A Clinical Analysis of COVID Associated Mucormycosis in a Tertiary Care Hospital

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Abstract

Background: With an increase in the spread of the pandemic, ailments related to the COVID illness started to appear. Patients with COVID - 19 infection experienced a worse outcome with an increase in the prevalence of opportunistic infections in the infected person especially Mucormycosis. It was recognized that people with diabetes, cancer, patients undergoing chemotherapy and other immune-compromised conditions can develop Mucormycosis. Systemic steroids and other immune-modulating agents which are the mainstay of treatment for COVID-19 predisposes to the chance of developing invasive fungal infections.

Methodology: Here we provide a retrospective analysis in which out of 212 patients who were subjected to screening 13 individuals were KOH mount positive with unique clinical characteristics as well as demographic and therapeutic profile. The information was gathered retrospectively at a single facility that serves a sizable group of patients with varying severity of the Corona virus infection.

Results: Of the total in-patients taken into consideration 13 were diagnosed with mucormycosis post COVID-19 infection. The median age was greater among individuals who survived the infections (49.5 years) and those with severe COVID had high chance of dying (23.8), with an overall mortality rate of 64.3 percent. Additionally 61.5 percent of patients had diabetes mellitus and 75% of them died. 11 patients (84.6%) had previously been on steroids for COVID-19. Both the individuals who survived and succumbed to the disease had same level of hyperglycemia.

Conclusion: The prevalence of mucormycosis among COVID-19 patients appears to be rising, which may be attributed to increasing usage of steroid, a potential immunocompromised state brought about by the virus per se and the co-morbid conditions. A high index of suspicion and early diagnosis is necessary to bring down the mortality rate This is in addition to the preventive measures and sensible use of immune-modulators.

INTRODUCTION

The pandemic of COVID-19 is still a serious threat to well-being. COVID-19 had varied presentations ranging from a mild disease to severe Pneumonia that would cause death[1]. The treatment for COVID-19is still debatable despite the pandemic being more than a year old. Systemic steroids have, nevertheless, demonstrated advantages for survival. On the other hand, excessive use of glucocorticoid may cause secondary bacterial and fungal infections. Additionally, pre-existing morbidities such as uncontrolled diabetes, COPD, Bronchial Asthma, carcinomas and the immune-compromised state may be blamed for the higher prevalence of secondary infections. Less than 1% of secondary infections during the early stages of the pandemic were fungal [3]. The bacterial infections were the most commonly seen opportunistic infections seen among the patients who were COVID positive. But reports showed an alarming increase in systemic fungal infections. In the general population, mucormycosis incidence varied from 0.005 to 1.7 per million population[4]. Fungal infection was common in the 2003 SARS CoV outbreak, occurring in 14.8–27% with severe acute respiratory syndrome and death[5-7]. This situation demonstrated that there was a significant likelihood of an increase in the incidence of fungal infection in patients with SARS CoV.

MATERIALS AND METHODS

Case Presentation:

Our specialized COVID facility has provided care for thousands of patients ever since the coronavirus outbreak in India.

Between November 2020 and January 2021,we screened 212 patients who had clinical signs suggestive of Mucormycosis. Of those 13 patients were positive for KOH mount. The treatment details pertaining to the patients were collected retrospectively. In addition to clinical signs and symptoms a positive KOH mount was used to establish the diagnosis of mucormycosis.

The patient's age, gender, clinical and laboratory data, co-morbidities and duration of hospital stay were all included as part of the demographic information. Information regarding the type of respiratory support provided, the severity of the COVID, the use of steroids and antifungal medications and need for the surgical procedures were also collected (Table 1). Information relating to the discharge or that of the death was also noted.

