Original Article

Epidemiology, Clinical Profile, and Analysis of Risk Factors in COVID Associated Rhino-orbito-cerebral Mucormycosis Patients - An Observational Study

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Abstract

Aim of Study: To study the clinico-epidemiological profile and identify risk factors for the development of COVID-19-associated mucormycosis (CAM) among the patients treated at our regional mucormycosis center. **Materials and Methods:** This was a cross-sectional single-centre observational study. All CAM patients admitted to Government Rajaji Hospital, Madurai from April 2021- August 2021 were included in the study. Information regarding clinical features, potential risk factors, diagnostic workup, and comorbid illness was collected. **Results:** A total of 164 patients of CAM were admitted to our hospital with a mean age of 51.7 years. Out of 164 patients, 12 patients were not covid positive, based on imaging and RT-PCR, however subclinical infection could not be ruled out. Out of the 164 patients studied, 160 patients had diabetes, out of which 66% (n = 105) patients had a previous history of diabetes, and 34% (n = 55) had newly detected diabetes. Most of the patients admitted with mucormycosis had uncontrolled diabetes (94%) and were not on insulin therapy, but were on oral antidiabetic drugs alone. The majority of the patients (68%) have received steroids (IV/oral) during the COVID-19 illness. 74% of these patients were under hospitalization for COVID-19 disease. Only 30% (n = 50) of CAM patients had a history of oxygen therapy and 7% of these patients were treated in ICU during active COVID-19 illness. 59% of patients used cloth masks without adequate hygiene, rest 41% (n = 67) patients reused disposable masks. We also found that 87% of the patients developing mucormycosis had exposure to organic material in the convalescence period of COVID-19 illness. **Conclusions:** From our study, we found steroid use, poorly controlled diabetes mellitus, reuse of masks, daily steam inhalation, and exposure to organic matter to be more associated with CAM, but oxygen therapy was less associated with CAM. Hence, we could suggest screening for hyperglycemia and daily use of disposable surgical masks to be continued for at least 4 weeks post-COVID-19. It is preferable to continue insulin in titrated doses along with OHA for at least 4 weeks following steroid cessation in the post-COVID-19 period as there is are considerably increased inflammatory cytokine levels in the convalescence phase. Clean environmental hygiene would also help prevent CAM.

Keywords: COVID associated mucormycosis, COVID-19, SARS CoV2, Diabetes and Glucocorticoids

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) virus has caused a global pandemic of Coronavirus (COVID-19) disease. There are more than 607,083,820 million confirmed COVID-19 cases worldwide with over 6496721 deaths as of September 2022.[1] SARS CoV-2 has been associated with co-infections and superinfections with fungi, bacteria, and atypical pathogens like mycoplasma, legionella, etc., which is also associated with more severe disease and poorer outcomes.[2] The second wave of COVID-19 showed an unprecedented surge in superinfection with Mucormycosis.[3]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_372_22

Mucormycosis is an angioinvasive fungal infection, caused by the fungi of the order Mucorales. Based on the presentation it may be classified as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other, which includes

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Submitted: 23-Sep-2022 **Revised:** 03-May-2023
Accepted: 16-May-2023 **Published:** 11-Jan-2024

How to cite this article: Jog K, Nazirudeen R, Eagappan S, Santharam RK, Sridhar S. Epidemiology, clinical profile, and analysis of risk factors in COVID associated rhino-orbito-cerebral mucormycosis patients - An observational study. Indian J Endocr Metab 2023;27:519-23.

