care centre

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### ABSTRACT

**Background:** New pandemic Coronavirus disease 2019 (COVID-19) shows wide range of disease pattern from mild to life threatening pneumonia in association with bacterial and fungal infections. Invasive fungal infections are becoming new burden in COVID-19 patients especially when associated with diabetes mellitus.

**Methods:** We have studied 90 patients of invasive fungal sinusitis at tertiary care centre over a period of 3 months from March 2021 to June 2021 prospectively. All patients suspected for invasive fungal sinusitis in association with covid19 are included.

**Results:** 67 males and 23 females of age group 41 to 70 years were presented as case of invasive fungal sinusitis with suspicion of Mucormycosis. Disease extended to orbit in 90 patients, to hard palate in 33 and skin involved in 5 patients. Diagnosis based on clinical presentation, computed tomography (CT scan) findings, KOH preparation and culture. KOH showing fungal elements in 62 patients and fungi isolated in 37 patients. Aspergillus group and mucorales contribute equally being found in 17 samples each. 23 patients lost their life due to this disease. This study is done and reported first time from this tertiary care centre.

**Conclusions:** Invasive fungal sinusitis including Mucormycosis otherwise rare disease has significantly increased in COVID-19 pandemic. Immune dysregulation due to COVID-19, Diabetes mellitus and wide spread use of corticosteroids/antibiotics all contributed to this rise in cases of invasive fungal diseases. Early diagnosis, surgical intervention and antifungal treatment help to reduce mortality and morbidity.

**Keywords:** COVID-19, Mucormycosis, Diabetes mellitus, SDA

### INTRODUCTION

The disease pattern of Coronavirus disease 2019 (COVID-19) can range from mild to life threatening pneumonia with associated bacterial and fungal infections.<sup>1</sup> Due to the associated comorbidities (example- diabetes mellitus, chronic obstructive pulmonary disease) and immunocompromised conditions (example- Corticosteroid therapy, ventilation, intensive care unit stay), these patients are prone to develop severe opportunistic infection.<sup>2</sup> Mucorales infections are emerging as a matter

of concern in COVID-19, as poorly controlled diabetes mellitus and other co-morbidities are risk factors for both severe COVID-19 and Mucormycosis.<sup>3</sup>

Mucormycosis infection of the sinuses is a form of life-threatening invasive fungal sinusitis that typically affects immunocompromised individuals with an impaired neutrophilic response.<sup>4</sup> Mucormycosis frequently infects the sinuses, brain, or lungs. Mucormycosis is a rare but severe invasive fungal infection occurring mostly in immune compromised patients, especially in individuals

diagnosed with uncontrolled diabetes mellitus or hematological malignancies and in previously healthy subjects with open wounds contaminated by mucorales.<sup>5,6</sup>

Various studies had published till now reporting Mucormycosis in covid19 patients either along with COVID-19 or as a post COVID-19 sequelae.<sup>1-4</sup> In last few months our tertiary care hospital has seen sudden rise of cases with invasive fungal sinusitis. Here we present our experience of 90 patients of invasive fungal sinusitis over past 3 months patients being presenting along with COVID-19 or as a post covid19 sequelae.

**METHODS**

**Study type**

The study is a prospective observational study.

**Study place**

The study was conducted at DR. Shankarrao Chavan Government medical college, Vishnupuri, Nanded, Maharashtra, India.

**Study period**

The study was conducted for a period of 2 months i.e., from March 2021 to May 2021.

**Selection criteria**

Patients presented to ENT outpatient or in patient department with clinical suspicion of invasive fungal sinusitis. Patients with suspicion of invasive fungal sinusitis and having past history of COVID-19. Diagnosed/ confirmed COVID-19 Patients presented with invasive fungal Sinusitis.

**Statistical analysis**

It is not applicable.

