Original Article

COVID-19 associated mucormycosis: A Descriptive Multisite Study from India

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ABSTRACT

Background and aims: Mucormycosis is an invasive fungal infection and carries a significant morbidity and mortality. A number of cases of mucormycosis have been reported in association with COVID-19. In this study, a consortium of clinicians from various parts of India studied clinical profile of COVID-19 associated mucormycosis (CAM) and this analysis is presented here.
Methods: Investigators from multiple sites in India were involved in this study. Clinical details included the treatment and severity of COVID-19, associated morbidities, as well as the diagnosis, treatment and prognosis of mucormycosis. These data were collected using google spreadsheet at one centre. Descriptive analysis was done.
Results: There were 115 patients with CAM. Importantly, all patients had received corticosteroids. Diabetes was present in 85.2% of patients and 13.9% of patients had newly detected diabetes. The most common site of involvement was rhino-orbital. Mortality occurred in 25 (21.7%) patients. On logistic regression analysis, CT scan-based score for severity of lung involvement was associated with mortality.
Conclusion: Universal administration of corticosteroids in our patients is notable. A large majority of patients had diabetes, while mortality was seen in ~1/5th of patients, lower as compared to recently published data.

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Though the primary pathology in COVID-19 is pneumonia and respiratory failure, secondary infections are common and contribute significantly to morbidity and mortality [1]. Fungal infections are less common than the bacterial infections, however are usually more invasive and carry worse outcomes [2]. Mucormycosis is a fungal infection caused by fungi belonging to Mucorales. It is highly aggressive with a tendency for contiguous spread. This infection occurs by inhalation of spores which are ubiquitous. Spores seed onto the epithelium of airways and germinate into angioinvasive hyphae leading to endothelial damage, thrombosis and necrosis. The fungus can then disseminate to various organs rapidly. Prognosis is poor if the diagnosis and management are delayed [1].

There are several factors which increase the risk of invasive fungal infections and mucormycosis in patients with COVID-19. The most important factor is uncontrolled glycemia which may decrease immunity to several infections [3]. Further, prolonged use of high dose of corticosteroids and drugs like tocilizumab used in moderate and severe disease may also increase predisposition for fungal infections [4]. The cytokine storm which heralds the severe disease is associated with insulin resistance and hyperglycemia and use of steroids further exacerbates it thus providing the milieu for seeding by mucor. One more putative factor for increased risk of mucormycosis in COVID-19 is intracellular iron overload signified by increased ferritin levels, which leads to the formation of reactive oxygen species [5]. Widespread endothelial injury in patients with severe disease can upregulate endothelial receptor glucose-regulated protein (GRP 78), which is responsible for increased adhesion and penetration of Mucorales to the endothelium [6].

The commonest reported form of mucormycosis was rhino-orbital followed by rhino sinusal and rhino-orbital-cerebral [7]. There are some other recently published reports as well including large series [8,9]. The aim of this study is to understand the clinical profile of patients with CAM, especially associated co morbidities and risk factors.

1. Methods

For conducting this research, a consortium of diabetologists and endocrinologists was formed. Further, ophthalmologists and ENT specialists working in respective centres were included as investigators. These centres were located in New Delhi, Trivandrum (Kerala), Pune (Maharashtra), Ahmedabad (Gujarat), Himmatnagar (Gujarat), Gurugram (Haryana), Hyderabad (Telangana), Chennai (Tamilnadu) and Kolkata (West Bengal). Permissions from ethical committees of respective centres were taken. All confirmed cases of mucormycosis with clinical and radiological features and demonstration of Mucor on KOH mount or histopathological examination were included in the study. In next three months, all cases of mucormycosis were extracted and reviewed centrally for accuracy.

Clinical data were retrieved from the clinical records. These included the demographic data like age, gender and place of residence. Details of COVID-19 infection were noted which included the mode of diagnosis CT scan-based score for severity of lung involvement, duration of hospitalization and ICU stay, need for non-invasive and invasive ventilation, and use of corticosteroids and other medicines. History of co-morbidities like diabetes, coronary heart disease, kidney disease, cancer, organ transplant, chronic lung diseases etc. was recorded. Finally, the clinical details of mucormycosis were extracted including the clinical features, site of involvement, mode of diagnosis, treatment and outcome. Some investigations and other findings were not available from retrospective review of records. All data were entered in a central Google spreadsheet and the patient information was deidentified. The data was double checked by two investigators.

2. Results

A total of 115 patients with CAM from 23 centres in different cities in India were included in the study. Table 1 lists the clinical and laboratory features. Mean age was 54.2 years with 81 males (70.4%) and 34 females (29.6%). Table 2 gives the details of treatment received for COVID-19. 86.08% (99) patients were hospitalized with the mean length of stay being 10.3 days. Intensive care was needed in 26.9% (31) of patients with the mean duration of stay in ICU being 7.5 days. Mean pneumonia severity score on CT scan was 12.2. All patients had received systemic corticosteroids. Supplemental oxygen was required by 67.8% (78), while invasive ventilation was required by11.3% (13) of patients.

