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ORIGINAL ARTICLE

Mucormycosis Epidemic in Covid Era: A Sinister Superinfection

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Abstract
In this study, we attempt to look at the various presentations, comorbidities and association of the recent epidemic of rhino-orbital cerebral mucormycosis with Covid-19 in central India. A prospective study of 612 patients diagnosed with mucormycosis from April to July 2021. Detailed history was taken and thorough clinical examination was done. The relation of mucormycosis with Covid-19 and other morbidities was studied. Nasal endoscopy, imaging and management findings were tabulated and analyzed. Male predominance of the disease was noted. The most common age group affected was found to be 41–50 years group having 33.1% of all patients. 83.2% patients had history of Covid-19 infection. Majority of the patients (41.6%) had mucormycosis symptoms within 1 month of Covid-19 symptom onset. Nasal symptoms predominated with 61.1% patients having one or more of the several nasal symptoms. Most common comorbidity was diabetes mellitus (75.8% cases). Nasal and sinus debridement was performed in 584 patients (95.4%). Mucormycosis turned into a widespread epidemic during the second wave of Covid-19 in India. Diabetes mellitus was the most common associated comorbidity that increased the risk of mucormycosis in patients with history of Covid-19 infection. A high index of suspicion in patients presenting with early symptoms in the context of Covid-19, along with prompt diagnosis using radiological, endoscopic and microbiological tools will help reduce mortality to a great extent. Mainstay of treatment is aggressive surgical and medical management, controlling comorbidities and adequate post-operative care.

Keywords Mucormycosis · Covid-19 · Debridement · Comorbidities · Diabetes mellitus

Introduction

Amidst India's battle with the second wave of COVID-19, there has also been a recent spate of COVID-19-associated mucormycosis (CAM) cases which have garnered attention globally [1]. India, which has more than 3 crores confirmed COVID-19 infections—has so far reported more than 42,000 cases of mucormycosis, making it a notifiable disease [2]. The disease pattern of COVID-19 range from mild to life-threatening pneumonia with associated bacterial and fungal coinfections [3]. Due to the associated comorbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease) and immunocompromised conditions (e.g. corticosteroid therapy, ventilation, intensive care unit stay, cancer patients undergoing chemotherapy or Bone marrow transplant), these patients are prone to develop severe opportunistic infections [4]. The association of COVID-19 with the recent increase in incidence of rhino-orbital and cerebral mucormycosis has been linked to a number of possible etiological factors. SARS-CoV-2 may lead to impaired cell-mediated immunity, lymphopenia and associated reduction in $CD4^+$ and $CD8^+$ cell population [5]. Steroid-induced hyperglycemia and immunosuppression, often against a background of uncontrolled diabetes mellitus, is considered as a *sine qua non*. Further endothelial damage, endothelitis and thrombosis due to the interplay between COVID-19 and diabetes mellitus can also increase the risk of mucormycosis [6].

Mucor is a saprophyte widely found in the environment and it is also a common commensal in the nasal cavity. Several pathophysiological mechanisms have been proposed to explain the loco-regional growth and dissemination of mucormycosis [7]. Acidotic milieu in the presence of ketones along with hyperglycemia; glycosylation of ferritin (acute phase reactant which is increased in COVID-19)

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leading to generation of free iron, are some of the known factors which facilitates the growth and development of *Mucor*. Also, the combination of raised blood glucose levels, low pH, high iron and acidosis decreases the phagocytic activity of leucocytes and enhances the expression of GRP-78 (glucose receptor protein-78) of endothelial cells and fungal ligand spore coating homologue protein (CotH) present in the Mucorales. This interaction between CotH and GRP-78 may cause enhanced *Mucor*-induced angio-invasion and necrosis [1].

In this study, we attempted to look at the various aspects of CAM including the disease pathology, its various manifestations the correlation of this dreaded sequela of Covid-19 with the recent wave of Covid-19 infection in India.