Prospective observational study conducted at tertiary care centre over 3-month duration from March to May 2021. All patients with suspected invasive fungal infection who attended ear nose throat (ENT) outpatient or referred to ENT in patient department (IPD) are included in the study. The patient’s clinical presentation, imaging findings, comorbidities, management details, and follow-up information and outcome of patient were obtained, recorded and analysed. Patients operated depending upon clinical involvement and computed tomography (CT scan) findings. Nasal scrapings of suspected patients and surgical debridement tissues sent to microbiology laboratory for isolation and confirmation of fungal species. These samples first processed with KOH for presence of fungal hyphae then cultured on SDA (Sabaraud’s Dextrose agar) for growth of fungi. Growth on SDA then teased and stained with LPCB (lactose phenol cotton blue) and

studied under microscope for identification and confirmation of fungal species.

**RESULTS**

Total 90 patients were included in the study. 67 (74%) were males and 23 (26%) were females. Highest number of patients represent from 41 to 70 years of age group (Table 1).

**Table 1: Characteristics of 90 patients associated with Mucormycosis in COVID-19 patients.**

	No. of patients (n=90)	Percentage
<b>Male</b>	67	74
<b>Female</b>	23	26
<b>Steroid requirement</b>	51	56
<b>KOH positivity</b>	62	68
<b>Culture positivity</b>	37	41
<b>Comorbidity present</b>	84	93
<b>Vaccination (full, partial)</b>	1 & 4	1.1 & 4.4
<b>No vaccination</b>	85	93
<b>Surgical debridement</b>	48	53
<b>Death</b>	24	26

**Table 2: Extension of Mucormycosis in 90 patients.**

Extension of Mucormycosis	No. of patients (n=90)	
<b>Sinus involvement</b>	88	
<b>Orbit involvement</b>	60	
<b>Palate involvement</b>	33	
<b>Cutaneous involvement</b>	05	
<b>Fungal isolates</b>	<b>n=37</b>	<b>Percentage</b>
<i>Aspergillus niger</i>	10	27
<i>Aspergillus fumigatus</i>	4	11
<i>Aspergillus flavus</i>	3	8
<i>Mucorsp</i>	10	27
<i>Rhizopussp</i>	7	19
<i>Candida kruzie</i>	1	2.7
<i>Candida glabrata</i>	1	2.7
<i>Acremoniumsp</i>	1	2.7

All patients primarily presented for sinus involvement (100%). 60 (74%) patients presented with orbital extension of infection. Palate involvement was found in 33 (36%) patients. Very few patients with cutaneous involvement 5 (5.5%) were also seen (Table 2). In para nasal sinuses maxillary sinus was most commonly affected sinus in 88 patients followed by ethmoid in 66 patients and frontal in

63 patients. Sphenoid sinus is least involved sinus, affected in 39 patients (Table 3).

**Table 3: Sinus involvement in mucormycosis patients.**

Sinus involvement	No. of patient(n=90)
Maxillary	88
Ethmoid	66
Sphenoid	39
Frontal	63

**Table 5: Types of surgeries performed in COVID-19 patients.**

Type of surgery	No. of patients (n=50)
Fess	34
Fess with maxillectomy	7
Fess with Cald well luc	6
Cald well luc	1



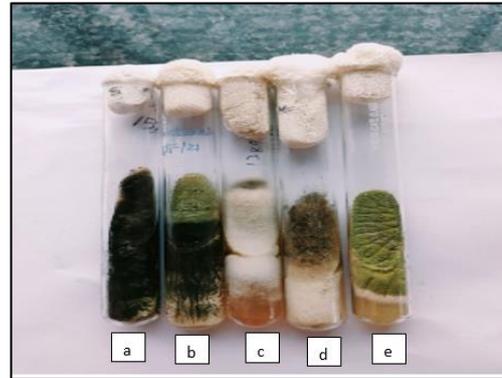
**Figure 1: KOH preparation from surgical debridement showing fungal Hyphae (power 10X).**



