

POST COVID MUCORMYCOSIS: AN OVERVIEW OF AETIOLOGICAL FACTORS

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Abstract:

Background and objectives: During the second wave of corona virus pandemic, we saw an increase in the case reports of rhino-orbital mucormycosis in patients with coronavirus disease (COVID -19) or in patients who had recovered from COVID -19 infection. We evaluated the patient characteristics and predisposing factors in these patients having mucormycosis.

Materials and method: This retrospective observational study included 84 patients with mucormycosis diagnosed during their course of COVID-19 illness between May 2021 to July 2021. Data regarding demography, underlying medical condition, extent of involvement of mucormycosis, COVID-19 status and treatment taken during COVID-19 illness were collected.

Results: Eighty-four patients presented with mucormycosis out of which 59 patients were males and 25 females. Majority were in the age group of 40-60 years (71.4%). Rhino-orbital was the most common form of mucormycosis. Intracranial spread was noted in 16 patients. Hyperglycemia at presentation (either pre-existing or new onset diabetes mellitus) was the single most important risk factor observed in majority of these cases (80 patients / 95.23%) followed by

history of Corticosteroid use in 68 patients (80.95%) and oxygen administration during their course of treatment for COVID-19 illness in 64 patients. (76.19%)

Conclusion: The association between coronavirus and mucormycosis must be given serious consideration. Uncontrolled diabetes and over-zealous use of corticosteroids are the two most important factors aggravating the illness. All efforts must be made to maintain optimal glucose levels in COVID-19 patients and use corticosteroids judiciously.

Keywords: COVID-19, Mucormycosis, Diabetes mellitus, Corticosteroids

Introduction:

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome corona virus -2(SARS CoV-2) has been associated with wide range of opportunistic fungal and bacterial infections. Cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide and in particular from India.^[1] During the second wave of COVID-19 pandemic in India, an unprecedented surge in cases of mucormycosis was observed. Immune dysregulation caused by SARS CoV-2, use of broad-spectrum antibiotics and corticosteroids, particularly in patients with poorly controlled diabetes and ketoacidosis is likely to have contributed to the rise.^[2]

Mucormycosis is an angio-invasive fungal infection caused by fungi belonging to the order Mucorales (Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia) and is associated with high morbidity and mortality.^[1] Globally the prevalence of mucormycosis varies from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000 population) in India compared to developed countries.^[1] In other words, India has the highest number of mucormycosis cases in the world owing to India being the second largest population with diabetes mellitus.^[1] Predisposing factors vary geographically with diabetes mellitus being the most common risk factor in Asia, whereas hematological malignancies and organ transplantation are the major risk factors for mucormycosis in European countries and in the United states.^[3]

Mucormycosis infection is characterized by the presence of invasion of sinus tissue by the fungi, clinically presenting with atypical signs and symptoms similar to complicated sinusitis such as nasal blockade, crusting, proptosis, facial swelling, pain, oedema, ptosis, chemosis and even ophthalmoplegia. Headache, fever and various neurological signs and symptoms develop if intracranial extension occurs.^[4] A black eschar may be seen in the nasal cavity or even sometimes over the hard palate. Histological features include aseptate hyphae invading the blood vessels causing vasculitis, thrombosis, tissue infarction, haemorrhage and acute neutrophilic infiltration.^[4] Rapid diagnostic methods include biopsy, potassium hydroxide (KOH) mount and calcofluor stain. Mucor is difficult to routinely culture, biopsy remains the mainstay of diagnosis.^[5]

Without early diagnosis and treatment there may be rapid progression of the disease, with reported mortality being as high as 50-80%.^[4] Control of hyperglycemia, early treatment with systemic antifungal agents and surgery are essential for the successful management of

mucormycosis. A delay of even 6 days in initiating treatment doubles the 30 days mortality from 35 to 66 %.^[6]

The prevalence of diabetic population is estimated to rise from 366 million in 2011 to 522 million in 2030 globally. China tops the list followed by India and the United States.^[3] Considering the rise in diabetic population, the rise in the number of mucormycosis cases is also predicted.