Methods

A prospective study was conducted from April 2021 to July 2021 in which we included 612 patients who presented to the OPD, Department of ENT or Emergency Department of a tertiary Government hospital in Central India, Maharaja Yashwantrao Hospital, Indore with complaints suggestive of mucormycosis like unilateral or bilateral facial pain, foul smelling nasal discharge, nasal obstruction, bleeding from nose, periorbital pain, orbital swelling or headache. A detailed history of present and past complaints was elicited with special emphasis on Covid-19 RT-PCR/RAT positivity date, hospital/home treatment, details of the treatment taken by the patient and Covid-19 RT-PCR negative date. Further history was elicited regarding any pre-existing co-morbid conditions such as diabetes mellitus, hypertension etc. A detailed account of all signs and symptoms were noted.

All the patients were subjected to primary nasal endoscopy under local anesthesia, wet KOH mount followed by all routine blood investigations and Magnetic Resonance Imaging of the paranasal sinuses with orbit and brain as well as Computed Tomography imaging of the paranasal sinuses. A multi-disciplinary approach was used to manage every patient. The findings were tabulated and analyzed in detail.

Inclusion Criteria

Patients of age 20–90 years presenting with symptoms suggestive of mucormycosis such as unilateral facial pain, foul smelling nasal discharge, bleeding from nose, periorbital pain, orbital swelling and/or headache and diagnosed with mucormycosis were included.

Exclusion Criteria

Patients who did not give consent to be part of the study; patients of non-invasive sinusitis with chronic history of rhinosinusitis in whom definitive diagnosis of mucormycosis was not made and patients who were operated before start of study were excluded from this study.

Results

The study was performed on 612 patients who were diagnosed with CAM. The most common age group affected was found to be 41–50 years group which covered 33.1% of all patients admitted for mucormycosis and the least common age group was 20–30 years having only 1.1% of all patients (Fig. 1).

In the study we found that there is a male predominance of the disease. Out of 612 patients, the number of males affected was 451 (73.7%) and the number of females affected was 161 (26.3%) (Fig. 2).

We observed that the number of patients with history of Covid-19 infection were 509 out of 612 patients (83.2%), which is way higher than the number of patients who presented without any history of Covid-19 infection, which was 103 (16.8%) (Table 1).

We observed that the majority of the patients—212 out of 509 (41.6%)—started having Mucormycosis symptoms within 15–30 days of Covid-19 symptom onset; 36% (n = 183) developed Mucormycosis symptoms within 30–60 days of Covid-19 onset; 21% (n = 107) patients developed mucormycosis symptoms either at the time or immediately after (within 15 days) Covid-19 symptom onset and diagnosis. Only a meagre 1.4% (n = 7) developed CAM symptoms after 60 days of being diagnosed with Covid-19 (Table 2).

327 (64.2%) of the 509 cases with Covid-19 history were hospitalized during the Covid positive period; with 189 (37.1%) having required oxygen therapy and 138 (27.1%) who maintained saturation on room air. 294 (57.7%) hospitalized patients were given oral or intravenous steroids, whereas only 33 (6.5%) patients were managed without steroid therapy in hospital. A total of 182 (35.8%) patients were treated for Covid-19 at home, out of which 126 (24.8%) were managed without steroids and 56 (11%) were prescribed oral steroids (Table 3).

Of all the symptoms, nasal symptoms predominated with 374 (61.1%) patients complaining of having either of the several symptoms discussed earlier. Orbital involvement and reduced vision were found in 335 (54.7%) cases. The next common symptom was headache, which was present in 308 (50.3%) patients. This was followed by facial swelling which was found in 259 (42.3%) cases. Palatal involvement in the form of palatal ulcers or erosions was seen in 78 (12.7%) cases (Table 4).