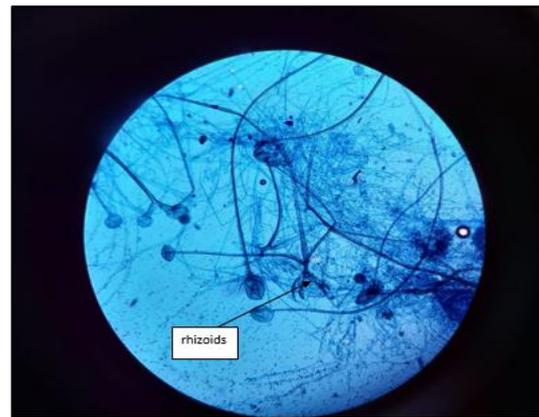
**Figure 2: KOH preparation from surgical debridement showing fungal Hyphae (power 40X).**

Diagnosis of Mucormycosis is mainly done with the help of CT scan finding which is supported by KOH finding and culture confirmation. KOH showed fungal hyphae in 62 (68%) of patients, whereas SDA agar showed growth of fungi in 37 (41%) of samples. Most common isolate was *aspergillus* group of fungi (17/37; 46%) followed by *Mucor*sp (10/37) then *Rhizopus*sp (7/37). One species of

*Acremonium* was also isolated. 2 species of *Candida*; one being *C. cruzie* and another *C. glabrata* were grown. 5 cases with mixed fungal infection were also found. In 2 cases combination of *Aspergillus* species such as *A. niger* and *A. fumigatus* was grown. In another case mixture *A. niger* and *Mucor*sp were isolated. In remaining 2 cases *Candida* was grown along with *Mucor* and *Aspergillus* respectively (Table 4).



**Figure 3: SDA showing growth of different fungal isolates. (A) *Aspergillus niger* (b) mixture of *Aspergillus niger* and *Aspergillus fumigatus* (c) *Mucor* sp (d) *Rhizopus* sp (e) *Aspergillus fumigatus***



**Figure 4: LPCB stained slide from growth on SDA culture: showing *Rhizopus* species.**

Only 6 out of 90 (7%) patients presented Mucormycosis without any comorbid condition. Remaining 84 (93%) patients presented with one or more comorbid condition. Diabetes mellitus remains most common comorbidity found in 71 (78%) patients followed by hypertension, hypothyroidism, ischemic heart disease, viral hepatitis, chronic kidney disease, etc. Most of the patients presented with more than one comorbidity. Corticosteroids were given to 78 (87%) patients during their treatment against COVID-19. (Table 1) Out of these 90 patients with Mucormycosis only one (1.1%) patient was found with full vaccination; who recovered without surgical need. 4 (4.4%) patients took single dose of vaccine and remaining 85 (94.5%) patients did not take vaccine. (Table 1) Among the 4 partially vaccinated patients 2 lost their battle and 2

after surgical cure discharged from hospital. All 4 were known cases of diabetes mellitus.

69 (77%) patients treated with surgical debridement and 21 (23%) patients cured with Amphotericin B only. (Table 5) Most of the patients (60) underwent functional endoscopic sinus surgery (FESS) with maxillectomy followed by FESS with Caldwell Luc in 30 patients. 25 patients underwent Caldwell luc procedure. Many patients underwent more than one surgery.

43 (48%) out of 90 patients had concomitant COVID-19 and Mucormycosis whereas remaining 47(52%) developed Mucormycosis as a post COVID-19 sequelae. Considering outcome of patients 24 (26%) patients lost their battle against this disease whereas 66 (74%) overcame and discharged after complete cure.

## DISCUSSION

Mucormycosis or zygomycosis, also called phycomycosis, initially described in 1885 by Paltauf, is an uncommon and aggressive fungal infection that usually affects patients with alteration of their immunological system.<sup>7</sup> The factors predisposing to the development of the infection are uncontrolled diabetes mellitus, neutropenia, elevated free iron levels, deferoxamine and organ transplant patients on immunosuppressants.<sup>8</sup> Disease known with very low incidence rate, from 0.005 to 1.7 per million populations, there is significant increase in its incidence in the wake of the ongoing corona virus pandemic.<sup>9,10</sup> In our study out of 90 patients 67 (74%) were males and 23 (26%) were females. Highest number of patients represent from 41 to 70 years of age group. Study done by John et al reported 34 (83%) out of 41 patients affected were males and highest number of patients from age group 41-60 years.<sup>3</sup> A systemic view of literature conducted by Garg et al showed that out of 8 case reports included in the study 7 (87%) were males.<sup>11</sup> Study done by Sharma et al reported 18 (78%) out of 23 affected patients were males.<sup>12</sup>