DIAGRAM:01 AGE IN YEARS

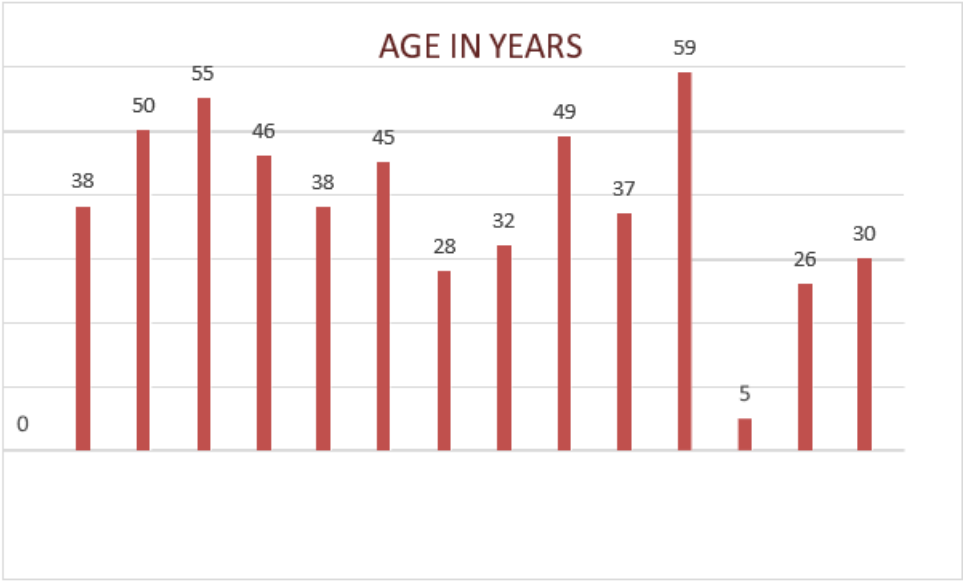


DIAGRAM 02 GENDER WISE DISTRIBUTION OF MUCORMYCOSIS

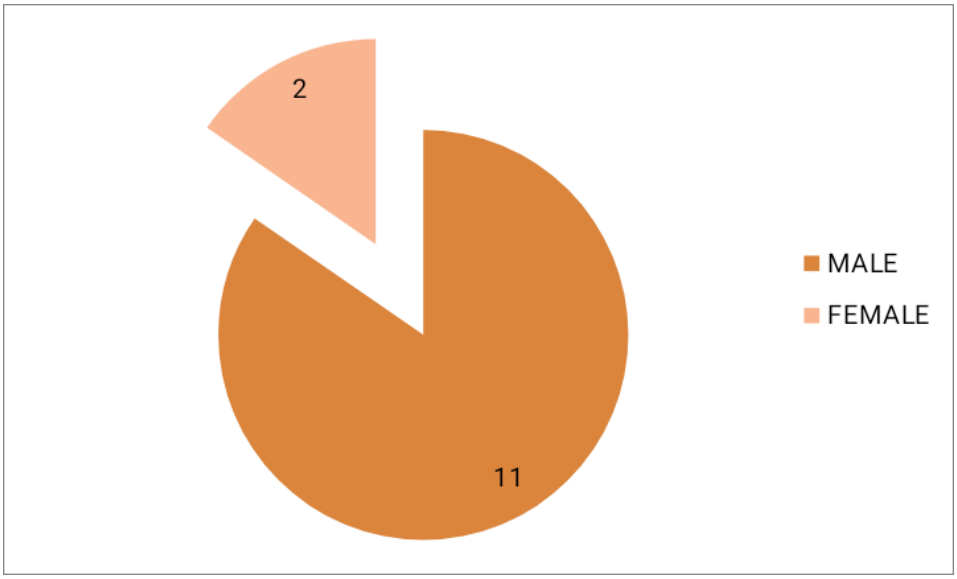
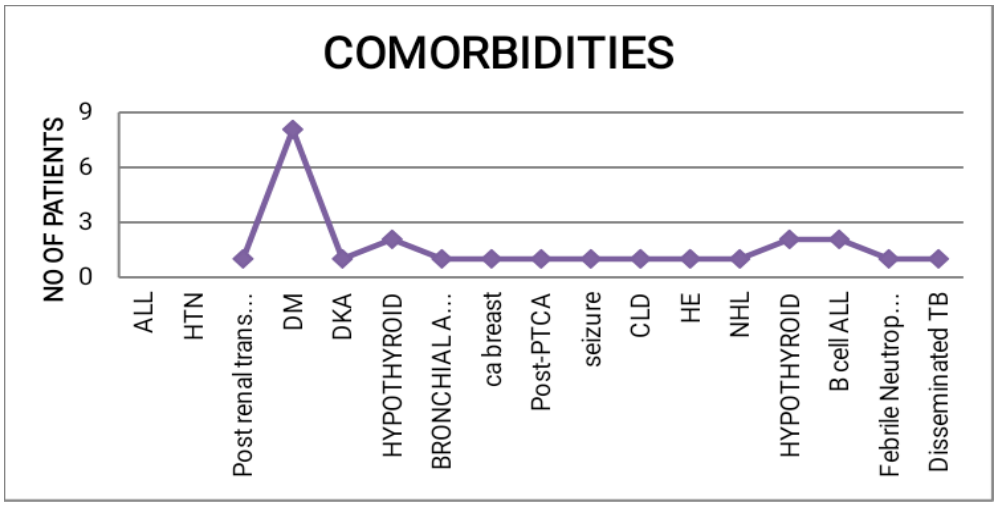