The most common comorbidity was established to be diabetes mellitus which was present in 75.8% of all patients

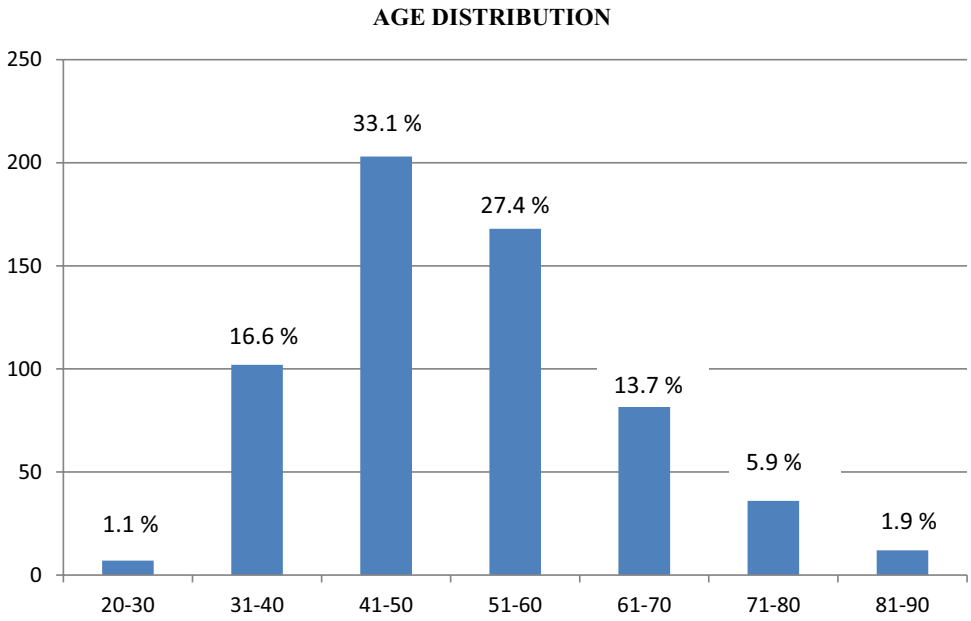

Fig. 1 Age distribution of the cases

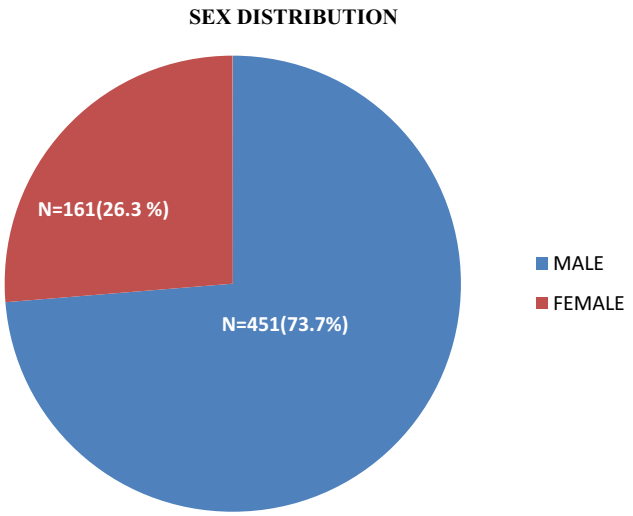

Fig. 2 Sex distribution of the cases

Table 1 Correlation between recent Covid positivity and mucormycosis onset

Total patients	Patients with history of Covid-19	Patients with no history of Covid-19
612	509 (83.2%)	103 (16.8%)

(n = 464). Out of these, 282 (46.1%) were old diabetic patients and 182 patients (29.7%) were newly diagnosed with Diabetes after Covid-19 hospital treatment. Hypertension was found in 157 (25.6%) patients. Coronary artery disease (CAD) was present in 80 (13.1%) cases. Hypothyroidism was observed in 63 (10.3%) cases. Renal disease was present in 45 patients (7.4%). There were 16 cancer patients undergoing chemotherapy (2.6%). Post-organ transplant patients takin immunosuppressive therapy were 7 in number (1.1%) (Table 5).