Our institute which is a tertiary care teaching hospital saw a sudden rise in cases of mucormycosis during the second wave of coronavirus pandemic with much of the operating theatres being occupied with patients coming for radical surgical debridement procedure for this condition. Here we present our experience of 84 cases of mucormycosis seen over a time period of three months, who had active or had recovered from COVID-19 infection or were never been COVID-19 positive. The aim of this study was to determine the incidence of aetiological factors and their impact on patients with invasive mucormycosis.

Materials and methods:

After taking institutional ethical committee approval, a retrospective observational study was undertaken in our hospital for a period of three months, from May 2021 to July 2021. All patients who presented with invasive mucormycosis of the paranasal sinuses, who were either COVID-19 positive or had recovered from coronavirus infection or were never COVID-19 positive were all included in this study. Patients' demographic details, presenting complaints, comorbidities, imaging details, treatment received for coronavirus illness and mucormycosis were collected and analyzed.

Results:

A total of 84 patients were included in this study, out of which 59 (70.23%) patients were males and 25 (29.76%) females. Most of the patients belonged to the age group 40-60 years (table 1). Table 2 shows the extent of involvement of adjacent tissues by mucormycosis. Out of 84 patients 64 patients had orbital extension of the disease, 16 had intracranial extension and 20 patients had involvement of the hard palate.

Out of 84 patients 80 patients (95.23%) were diabetics, either diagnosed recently or were on treatment for diabetes from a long time. Most of these diabetics had poor control of glycemic status, with their glycated haemoglobin (HbA1C) ranging from 6.5-15 g% and majority having HbA1C of more than 10 g%. Twenty-eight patients had hypertension and were on treatment, 9 patients had history of malignancy, 5 patients with underlying ischemic heart disease and 4 patients had chronic kidney disease (CKD).

Table 4 shows the treatment history for COVID-19 elicited from these patients after admission to our hospital for mucormycosis. Out of 84 patients, 64 patients (76.19%) gave history of oxygen support received during their stay at hospital for COVID-19 treatment. However, 20 patients had mild disease and were under home isolation and had not received oxygen support. Intensive Care Unit (ICU) admission was recorded in 34 patients. History of corticosteroids administration was noted in 68 patients either orally or intravenously. (80.95%)

Figure 1 shows the number of patients who were COVID-19 positive at presentation or had mucormycosis as post COVID-19 sequelae and those who had no history of being COVID-19 positive. 73(86.9%) patients were COVID-19 positive and 11 had never been COVID-19 positive.

Table 1: Age of the patients included in the study

Age (in years)	Cases n (%)
20-40	12 (14.28%)
40-60	60 (71.42%)
More than 60	12 (14.28%)

Table 2: Spread of infection to adjacent sites

Adjacent spread	Cases n (%)
Intra-orbital	64 (76.19%)
Intracranial	16 (19.04%)
Palate	20 (23.80%)

Table 3: Associated medical conditions

Comorbid condition	Cases n (%)
Diabetes mellitus	80 (95.23%)
Hypertension	28 (33.3%)
Malignancy	9 (10.71%)
Ischemic heart disease	5 (5.95%)
Chronic kidney disease	4 (4.76%)
Hypothyroidism	2 (2.38%)
No comorbidities	2 (2.38%)

Table 4: Treatment received for COVID -19 illness

Treatment received	Cases n (%)
Home isolation	20 (23.8%)
Oxygen support received prior	64 (76.19%)
*ICU management	34(40.47%)
Steroid administration	68 (80.95%)
Tocilizumab	0