DIAGRAM 03 PREVALENCE OF COMORBIDITIES



In statistical analysis the variables used to characterize the data could either be continuous or categorical. The frequency and percentages were used to represent categorical variables, whereas the means with standard deviations and interquartile ranges were used to display continuous variables. The limited sample size has an adverse effect on the generalizability of the results.

RESULTS

Over a period of three months, out of 212 patients who were RT PCR positive, 13 patients were positive for Mucormycosis. Among the 13 who were positive for mucormycosis, eight patients had involvement in the rhino-orbital region, two patients in the rhino-cerebral region, two patients merely had involvement of para nasal sinuses and one patient (n=1) had involvement in the lungs (in Figure 1). Only two patients received therapy at our institution (7–16 days) for rhino-orbital mucormycosis; all other patients had their mucormycosis symptoms identified prior to admission. We separated the patients into two groups individuals who survived the infections and those who succumbed to the infection and the demographic and clinical informations were included.

Table 02 – Demographic and Clinical Data

Variable	Full cohort(n=13)	survivors(n=5)	Non-survivors(n=8)	P-value	Odds ratio for mortality (95%CI)
Age in years	38 (31–52)	32 (27–37.5)	49.5 (40–58)	0.011*	
Gender					
Female	3 (23.1%)	1 (20%)	2 (25%)	1	1.33 (0.88 - 20.10)
Male	10 (76.9%)	4 (80%)	6 (75%)		
Comorbidities					
Diabetes Mellitus	8 (61.5%)	2 (40%)	6 (75%)	0.293	
Hypertension	7 (53.8%)	1 (20%)	6 (75%)	0.103	
Coronary Artery Disease	2 (15.4%)	1 (20%)	1 (12.5%)	1	
Chronic liver disease	1 (7.7%)	0 (0%)	1 (12.5%)	1	
Chronic kidney disease	0	0	0	-	
Malignancy	3 (23.1%)	1 (20%)	2 (25%)	1	
Asthma	1 (7.7%)	0 (0)	1 (12.5%)	1	