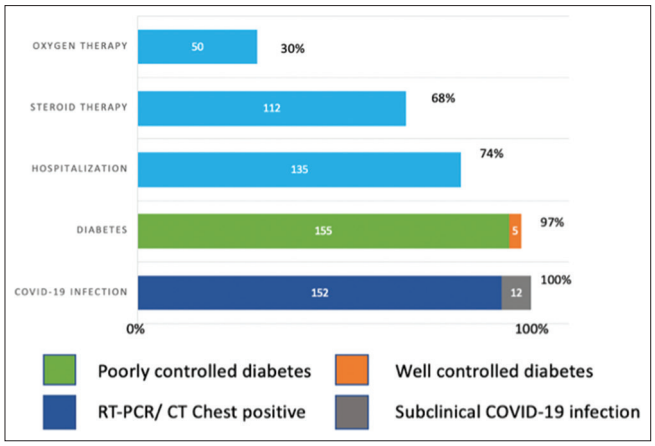

Figure 1: Analysis of risk factors for CAM during COVID-19 illness

uncommon rare forms, such as endocarditis, osteomyelitis, peritonitis, renal, etc., It usually attacks immunocompromised hosts such as diabetics, post-transplant recipients, and patients on steroids. In developing countries like India, poorly controlled diabetes is a more important cause rather than post-transplant recipients which is more common in the developed world.[4] Infections with Rhizopus arrhizus are the most common cause of mucormycosis worldwide, followed by the Apophysomyces species in India and Lichtheimia species in developed countries.[5] Infections due to Rhizopus microsporus and Rhizopus homothallicus are on the rise in India.[6]

COVID-19 disease has been found to be associated with fungal infections such as Aspergillus flavus, Candida glabrata, and Candida albicans.[7] Koehler *et al*.[8] found five out of nineteen critically ill patients with COVID-19 to be affected with invasive pulmoanary aspergillosis. However, during the second wave of COVID-19, India saw an unpredictable and sudden surge in cases of Mucormycosis in COVID-19-affected patients, contributing to 71% of global mucormycosis cases.[3] Poorly controlled diabetes and the use of corticosteroids and immunosuppressants provide fertile ground and may be some of the causes for the development of Mucormycosis in the setting of COVID-19 illness.[9]

In our descriptive observational study, we aimed to study the clinicoepidemiological profiles and identify other risk factors of COVID-19-associated mucormycosis (CAM) patients treated at our regional mucormycosis center.

Materials and Methods

Study setting

This descriptive study was conducted in a tertiary care center in Southern India from April 2021 to August 2021.

Methods

All patients with RT-PCR (Real Time Reverse Transcription Polymerase Chain Reaction) nasopharyngeal & throat swabs confirmed COVID 19 and patients with flu-like illness and CT chest showing ground glass opacities were defined as

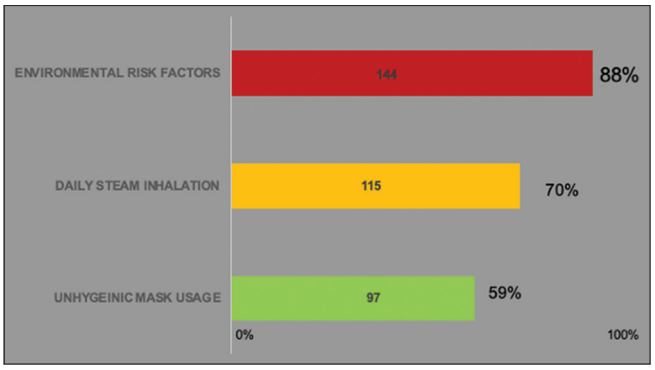

Figure 2: Analysis of risk factors for CAM during post COVID-19 period

COVID-19 illness and were admitted the COVID-19 specialty hospital and were given appropriate treatment according to their severity of illness. On discharge, these patients were given adequate antidiabetic management in the form of Insulin and/or OADs. Oxygen therapy and steroids were given during hospital admission according to the prevailing guidelines.

Patients were counseled regarding early symptoms of invasive fungal rhinosinusitis before and were asked to immediately report if symptoms like facial pain, tooth pain, or periorbital swelling appeared after discharge and these patients were admitted to a dedicated Mucormycosis ward for expert management. If the symptoms occurred during the hospital stay for COVID-19, these patients were transferred to the mucormycosis ward once they were RT-PCR negative, until which they received appropriate treatment in the COVID-19 center.

Mucormycosis was defined as clinical-radiological suspicion along with visualization of broad-branched aseptate fungal hyphae on KOH mount direct microscopy and histopathology specimen by fungal stains or isolation of zygomycetes on fungal culture. Written informed consent was taken from patients or nearest of kin.

Statistical analysis

Data was compiled in an MS Excel sheet. Descriptive statistics were presented as mean and range for quantitative data and frequencies and percentages for qualitative data.