All patients attending ENT OPD and IPD showed one or other sinus involvement, disease extended to orbit in 60 patients. Palate involvement presented in 33 patients and 5 patients presented with cutaneous involvement. Many patients presented with more than one system involved. Maxillary sinus is most commonly involved sinus in our study (88) followed by ethmoid sinus involvement (66) followed by frontal sinus (63). Least affected is sphenoid sinus which is affected in 39 patients. Study conducted by Garg et al showed orbital extension in 44% patients<sup>11</sup>. The study done by Sharma et al reported orbital extension was seen in 43% patients, hard palate was involved in 9 patients.<sup>12</sup>

India has the second-largest number of adults aged 20–79 years with diabetes mellitus.<sup>13</sup> In fact, diabetes mellitus is the single most common risk factor for Mucormycosis in India, being reported in over 50% of cases of Mucormycosis. In a recent nationwide multi-centre study

on Mucormycosis in India, 57% of patients had uncontrolled diabetes mellitus and 18% had diabetic ketoacidosis.<sup>14</sup> In our study diabetes mellitus is a risk factor in 78% of cases. Whereas the study done by John et al showed that diabetes mellitus present as risk factor in 94% of patients.<sup>3</sup> Study conducted by Garg et al diabetes mellitus was associated with 50% of patients as risk factor.<sup>11</sup> Whereas Sharma et al reported diabetes mellitus as risk factor in 93% of patients in their study.<sup>12</sup>

Glucocorticoids are inexpensive, widely available, and have been shown to reduce mortality in hypoxemic patients with COVID-19.<sup>11</sup> Glucocorticoids can increase the risk of secondary infections. Moreover, the immune dysregulation caused by the virus by reducing CD4 and CD8 lymphocytes and the use of concurrent immunomodulatory drugs such as tocilizumab could further increase the risk of infections in COVID-19 patients.<sup>11</sup> The frequent use of corticosteroids that exacerbated glucose homeostasis, may have predisposed patients to Mucormycosis. Corticosteroid use is a key risk factor for opportunistic mycoses, including Mucormycosis.<sup>3</sup> In our study 86% Mucormycosis patients received corticosteroid therapy. Study done by John et al showed that 88% patients received corticosteroid therapy.<sup>3</sup> Sharma et al reported all patients 100% received corticosteroid therapy during management of COVID-19.<sup>12</sup>

We have studied vaccination status of patients also. Maximum patients (85/90 i.e. 93%) were not vaccinated. Only one patient was fully vaccinated and cured from Mucormycosis with the help of Amphotericin B only. Surgical debridement not needed for him. Out of 4 partially vaccinated patients with all having diabetes mellitus 2 patients lost their life and 2 patients cured; one with surgical treatment and another without it. Our data is not enough to comment any role of vaccination on Mucormycosis. More research needed to be done on this. As per our knowledge no study has ever mentioned about vaccination in relation with Mucormycosis.

Diagnosis of Mucormycosis was supported by KOH preparation and confirmed by growth of fungal species on SDA. In our study KOH finding showed fungal hyphae in 62 (68%) cases whereas SDA grew fungi in 37 (41%) samples from surgical debridement. To our surprise most common isolates were *Aspergillus* group of fungi (17/37) followed by *Mucor* species (10/37) then *Rhizopus* (7/37). One species of *Acromonium* and 2 species of *Candida* also isolated. 5 cases with mixed fungal infection were also found. In 2 cases mixed growth of *A. niger* and *A. fumigatus* was found. In another case mixture of *A. niger* and *Mucor* sp were isolated. In remaining 2 cases *C. krusei* and *C. glabrata* were grown along with *Mucor* and *Aspergillus* respectively. John et al reported 100% culture positivity; most common species being unspecified *mucorales* 68% followed by *Rhizopus* (24%) and *Mucor* (5%).<sup>3</sup> *Rhizopus* isolated in one case report study done by Rennawar et al.<sup>15</sup> Study done by Sarkar et al included 10 cases of Mucormycosis. Culture positivity was 60% in