Charlson comorbidity index	3 (0–5)	2 (0–2.5)	4.5 (0.75–5.75)	0.93	
COVID severity					
Severe	10 (76.9%)	2 (40%)	8 (100%)	0.035*	23.8 (0.89–633.56)*
Non-severe	3 (23.1%)	3 (60%)	0 (0%)		
ICU admission	10 (76.9%)	2 (40%)	8 (100%)	0.035*	
Hospital-stay (days)	12 (7–22.5)	22 (14.5–23)	7.5 (5.5–20.25)	0.127	
Surgical outcome	2 (15.4%)	1 (12.5%)	1 (20%)	1	1.5 (0.07 – 31.57) ‡ odds of deathwhen not operated
Mortality	8 (61.53%)	-	-	-	-
Laboratory parameters (baseline)					
Haemoglobin	9.5 (7.5–11.5)	11.1 (7.5–14.4)	8.2 (7.52–10.87)	0.284	
TLC	7800 (6250–14050)	14100 (6755–15900)	7675 (5875–12075)	0.171	
PLT	197,000 (104,000–276,000)	213,000 (115,500–329,500)	166,000 (79,000–226,000)	0.524	
CRP	15.58 (7.95–23.2)	13.63 (12.19–13.63)	17.13 (5.37–26.48)	0.643	
IL6	483.23 (47.65–1308.87)	61.27 (34.0–61.27)	1063.64 (75.03–1399.56)	0.286	
Ferritin	920.1 (426.2 – 1373)	801.80 (611.6 - 801.80)	920.10 (361.72 - 1500)	1	
Bilirubin	0.9 (0.6–1)	1.0 (0.75–1.05)	0.70 (0.52–0.9)	0.171	
Albumin	2.4 (2.15–2.55)	2.5 (1.85–2.5)	2.30 (2.13–2.9)	1	
SGOT	37 (27–26.5)	34 (19–45.5)	51 (30.25–60.25)	0.22	
SGPT	34 (24.5–54)	36 (28.5–54.5)	32 (23.75–50.25)	0.524	

Urea	38 (24–63)	32 (23–125)	43.5 (25.25–72)	0.524	
Creatinine	0.9 (0.6–1.4)	0.9 (0.7–4.4)	0.95 (0.53–1.33)	0.622	
Na	135 (132–143)	135 (129–137.5)	135 (132–147.75)	0.524	
K	4.3 (4.45–4.8)	4.3 (2.95–4.65)	4.4 (3.7–4.88)	0.524	
RBS	220 (200–280)	280 (180–280)	220 (200–255)	0.882	
Laboratory parameters (course in hospital)					
LFT derangement	4 (30.8%)	2 (40%)	2 (25%)	1	0.5 (0.45–5.51)
RFT derangement	11 (84.6%)	4 (80%)	7 (87.5%)	1	1.75 (0.84–36.28)
Dyselectrolytemia					
Hypokalemia	9 (69.2%)	5 (100%)	4 (50%)		
Hyperkalemia	4 (30.8%)	0 (0%)	4 (50%)	0.105	11 (0.45–263.54)
Anti-fungal therapy					
a. L-AMB (only)	11 (84.6%)	4 (80%)	7 (87.5%)	1	1.75 (0.84–36.28)
b.Posaconazoleadditional to other drugs	2 (15.4%)	1 (20%)	1 (12.5%)		
Remdesivir	2 (15.4%)	0 (0%)	2 (25%)	0.487	4.23 (0.164–108.22)
Tocilizumab	1	0 (0%)	1 (20%)	0.385	0.17 (0.005–5.27)

Median (IQR) or n (%) have been presented where appropriate.

Column percentages are in parentheses of n (%).

*p-value < 0.05 has been statistically significant.

Mann-Whitney U test has been used for numerical data and Fischer's exact for categorical data.

The purely pulmonary mucormycosis case was excluded in this odds ratio calculation.

We noticed that the median age of the non-survivors was greater as compared to the survivors. At admission, all of the non-survivors had significant Corona Virus infection and required increased FiO2, HFNC, or intubation. People who were classified as severe Corona Virus Infection had a 23.8 percent chance of death [(0.89-633.56, p 0.05). When the patient required invasive breathing upon arrival, the chances of death were 28.6 [(1.118-731.58), p 0.05]. Every non-survivor required invasive ventilation while they were hospitalized. In total, 9 out of 13 patients—including the child—died. When the infant and instances of exclusively pulmonary mucormycosis were excluded, the risks of dying without surgery was 1.5 [(0.07-31.57), p > 0.05]. Equivalent changes were seen in the biochemical parameter in both survivors and non-survivors.