Ethical clearance

All procedures done were in accordance with the guidelines laid down by the Declaration of Helsinki. Ethical committee approval was obtained from the Institutional Ethical Committee [No: 11680/IEC/2023-27].

Results

Demographics

From the timespan of April 2021- August 2021, a total of 164 patients (113 males and 51 females) were admitted with CAM in our dedicated mucormycosis ward. The age ranged from 14 to 86 years (mean- 51.7 years). 7% (n = 12) patients were noncovid, based on RT-PCR and CT chest, however, subclinical infection could not be ruled out. Baseline

Table 1: Prevalence of risk factors in COVID-19 related rhino-orbito-cerebral mucormycosis

Column 1	Parameter	*n*=164	Percentage(%)
Sex			
	male	113	68
	female	51	32
Diabetes	Total Cohort n=160 (97%)		
	Known diabetics	105	64
	Newly diagnosed diabetics	55	33
	Poorly controlled diabetes	155	94
	Post discharge glycemic follow up after COVID 19	20	164
Other risk factors	IV or oral steroid usage	112	68
	History of oxygen administration	50	30
	History of ICU admission	12	7
	Daily steam inhalation	115	70
	PLHA positive (HIV)	1	0.6
	Lung involvement<30% on CT	58	35
	Lung involvement>30% on CT	82	50
	Unhygienic cloth mask usage	97	59
	Surgical mask reusage	67	40
	Exposure to organic matter	144	87

Table 2: Pattern of antidiabetic medication usage in the Post COVID period

Parameter	*n*	percentage(%)
No antidiabetic medications	15	9.1
OADs alone	149	90
Insulin + OADs	4	2
Insulin alone	0	0

characteristics of population and prevalence of risk factors have been described in Table 1.

Risk factor analysis

97% (n = 160) patients had diabetes, out of which 66% (n = 105) patients had previous history of diabetes, 34% (n = 55) had newly detected diabetes. In the known diabetic cohort, 4 patients were Type 1 Diabetes individuals and the rest were Type 2 Diabetes individuals. 94% (n = 155) of patients had poor control of diabetes before the onset of mucormycosis with fasting plasma glucose values greater than 140 mg/dl.

Also, 90% (n = 147) of patients with poor glycemic control were on oral antidiabetic medications alone after recovering from COVID-19 illness. Among this cohort, only 2% (n = 4) of patients were on insulin therapy for diabetes control in the convalescence period. Patients also did not monitor their blood glucose levels in the post-COVID phase and presented with hyperglycemia and associated CAM. Only 20% (n = 32) of patients were on follow-up with a physician or diabetologist for their glycemic control in the post-COVID-19 period. Only 2.4% (n = 4) of patients were nondiabetic. The pattern of anti-diabetic medication in post COVID period is shown in Table 2.

68% (n = 112) of patients have received steroids either intravenous or orally during illness as per prevailing guidelines for the treatment of COVID-19. These patients have received steroids by intravenous route in a hospital setting or oral steroids on an outpatient basis. The steroids given were in the form of Injectable methylprednisolone in 15% of patients (n = 17), Injectable dexamethasone in 48% of patients (n = 54), or Oral Prednisolone in 36% of patients (n = 41).

74% (n = 121) patients in our cohort had been hospitalized for COVID-19 illness, rest had received domiciliary care for COVID-19 illness. Only 30% (n = 50) of patients required oxygen therapy during COVID-19 illness. 4% (n = 7) patients had needed Intensive Care Unit (ICU) care during active COVID-19 illness, out of which 3 patients had required ventilatory support.

One patient was HIV positive on retroviral drugs. There were no cases of malignancy or organ transplant in our study.

59% (n = 97) patients have used cloth masks without maintaining proper hygiene, and rest 41% (n = 67) patients have reused disposable masks. Patients using reusable masks did not wash the masks daily and mask sharing within families was noted. Most of these patients used cotton masks either made at home or bought from local vendors.

The risk of acquiring mucormycosis is present in environments containing organic matter, based on this, 88% (n = 144) of patients had susceptible environmental exposure. Most of the patients were of rural background and having exposure to vegetation, crops, and animal fecal matter which may have precipitated CAM in the fertile background of uncontrolled diabetes and steroid usage.

