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Clinical Spectrum of Mucormycosis among COVID -19 Patients Attending Tertiary Health Care Facility: Hospital based Descriptive Study

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Abstract

Diabetes Mellitus predisposes patients to invasive fungal infections. There has been a recent surge of Mucormycosis with COVID 19 infection particularly in patients with diabetes. This study aims to study the clinical spectrum of CAM (COVID -associated Mucormycosis) with diabetes and subsequent outcomes.

Material and methods: Descriptive study was conducted among the patients attending Ophthalmology OPD in a Tertiary Care Centre in Telangana with COVID Associated Mucormycosis(CAM) from March 2021 to June 2021.

Results: Among 200 patients who attended OPD with CAM, Diabetes Mellitus was the most common co-morbidity. The majority of the patients had poor glycaemic control with a mean HbA1c of 9.06%. Pre-existing diabetes mellitus (DM) was present in 84% of cases. Out of the total study population, 89% had prior exposure to high dose corticosteroids.

Conclusion: The disease has surged in COVID 19 pandemic due to uncontrolled diabetes and improper corticosteroid use.

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

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a form of β-Coronavirus of the Coronaviridae family, has been causing infection among humans worldwide leading to a pandemic emergency. There are more than 170 million confirmed COVID-19 cases worldwide with over 3.5 million deaths as of May 2021[1].

New strains of SARS-CoV-2 have been evolving unceasingly, presenting with various systemic and ocular manifestations. There has been an increase in the incidence of secondary infection in the coronavirus infected individual either due to pre-existing factors or the virus by itself is causing such

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infection, which is still unclear. There has been reports of increased incidence of fungal infections in patients with COVID-19. There were earlier reports of COVID associated Pulmonary Aspergillosis (CAPA) and candidemia[2,3]. However, recently there has been sudden surge in cases of Mucormycosis in patients with COVID-19[4].

Mucormycosis is a formidable angioinvasive opportunistic infection in an immunocompromised host. The spectrum of mucormycosis involves rhino-orbital-cerebral, pulmonary, disseminated, cutaneous, gastrointestinal and disseminated form of disease.

The major risk factors for the disease are diabetes, neutropenia, iron overload, malignancy and organ transplant[5]. As it is already known, immunocompromised and uncontrolled diabetic patients have an increased chance of developing mucormycosis Diabetes is the most common metabolic disorder and is an independent risk factor for Severe COVID-19 and Mucormycosis. In patients with diabetes, affected with COVID-19 superinfection with Mucormycosis may present with a swelling in the left cheek, eye, and avascular necrosis intraorally, post COVID-19 infection and may lead to adverse clinical outcome and prolonged hospital stay. This study aims to study the clinical spectrum of Mucormycosis in patients with COVID-19 and diabetes and their subsequent outcomes.

Material and Methods

Study Design: hospital based descriptive study

Study setting: Ophthalmology OPD in a Tertiary Care Centre in Telangana

Study duration: The study period was for a period of 1year from March 2021 to June 2021.

Study population: Patients attending Ophthalmology OPD in a Tertiary Care Centre in Telangana during the study period.

Inclusion criteria:

- Laboratoryconfirmed COVID-19 cases by RTPCR (Real Time Reverse Transcription Polymerase Chain Reaction) nasopharyngeal & throat swab with COVID Associated Mucormycosis (CAM) presenting with complaints related to eye.
- Patients willing to participate in the study and who gave informed written consent.

Sample size: 200 patients

Study tool: pre-tested semi structured questionnaire

Study Variables: Socio-demographic variables, Case-history, symptoms, risk factors like co-morbidities, Hospital case sheets, Lab reports, CT/ MRI reports.

Methodology: Patients attending the Ophthalmology out patient department (OPD) came with the COVID Associated Mucormycosis (CAM) presenting with complaints related to eye were given appropriate management and followed till discharge. All the relevant data was collected during their stay in the hospital.

Operational definitions:

- **Severe COVID-19 infection** was defined by Sp02 < 90% or Respiratory rate >30/min at admission or during hospital stay. Post COVID 19 cases were defined who had either clinical recovery from respiratory symptoms or had passed 28 days since the onset of symptoms of COVID 19.
- **Mucormycosis** was defined by clinico-radiological suspicion with visualisation of broad branched aseptate fungal hyphae on KOH mount direct microscopy and histopathology specimen by fungal stains or isolation of zygomycetes on fungal culture.

Permissions and Ethical considerations:

- Permission was obtained from Institutional heads ie. Superintendent and Head of the department of Ophthalmology. Written informed consent was taken from patients. Institutional Ethics Committee approval was taken. Patient confidentiality was ensured.
- **Statistical analysis**

Data was compiled in MS Excel and analysed using SPSS ver 20.0. Descriptive statistics were presented as mean and standard deviation for quantitative variables and as frequencies with percentages for qualitative data.