Both positivity rate of KOH mount was almost same among survivors and non-survivors. As all of them were COVID positive methylprednisolone was given to them. The data are only provided for descriptive purposes, and the small sample size limits the generalizability of these conclusions. The average hospital stay was (5.5-20.25) days for the deceased and 22 days (14.5-23) for the survivors (Figure 2). Two out of the five patients who survived had recently undergone chemotherapy.

DISCUSSION

Two years into the pandemic, oxygen supplementation and immunosuppressant like steroids and Tocilizumab remain the relatively effective COVID-19 therapeutic choices [8,9]. However, it is well- known that use of steroid increases the likelihood of subsequent infection [10]. There haven't been many case reports published until lately, but there is still evidence to support a strong, maybe a catalytic link between COVID-19 and a increase in the incidence fungal infections. In May 2021, Maini et al. reported the lone incidence of rhino-orbital mucormycosis in COVID-19, which affected a 38-year-old male [11]. A mucormycosis case report including two patients who underwent corticosteroid treatment during COVID-19 was also released in April 2021 [12]. Various other authors have also published case reports on rhino-orbital mucormycosis that are similar to one another.

A total of 13 instances, including 1 paediatric patient, were reported for our study. In our research population11 men made up the majority (78.5%), which is consistent with findings from earlier studies [2,3,7]. The total average age was 38 (31-52) years, with an average among the survivors being 32 and among the non-survivors being 49.5 indicating an increase in mortality with increasing age.

Similar to our findings, Patel et al study. [14] Discovered that older people have a higher chance of death. Garg et al. recently published a systematic study on the coronavirus-associated mucormycosis. The median age of the patients was found to be 57.5 (22-86 years), which is also similar to our study. Recently, Garg et al study also pointed towards increasing mortality among the individuals who developed mucormycosis[15].

In COVID-19, diabetes mellitus has been linked to severity. Diabetics are at a higher risk for COVID- 19,diabetes mellitus has also been linked to severity. Diabetics have been shown to have a higher death rate than people without the condition, which is still a major cause for concern [16,17]. In our study, diabetes mellitus was the most frequent risk factor, and diabetic patients had higher fatality rates. None of the cases had diabetes at the time of admission, however, we were unable to gather data on glycated hemoglobin. In addition, the individuals had elevated blood sugars on admission indicating a poorly controlled diabetes. Similar results were obtained in the study about diabetic mellitus by Garg et al. [15].

Additionally, uncontrolled diabetes (62.7 percent) was shown to be the most prevalent underlying condition in both the CAM and non-CAM groups, according to Patel et al. in a multicenter, retrospective investigation [14]. According to research, SARS-CoV-2 can disrupt the pancreatic beta cells, which can result in metabolic abnormalities and diabetes mellitus [19]. The aforementioned information makes it impossible to say if the diabetes-like environment caused by the highly widespread SARS-CoV-2 predisposes people to mucormycosis, or if the rise in home-based anti- COVID steroid medication is to blame.

Patients with poorly regulated blood sugar levels may have underlying renal impairment, increasing the risk of fungus infections [16]. The majority of the participants in our study (n=11, or 84.6 percent) had renal dysfunction and the odds ratio for death rose to 1.75 among non-survivors (n=7, or 87.5 percent), who had more renal dysfunction than survivors. The likelihood and severity of a fungal infections both increased in the presence comorbidities in COVID-19 patients, as well as by the additional immunosuppression brought on by steroids and perhaps other immune-modulatory drugs [9,10].

The management of COVID-19 has been recommended using steroids, mainly glucocorticoids [20]. For COVID-19 treatment, the majority of the study participants (n = 11, or 84.6 percent) had taken steroids, some even before being admitted to our hospital. Tocilizumab had only been administered to one patient as a second immune modulator. A multi centric investigation discovered a separate relationship between late CAM and improper steroid use. Although it hasn't been established, it's possible that SARS-CoV-2 produces immunological dysregulation similar to the original SARS-CoV, which puts the patient at risk for an invasive fungal infection [21,22]. In Mucormycosis the use of Tocilizumab in COVID-19 has additionally been linked to an increased [23]. And so the association between the two cannot be established on the basis of a very few number of cases. It has also been noted that using Tocilizumab in COVID-19 predisposes to the development of an invasive fungal infection [23]. In our case only one patient was on Tocilizumab therapy.