Table 3 lists the associated co-morbidities. Pre-existing diabetes was present in 71.3% (82) patients while 13.9% (16) were detected to have new-onset diabetes. Mean duration of pre-existing diabetes was 9 years and mean fasting blood glucose was 192.9 mg/dl.

Fig. 1 lists the types of mucormycosis based on site of involvement. Rhino-orbital mucormycosis was the most common type. 21.7% (25) patients died while 2.6% (3) patients were lost to follow up.

On logistic regression analysis, only the CT scan-based score for severity of lung involvement was found to be associated with mortality (OR 0.82, 95% CI 0.68−1.0, P value 0.0464).

3. Discussion

In this multicentric observational study of patients with CAM, a vast majority of patients had diabetes. The disease was fatal in about 1/5th of patients. Pneumonia severity on CT scan was found to be significantly corelated with mortality. These findings of patients from across the country are in line with other recent reports from India.

While prevalence of mucormycosis infection in current COVID-19 epidemic has not been reported in most of the studies, available data show it to be 3.36% (32/953) and 1.8% (47/2567) [10,11] in two studies. In a multicentre retrospective study across India among 287 mucormycosis patients, 187 (65.2%) had CAM. In this study, prevalence of mucormycosis was 0.27% among hospitalized COVID-19 patients [8].

Importantly, majority of the reported mucormycosis cases before and during this COVID-19 epidemic are from India. A systematic review of 101 cases of CAM globally published in July 2021 showed diabetes in 80% of patients and steroid use in 76% of patients [12]. A recent retrospective nationwide study showed that diabetes is prevalent in 79% and steroid use in 87% of patients with rhino-orbito-cerebral mucormycosis associated with COVID-19 [9]. In an updated systemic review, 233 patients from India and 42 from the rest of the world were included. Specifically, diabetes was the most common underlying risk factor for CAM in India than in other countries. A small study from Egypt in 21 patients with CAM also found a high prevalence of diabetes (90%) [13]. Not only is diabetes prevalent in patients with CAM, glycemia is uncontrolled in most patients. A single centre study showed that average HbA1c level was 9.06% in patients with CAM [10].

All patients in our study had received systemic steroids during treatment of COVID-19 and diabetes was present in 86% of patients. It is interesting to note that while prevalence of diabetes was similar in most studies, use of corticosteroids is lesser in some studies (85% in a recent systemic review) [14].

Mortality data from recent studies have been given in Table 4. Another interesting fact was that the fatality rate of cases reported from India (36.5%) was less than the globally reported cases (61.9%), probably due to the predominance of rhino-orbital mucormycosis [15] which may pose less hurdles in medical and surgical

Table 1
Clinical and laboratory characteristics.

Parameter (N)	n	Mean (Range)
Age (y)	115	54.2 (29−76)
Sex	115	Males 81 (70.4%)
		Females 34 (29.6%)
CT scan-based score for severity of lung involvement	87	12.2 (3−25)
C-reactive protein (mg/L)	76	49.4 (0.72−211)
D Dimer (ng/mL)	67	744 (90−3826)
Erythrocyte sedimentation rate (mm 1st hour)	59	36.7 (8−120)
Ferritin (ng/dL)	43	399.6 (13−1370)
Total leukocyte count (/cc)	81	9769.5 (2400−24000)
Serum albumin (mg/dL)	69	3.35 (1.6−4.8)
Mean levels of fasting blood glucose (mg/dL)	72	192.9 (76−442)

Table 2
Details of treatment received for COVID 19.

Parameter (N)	Percent of patients (n 115)
Hospitalization	86.08 (99)
Stay in Intensive Care Unit	26.9 (31)
Systemic Steroids	100 (115)
Oral	47 (54)
Intravenous	53 (61)
Tocilizumab	0
Remdesivir	60.8 (70)
Plasma exchange	0.1 (1)
Oxygen requirement	67.8 (78)
Non-invasive ventilation	20.8 (24)
Invasive ventilation	11.3 (13)

Table 3
Prevalence of Co-morbid conditions (n, 115).