Out of the 612 admitted patients who were part of the study, nasal and sinus debridement was performed in 584 patients (95.4%), since the remaining patients were unfit to undergo surgery at that time.

Discussion

Mucormycosis is a dreaded fungal infection that used to be a rare entity presenting only in severely immunocompromised patients. Since the recent onset of the second wave of Covid-19 in India that began in the middle of March 2021, there has been a rapidly increasing number of CAM cases in India, turning a rare disease into a widespread epidemic and making Mucormycosis a notifiable disease.

The most common age group affected was found to be 41–50 years group which covered 33.1% of all patients admitted for mucormycosis, followed by the 51–60 years age group consisting of 27.4% of all patients; 16.6% patients were in 31–40 age group; 13.7% patients were in 61–70 age group; 81–90 years age group had 1.9% of all patients; another 5.9% in 71–80 age group; and the least common age group was 20–30 years having 1.1% patients (Fig. 1).

In our study, we found that 73.7% of all patients were males (Fig. 2). This is comparable to the study by Singh et al. which showed that mucormycosis was predominantly seen in males (78.9%) [8].

Table 2 Duration between covid symptom onset to mucormycosis symptom onset

Duration between covid symptom onset to mucormycosis symptom onset	No. of patients	Percentage	Covid-19 infection
0–15 days	107	21	RECENT
15–30 days	212	41.6	
30–60 days	183	36	
> 60 days	7	1.4	OLD
Total	509		

Table 3 Details of Covid-19 treatment received by the cases

COVID treatment given	Number of cases	Percentage (out of 509 cases) (%)
Home isolation		
Steroids	56	11
No steroids	126	24.8
Total	182	35.8
Hospital admission		
Oxygen	189	37.1
Room air	138	27.1
Total	327	64.2
Steroids	294	57.7
No steroids	33	6.5

Table 4 Various signs and symptoms found

Symptom	Number	Percentage
Nasal symptoms	374	61.1
Eye/orbital involvement	335	54.7
Headache	308	50.3
Facial swelling	259	42.3
Palatal involvement	78	12.7

Table 5 Various co-morbidities present

Co-morbidity	Number	Percentage
Diabetes mellitus		
Old diabetic	282	46.1
Newly diagnosed post-covid	182	29.7
Total diabetics	464	75.8
Hypertension	157	25.6
CAD	80	13.1
Hypothyroidism	63	10.3
Renal disease	45	7.4
Cancer patients undergoing chemotherapy	16	2.6
Post-transplant patients	7	1.1

It was noted that the vast majority (83.2%) of patients had Covid-19 infection with 98.6% of patients having mucormycosis symptom onset within 60 days of Covid-19 symptom onset (Tables 1, 2). This staggering correlation is probably due to a new strain of the virus that started spreading in the second wave in India. Since all treatment and hospital modalities have remained roughly the same in the late first wave and the second wave of Covid-19 pandemic in India, it may be safe to assume that a new strain of Covid-19 in the second wave is responsible for causing even more immunosuppression and inflammatory state in the patients, making them vulnerable to mucormycosis. 16.8% of the patients had no history of Covid-19, but we cannot rule out the absence of asymptomatic Covid-19 infection that may have predisposed them to Mucormycosis. In patients with documented history of Covid-19 infection, 98.6% had tested positive within 60 days of onset of Mucormycosis symptoms (Table 2).

As per article by Moona et al., the airways of covid patients are favorable for black fungus due to the exposure to humidity and moisture during ventilation in ICU. They also cited the indiscriminate use of steroids and antibiotics, hospital hygiene, and comorbid diseases as possible contributing factors for this sharp spike of black fungus infection [9]. But in our study, we found that 35.8% of the patients had undergone home isolation and 64.2% of patients underwent hospital admission for Covid-19 (Table 3). This wouldn't have been the case if hospital hygiene, ventilator support or intravenous steroids were the main cause for the onset of Mucormycosis.