The severity of COVID-19 was another factor contributing to the high death rate in CAM [1]. In our analysis, 10 mucormycosis patients presented with severe COVID-19, 8 of whom did not survive, increasing the risk of death by 23 times and Similar findings were observed by Garg et al. [15]. A mortality of 40% in 10 in the cases of orbital mucormycosis was reported by Sarkar et al. in a letter to the editor [24]. Numerous case reports were released and the majority of the survivors had dismal outcomes [24,25].

There were numerous published case reports and the majority of the survivors had dismal outcomes [24,25]. Surprisingly, Sharma et al case's series of 23 CAM patients revealed no deaths [18]. There are numerous factors that can contribute to zero mortality, including early diagnosis, prompt antifungal medication initiation, early debridement, and surgical intervention. The management of mucormycosis has relied heavily on appropriate and prompt antifungal therapy. The preferred medication for this condition is liposomal amphotericin B, however alternative medications like posaconoazole and is avuconazole can also help with therapy. However, there isn't enough support for combination of antifungal medication in the treatment of mucormycosis [26]. If cancer had spread and is unresponsive to treatment, prompt surgical removal is preferred. Only three (out of 13) patients in our series required surgical intervention; two of these patients were discharged, and the third patient died. In their case series, Sharma et al. reported that all 23 patients had surgical debridement and all survived, however long-term survival and recurrence are still in question.

Patients with COVID-19 have also reported mucormycosis affecting various organ systems, including the pulmonary, gastrointestinal, and others [27]. Here one patient with pulmonary mucormycosis who has been treated for tuberculosis succumbed to the disease. In The works of Mekki et al. and Passer et al similar results were observed. [28,29]. It is noteworthy that fewer cases of pulmonary mucormycosis have been documented than at other sites. A number of cases of pulmonary mucormycosis may not have ever been diagnosed because it was difficult to collect lung secretions from COVID-19 patients. A case report of gastrointestinal mucormycosis was also observed. [30].

Medical & Surgical management along with a proper glycemic control is crucial for the effective management of mucormycosis. In COVID-19 individuals, irrational steroid use has led to a worsening of hyperglycemic state and a concomitant rise in the fungal infections. The degree of COVID-19 that coexisted with multi-organ involvement increased patient mortality. An overworked, understaffed laboratory, an increase in the number of COVID-19 cases, the high mortality rate among the patients, the low index of suspicion for fungal infection had made the process of management difficult. Inhaled fungal spores is the main route of spread[14]. The use of masks to stop COVID-19 may also help to stop the spread of mucormycosis. Therefore, use of masks should be promoted among high-risk groups including diabetics and the immunocompromised at least until the incidence of COVID-19 and mucormycosis declines.

We only acknowledge a few restrictions in this CAM case study series. The first drawback is that the majority of the patients at the single-center tertiary care hospital where our study is based are referrals. As a result, patients who are complicated or who have only received partial treatment come to our center with selection bias. The data were gathered in retrospect, therefore the sample size is modest. As a result, certain data regarding the glycemic index, antifungal therapy and the steroidal therapy could not be documented appropriately.

CONCLUSION

To conclude the physicians should be vigil of the warning signs in patients with COVID-19 and also who are recovering from it, particularly in those who have the risk factors. While treating COVID-19 patients, a high index of suspicion is necessary because unlike COVID-19, mucormycosis might be curable if diagnosed early. Additionally, the wise usage of steroids must be emphasized. It would be advisable to refrain from using steroids and immunosuppressive agents on COVID-19 cases where there is no oxygen requirement and no signs of a florid inflammatory reaction. The use of antibiotics too soon or too aggressively may potentially be dangerous.

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