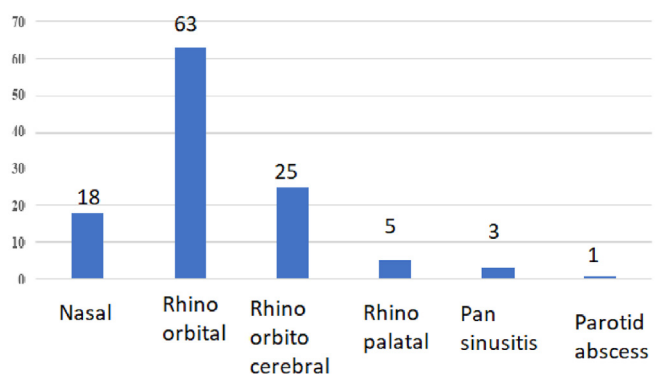| Condition	Percent of patients (n 115)
Diabetes	Present 85.2
	Pre-existing diabetes 71.3
	Newly detected diabetes 13.9
Coronary artery disease	15.6
Chronic kidney disease	10.4
Renal Transplant	2.6
Bronchial Asthma	0.1
Interstitial lung disease	0.1

Fig. 1. Distribution of patients according to the site of involvement by mucormycosis (n,115).

management. In a multicentre study of mucormycosis, case-fatality rate at 12 weeks was 45.7% but was similar for CAM and non-CAM patients [16]. Reason for lower mortality rate in our study is not clear but may have been due to less involvement of brain, and aggressive surgical and medical treatment. In this context, a recent review showed that adjunct surgery, which was undertaken in 81% of patients, was associated with better clinical outcomes [8].

A notable finding of our study is that 13.9% of patients were detected to have diabetes after the diagnosis of COVID-19. New onset diabetes has been reported earlier in association with COVID-19 [17]. Since diabetes is a major risk factor for the development of mucormycosis, it is important to monitor blood glucose values and aim for maintaining good glycemic control in all patients with COVID-19. This is particularly important given that elevated blood glucose, its variability and inability to maintain it within time-in-range leads to increased morbidity and mortality in COVID-19 [18,19]. In severe COVID-19 treated with corticosteroids, it is challenging to manage hyperglycemia but frequent and judicious use of insulin is useful [20]. In such a situation, use of remote monitoring could reduce the exposure risk of the hospital staff and a large majority of patients can be empowered for self-management.

A recent review showed that the median time interval between diagnosis of COVID-19 and clinical diagnosis of mucormycosis infection was 15 days [10]. This is particularly important for clinicians who should keep vigilance for occurrence of mucormycosis for 2−3 weeks after COVID-19 infection subsides. During this time, corticosteroid therapy should be rapidly tapered off and frequent interaction with patients is necessary to keep blood glucose in control.

We found a significant association between severity of COVID-19 pneumonia on CT scan and mortality due to mucormycosis. This is not unexpected as patients with more severe pneumonia are likely to have received higher doses of corticosteroids and more likely to have received supplemental oxygen and invasive ventilation, all of which are known risk factors for mucormycosis. In a recent case series, most cases of mucormycosis were unvaccinated and majority (91.5%) had moderate-to-severe pneumonia, and 42.6% required invasive ventilation [11]. We did not find an association between C-reactive protein or ferritin levels and mortality. This could be because most patients in our study anyway had elevated C-reactive protein and ferritin levels (mean levels being 49.4 mg/dl and 399.4 ng/dl, respectively). Elevated levels of these markers might predispose to the development of mucormycosis, however once there is mucormycosis, there could be other factors which may be more important to define disease severity and mortality [21]. Other reported predictors of survival in Indian patients during recent epidemic include age, high HbA1C levels and the presence of cerebral involvement [2,22].

4. Limitations

We could not assess the glycemic control prior to diagnosis of mucormycosis as the baseline HbA1C values were not available in records. Also, the precise doses of corticosteroids used during COVID-19 could not be ascertained. For logistic regression analysis,

Table 4
Mortality due to COVID-19 associated mucormycosis in different studies.

Author	Site	N	Mortality
Alfishawy et al. [13]	Cairo, Egypt	21	33.3% (7/21)
Mishra et al. [10]	Pune, Maharashtra	32	12.5% (4/32)
Sen et al. [9]	102 centres across India	2826	14% (305/2218)
Present study	14 centres across India	115	21.7% (25/115)
Singh et al. [12]	Systematic review	101	30.7% (31/101)
Pal et al. [14]	Systematic review	99	34% (33/96)
Muthu et al. [15]	Systematic review	275 (233 from India and 42 from elsewhere)	India 36.5% (85/233)
			Rest of the world 61.9% (26/42)
Patel et al. [16]	16 centres across India	187	44.1% (75/170)

all factors were not available in many patients. Finally, a longer follow up is required to assess long-term prognosis of these patients.

5. Conclusion

This multicentric observational study from centres across India found a high prevalence of diabetes and history of steroid use for COVID-19 in patients with CAM. There was a significant correlation between pneumonia severity on CT scan and mortality.

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Declaration of competing interest

There is no conflict of interest of any author regarding the manuscript "COVID-19 Associated Mucormycosis: A Descriptive Multisite Study from India".

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