70% (n = 115) had taken daily steam inhalation.

The risk factors for developing CAM in the COVID & post COVID phase have been represented in Figures 1 and 2.

Temporal Relation of CAM to COVID-19

The onset of CAM was usually 1-2 weeks after the resolution of COVID-19. Only 35% (n = 59) of patients had the onset of mucormycosis during active COVID-19 illness.

Clinical presentation of CAM

Of the total patients, 2% had presented Stage 1 rhinocerebral mucormycosis disease, 21% had Stage 2 disease, 52% had Stage 3 disease and 23% patients had Stage 4 disease based on clinical CT Scan findings.

The most common complaint was headache. Other symptoms included facial pain, periorbital swelling, rhinorrhea, nasal stuffiness loosening of teeth, and hemiparesis.

4% of patients (n = 7) had symptomatic diabetic ketoacidosis during CAM presentation, needing intravenous insulin infusion and fluids.

During active COVID-19 pneumonia illness, 14% (n = 23) patients had <15% lung involvement, 21% (n = 35) patients had 15-30% lung involvement, 34% (n = 56) patients had lung involvement of 30-45%, 11% (n = 19) patients had lung involvement of 45-65% and 4% (n = 7) patients had lung involvement >65% based on computed tomography imaging of the lungs. The rest 24 patients had not undergone CT imaging of the lungs.

Discussion

The annual incidence of mucormycosis seems to be increasing in India. Diabetes mellitus, hematological malignancies, solid organ transplant, and immunocompromised state are some of the major risk factors involved in the development of mucormycosis.[5] In India, Chronic kidney disease, steroid use and abuse, pulmonary tuberculosis, and chronic obstructive pulmonary disease are the additional risk factors.[10]

The recent wave of COVID-19 saw an unprecedented rise in mucormycosis. The common contributing factors noted in the patients were steroid usage and uncontrolled diabetes mellitus across various states and hospitals in India.

The usual onset of mucormycosis was around 10 days after recovery from COVID-19, however, in our study, 35% of patients developed the disease during active COVID-19 infection as well. The median incubation time of mucormycosis is thought to be 7-10 days.[11] Hence acquirement of infection during hospitalization requires consideration.

There are numerous reasons for the emergence of mucormycosis in COVID-19 infections. Poorly controlled diabetes is one of the most important factors for the same. Diabetes mellitus and COVID-19 share a bidirectional relationship with adverse outcomes. Diabetes is a pro-inflammatory state which leads to severe COVID-19 infections.[12] SARS-CoV-2 infection leads to decreased insulin secretion due to a direct pathogenic effect on pancreatic islet cells. It also induces insulin resistance due to a transient hyper-inflammatory state.[13]

Diabetes is an important risk factor for mucormycosis. Nearly 24–64% of the mucormycosis cases reported from India are in patients with uncontrolled diabetes, with or without ketoacidosis.[14] In our study also, uncontrolled diabetes was the most common association with the onset of mucormycosis. Poor glycemic control, i.e., fasting blood glucose >140 mg/dl was seen in 94% (n = 155) patients. 90% (n = 147) of these patients were on oral antidiabetic drugs alone. Post-discharge after COVID-19 illness, only 20% (n = 32) of these patients monitored their glucose levels and visited their treating physician for follow-up care of diabetic management.

In our study, three patients known with Type 1 diabetes on regular insulin therapy, who acquired COVID-19 illness followed by CAM. In our study, 34% (n = 55) of patients had new onset diabetes during admission for mucormycosis and had not been on follow-up for glycemic control in the post-COVID-19 period.

Corticosteroids and immunosuppressants form a vital part of the treatment of mucormycosis with lung involvement and those with hypoxemia needing oxygen therapy. Upto 10 days course of dexamethasone, 6mg/day improved the 28-day outcome in patients on respiratory support.[15] However, there are other ramifications of this therapy. Steroids can lead to hyperglycemia even in normal individuals, and may even lead to immunosuppression, providing fertile ground for the development of invasive fungal infections.[16] In our study, 68% of patients (n = 112) had received corticosteroid therapy. The steroids may have unmasked underlying Type 2 Diabetic milieu, however, HbA1c estimation will be needed to confirm underlying undetected diabetes. Rampant indiscriminate use of steroids in India may have worsened the scenario.