The most common symptom group was nasal symptoms which included nasal obstruction, foul smelling discharge or bleeding from nose; but the most common symptom that significantly reduced quality of life was reduced vision or blindness (Table 4). In the study by Singh et al., commonest organ involved with mucormycosis was nose and sinus (88.9%), followed by rhino-orbital (56.7%) and ROCM type (22.2%) [8].

The most common co-morbidity present in these patients was found to be Diabetes Mellitus, which was seen in 464 patients (75.8%), in which old diabetics constituted 60.8% of cases with diabetes. In a nationwide multi-center study of 388 confirmed or suspected cases

of mucormycosis conducted in 2019 in India before the COVID-19 pandemic, Prakash et al. found that 18% had DKA and 57% of patients had uncontrolled DM [8, 10]. This goes to prove that the most common co-morbidity and pre-disposing factor for Mucormycosis both in pre-covid and Covid era is Diabetes mellitus. The study by Melvin R. Hayden shows the pathophysiology and mechanism of Covid-19 causing onset of Diabetes mellitus by directly affecting pancreatic islets and β-cells. In old diabetics, there is approximately a 50% decrease in β-cell function of those with T2DM and a 40–50% loss of β-cells in individuals with impaired glucose tolerance or prediabetes [11]. It was also noted that 25.6% of patients were hypertensives, 13.1% patients had Coronary Artery Disease and 10.3% had hypothyroidism. Renal disease was present in 45 patients (7.4%). There were 16 cancer patients undergoing chemotherapy (2.6%). Post-organ transplant patients taking immunosuppressive therapy were 7 in number (1.1%) (Table 5). According to the study done by Patel et al. in pre-covid era, the major predisposing factors associated with risk of mucormycosis in Indians included DM (73.5%), malignancy (9.0%) and organ transplantation (7.7%) [12]. Our data differs slightly from study by Patel et al. because of the already existing immunosuppression caused by Covid-19 infection and its treatment.

Out of the 612 admitted patients who were part of the study, nasal and sinus debridement was performed in 584 patients (95.4%) since the remaining patients were unfit to undergo surgery at that time.

The post-operative care by both patient and doctor is also equally important, if not more. Patient care includes compliance to medications and frequent alkaline nasal douching (at least 3 times a day). Post-operative care should include alkaline nasal douching and amphotericin gel application by inhalation in bilateral nasal cavity. Post-operative suction cleaning of nasal cavity should be done at least 3 times before discharge. In this epidemic situation of Mucormycosis, marathon OTs of 10–12 patients a day were required to sufficiently manage the growing number of admissions that occurred each day.

In the literature review study conducted by Hariprasath Prakash and Arunaloke Chakrabarti in 2021 which compares case series of different authors, we can see that Chakrabarti et al. performed one of the longest case studies on Mucormycosis in India, which lasted 15 years and 6 months and included a total of 382 cases of Mucormycosis [13–16]. Our study shows the disease pattern of Covid associated Mucormycosis, its age and sex distribution, various comorbidities and their association with the disease, relation with Covid-19 positivity and its symptomatology. We have also discussed the plan of management of the disease so that we can be well prepared for an epidemic of this magnitude in the future.

In conclusion, Covid associated Mucormycosis has scourged India in a sudden and unexpected turn as the second wave of Covid-19 began in Mid-March 2021. Diabetes mellitus was found to be the most associated comorbidity that increased the risk of mucormycosis in patients with history of Covid-19 infection. A high index of suspicion in patients presenting with early symptoms in the current context of Covid-19 along with prompt diagnosis using radiological, endoscopic and microbiological tools will help reduce mortality to a great extent. Adequate surgical and medical management in the form of thorough debridement, and controlling associated comorbidities should be the mainstay of treatment. We learned that the sequelae of Covid-19 have been disastrous and realize that we have to be prepared to face even more challenging scenarios in the future.

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Declarations

Competing interests The author(s) declare none.

Ethical Approval The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008.

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