*ICU-Intensive care unit

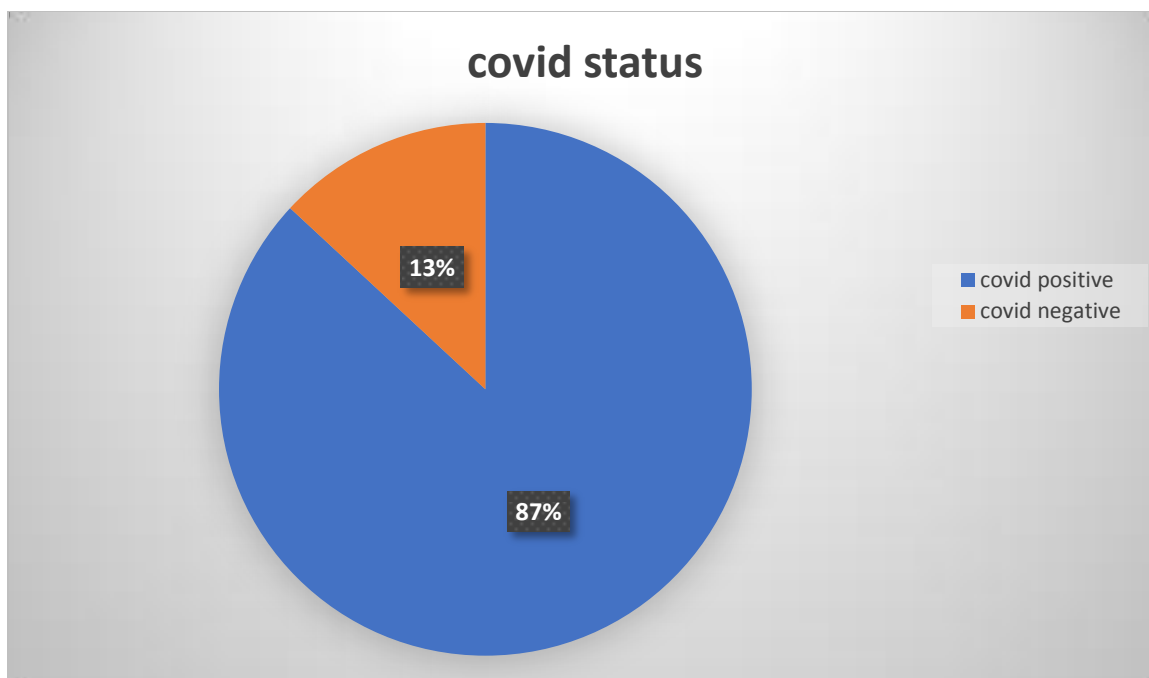


Figure 1: Number of COVID-19 positive and negative mucormycosis patients

Discussion:

Mucormycosis can involve nose, sinuses, orbit, central nervous system(CNS), lung, gastrointestinal system(GIT), skin, bones, joints, heart, kidney and mediastinum, but rhino-orbital-cerebral mucormycosis (ROCM) is the most common form observed worldwide and most common form associated with diabetes (88%) and diabetic ketoacidosis (DKA).^[1,3] Pulmonary type is the second most common form of mucormycosis seen mostly in transplant recipients and those having hematological malignancies. Cutaneous form often occurs following trauma or breach in skin even in immunocompetent host while GIT gets involved in malnourished individuals and is the most difficult to diagnose.^[3]

Diabetes predisposes to infections through alterations in innate and acquired immune defenses, more so in uncontrolled diabetics and infections can worsen hyperglycemia in hitherto well controlled diabetics (bidirectional relationship). Diabetes does not increase the risk of infection with COVID-19 per se, but predisposes to severe disease and poor outcomes.^[7,8] There is increasing reports of new onset diabetes following COVID-19 infection mainly from the United States, but increasingly from elsewhere in the world as well. It is likely that the novel SARS coronavirus has direct diabetogenic potential by its effect on the pancreas, as the angiotensin converting enzyme 2 (ACE 2) receptors through which the virus enters the target cells are expressed on the pancreatic beta cells.^[7]