In our study, 74% (n = 135) had been hospitalized for the primary COVID-19 illness, rest had received domiciliary care. In our study, we did not find any significant association of oxygen therapy with mucormycosis. Only 30% (n = 50) of patients had required oxygen therapy during COVID-19 illness. 4% (n = 7) patients had needed Intensive Care Unit (ICU) care during active COVID-19 illness, out of which 3 patients had required ventilatory support.

The second wave of COVID-19 has been attributed to the B.1.617 variant of SARS-CoV-2, also called a 'double mutant' or the 'delta' variant which is considered more infections with increased virulence.[17] The effect of the B1.617 variant on the increased risk of Mucormycosis requires further consideration and research since the first wave of COVID-19 due to the D614G strain was not associated with mucormycosis.

In our study, we also found that 59% (n = 97) of patients had unhygienic cloth mask usage. The rest 41% (n = 67) of individuals had reused the surgical disposable masks. These patients on interviewing were found to reuse surgical masks or use cloth masks without washing with mask sharing among family members.

Also, 88% (n = 144) of patients were found to have exposure to organic matter such as animal dung, and decaying vegetation

at home or in the workplace. In the background of uncontrolled diabetes and steroid usage, these patients are at increased risk to acquire mucormycosis when exposed to organic matter.

70% (n = 115) of the patients had taken daily steam inhalation during the COVID-19 illness or during convalescence.

In our study, 2% had presented Stage 1 rhinocerebral mucormycosis disease, 21% had Stage 2 disease, 52% had Stage 3 disease and 23% patients had Stage 4 disease. Most patients presented with rhino orbital mucormycosis, however in our study 37 patients also had central nervous system involvement. These patients presented with stroke, cerebral venous thrombosis, and seizures. In our study, during the primary COVID-19 pneumonia illness, 14% (n = 23) patients had <15% lung involvement, 21% (n = 35) patients had 15-30% lung involvement, 34% (n = 56) patients had lung involvement of 30-45%, 11% (n = 19) patients had lung involvement of 45-65% and 4% (n = 7) patients had lung involvement >65% based on computed tomography imaging of the lungs.

Our study has the strength of a large sample size from a large tertiary care referral center for CAM. Also, we have enquired about the patient's environmental exposure at his residence and workplace to elicit more subtle risks of developing mucormycosis.

Our study has a few limitations. There was no comparison done between COVID-19 patients who did and did not develop mucormycosis. We did not do glycated hemoglobin, so we could not differentiate between newly detected diabetes and steroid-induced diabetes.

Conclusion

From our study, we could suggest that screening for hyperglycemia in all patients with COVID-19 illness is very important to detect new-onset diabetes. In our study, 34% (n = 54) of the patients had newly detected hyperglycemia while evaluating for CAM. This new onset hyperglycemia is probably due to the unmasking of the Type 2 Diabetic milieu in these individuals following steroid treatment as well as due to the persistence of elevated inflammatory cytokines like TNF-alpha in the convalescence period of COVID-19 pneumonia. In our study, we found that 80% of the diabetic individuals have not monitored blood glucose in the convalescence period and were not on follow- up care with their physicians. In our study, 90% of diabetic individuals were not under good glycemic control and they have been switched from insulin therapy to oral antidiabetic drugs in the convalescence period. Due to the persistence of residual cytokine and steroid effect, we suggest that insulin has to be continued in the convalescence period and be gradually weaned later in a phased manner with concomitant reintroduction of oral antidiabetic drugs. It is evident from our study that unhygienic mask usage was associated with the development of CAM and hence daily use of disposable masks is encouraged in these patients in the convalescence period. It is also evident from our study that organic matter from the environment has contributed to the development of CAM. Hence clean environmental hygiene may help in preventing the development of CAM in these patients. Contrary to the initial suspicion, our study findings suggest that oxygen therapy during COVID-19 was not significantly associated with the development of CAM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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