their study and most common isolate was *Rhizopus sp.* (67%) grown in 4 out of 6 biopsy specimens followed by *Mucor sp.* (23%) in 2/6 patients.<sup>2</sup> Various studies reported *Rhizopus* as causative fungus in their studies.<sup>1,2,9</sup> Lahane et al in their study of 6 rhino-orbital Mucormycosis reported *Mucor sp.* in 4 (67%) patients and *Aspergillus* in one patient.<sup>8</sup> El-Kholy et al reported *Aspergillus* isolated in 30% of cases and *Mucor sp.* in 77% of cases and 8.3% of cases also reported mixed infections.<sup>16</sup> Sabisten et al also reported one case of mixed infection with *Aspergillus* and *Mucor* together.<sup>17</sup>

Surgical debridement of the infected area should be performed as soon as possible once the diagnosis is confirmed. Surgery alone has been reported not to be curative, but an aggressive surgical approach has been shown to improve survival.<sup>12</sup> In our study 48 out of 90 (53%) patients need surgical cure. One of these patient cured by Caldwell Luc surgery. Most of the remaining patients either operated with functional endoscopic sinus surgery (FESS) alone (70%) or combined with Caldwell Luc (12.5%) or maxillectomy (14.5%). The study done by John et al reported 80% of patients needed surgical assistance for cure from Mucormycosis.<sup>3</sup> Whereas in study done by Sharma et al all 23 (100%) patients needed surgical debridement.<sup>12</sup> Sarkar et al reported 7 (70%) out of 10 patients were operated for Mucormycosis.<sup>2</sup> In present scenario Mucormycosis develops as secondary or concomitant infection along with COVID-19.<sup>18,19</sup> In our study Mucormycosis is found to be associated with COVID-19. Out of this 43 (48%) patients presented Mucormycosis along with COVID-19 whereas 47 (52%) patients developed it as post COVID-19 sequelae. Study done by Garg et al showed that 2 (25%) out of 8 patients presented Mucormycosis along with COVID-19.<sup>11</sup> John et al reported 16 (39%) out of 41 developed Mucormycosis along with COVID-19 whereas 25 (61%) patients developed it as a post-COVID-19 sequelae.<sup>2</sup> Sharma et al showed in their study 4 (17%) out of 23 patients had Mucormycosis and COVID-19 simultaneously and remaining 19 (83%) developed Mucormycosis as a post COVID-19 complication.<sup>12</sup>

Considering outcome of patients in our study 24 (26%) out of 90 patients lost their battle against this disease whereas 66 (74%) were discharged after complete cure. John et al reported 49% (20/41) mortality due to Mucormycosis.<sup>2</sup> 2 (8.6%) out of 23 patients lost life due to Mucormycosis in study done by Sharma et al.<sup>12</sup>

A high degree of clinical suspicion is needed to diagnose Mucormycosis and timely aggressive management is necessary to improve outcome in Mucormycosis.

#### **Limitations of the study**

Number of patients included in study are limited. Though we have commented on vaccination status of the patients, data is very limited to get any conclusion.

## **CONCLUSION**

As we are learning to live along with COVID-19 and it is becoming new normal to life; its associations with different complications are coming into light. Covid19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. Additionally, the widespread use of corticosteroids/monoclonal antibodies/broad-spectrum antibiotics as part of the treatment against COVID-19 may lead to the development/exacerbation of pre existing fungal diseases. Uncontrolled diabetes and over-zealous use of corticosteroids are two of the main factors aggravating the invasive fungal infections including Mucormycosis. Physicians must be alert of this while attending patients. Early surgical intervention and intravenous anti-fungal treatment should be sought for management. With which a good prognosis can be achieved and mortality as well as morbidity can be reduced.

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