A multicentric observational study conducted by Prakash et al in 2019 in India, before the coronavirus pandemic showed that 388 confirmed or suspected mucormycosis cases were reported nationwide and in them 57% patients had uncontrolled diabetes and 18% had DKA.^[9] Presence of diabetes mellitus significantly increases the odds of contracting ROCM by 7.5 fold(odds ratio 7.55, P=0.001) as shown in a study prior to COVID-19 pandemic.^[1] In a recent

systemic review conducted by John et al in April 2021, 41 cases of mucormycosis were reported in people with COVID-19 and diabetes mellitus was reported in 93% cases while 83% were receiving corticosteroids.^[10] These findings are consistent with our findings of even larger case series of 84 patients where 80 patients (95.23%) were diabetics and 68 patients (80.95 %) had history of steroid intake.

Another possible explanation for association between COVID-19 and mucormycosis is the presence of endothelial inflammation. Acidemia and hyperglycemia induce the endothelial receptor glucose-regulated protein (GRP 78) and the Mucorales adhesin spore coat protein homologs (CotH), increasing the chances of adhesion and penetration of Mucorales to the endothelium.^[10]

The National Institute of Health's RECOVERY trial recommended dexamethasone at a dose of 6 mg per day oral or intravenous for a maximum of ten days for the treatment of COVID-19 patients who are on ventilator or required supplemental oxygen, but not in milder cases.^[4,11,12] Current guidelines by ministry of health and family welfare in India recommends use of intravenous methylprednisolone 0.5-1mg/kg/day for three days in moderate cases and 1-2mg/kg/day in severe cases.^[13,14] The guidelines specifically mention the risk of developing secondary infection. Systemic use of steroids impedes with the body's immune system by reducing the phagocytic activity of white blood cells, reducing macrophagic migration, ingestion and phagolysosome fusion. Corticosteroids could further aggravate the underlying hyperglycemic status as well making diabetics exceptionally vulnerable to mucormycosis.^[1] Thus use of corticosteroids in mild cases without hypoxemia or use of high doses should be avoided.

Furthermore, in the absence of clear benefit, drugs like monoclonal antibodies which targets the immune pathways should be discouraged. Tocilizumab may be considered in patients with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not improving despite use of steroids at a dose of 8 mg/kg (maximum 800 mg at one time).^[13]

An alteration of iron metabolism is known to occur in severe COVID-19 patients as increase in cytokines especially interleukin -6 increases free iron by increasing ferritin levels leading to hyper-ferritinemic state (increased synthesis but decreased iron transport). But whether increased ferritin is a marker of severe systemic disease is unknown. Hyperglycemia causes glycosylation of transferrin and ferritin and reduces iron binding, allowing increased free iron. High ferritin levels lead to excess intracellular iron that leads to increased production of oxygen free radicals causing tissue damage. Iron overload and excess free iron seen in acidemic states are one of the key risk factors for mucormycosis.^[10]

Management of mucormycosis aims at early diagnosis, treatment of underlying predisposing factors, early administration of systemic antifungal agents and broad surgical debridement of infected tissue. Systemic liposomal Amphotericin B and Posaconazole oral suspension are treated as first line antifungal monotherapy while Isavuconazole is strongly supported as salvage treatment.^[5] Surgery is required when there is rhino-cerebral and skin/soft

tissue involvement. Surgical approach involves excision and debridement of all infected and necrotic tissue or even partial or total maxillectomy.^[15]

In-depth studies are required to investigate how COVID-19 is triggering mucormycosis infections in patients and why mainly cases are being reported in India as compared to other countries.

Conclusion:

Mucormycosis has emerged as a serious but rare opportunistic fungal infection that spreads very rapidly causing tissue infarction and necrosis in post COVID-19 patients. With more patients presenting with post COVID mucormycosis, all anaesthesiologists must have a good knowledge of underlying risk factors associated with mucormycosis, the pathogenesis and prepare themselves to manage this poorly understood patient population coming for surgery.

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