Results

Demography

During the study period, 200 patients were hospitalized had CAM (COVID-Associated Mucormycosis). All the patients were admitted in the Covid ward attached to Tertiary Care Centre Sarojini Devi eye hospital, Hyderabad.

The mean age of patients was 58.28 (±8.57) yrs. In 200 patients with CAM, 72% were males and the rest 28% were females. It was observed that mucormycosis was predominantly seen in males (72%) as compared to females as depicted in Figure:1

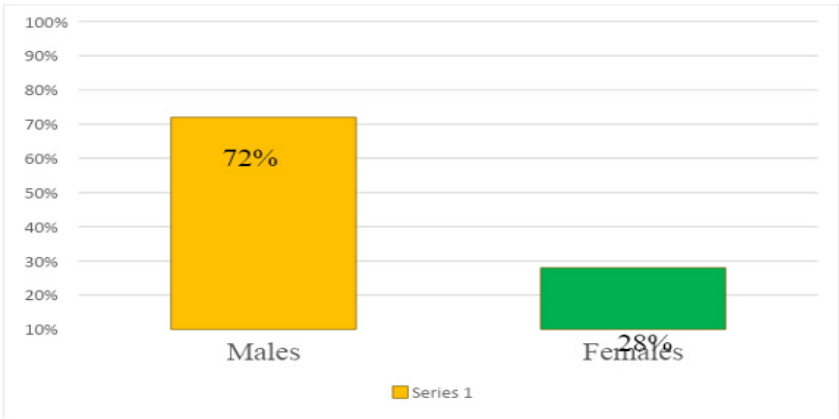

Figure: 1 Gender wise distribution of patients with Mucormycosis

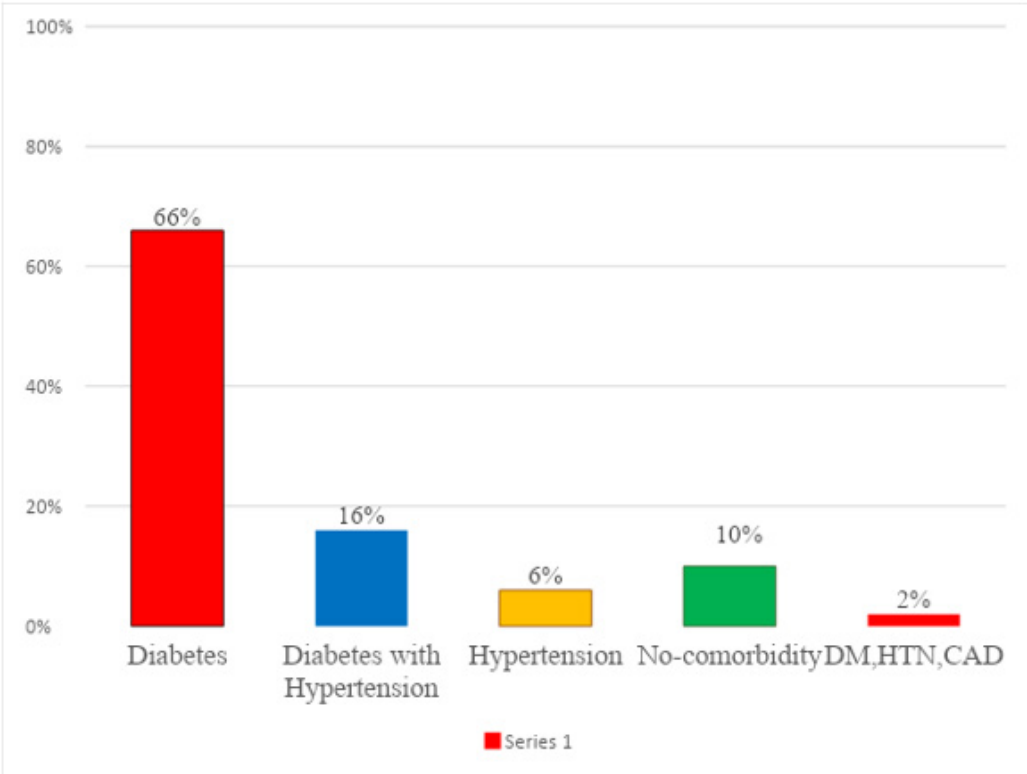

Figure: 2 Distribution of Co-morbidities among the patients with mucormycosis

In patients with CAM, pre-existing diabetes mellitus (DM) was present in 84% of cases while 66% had diabetes only as the most frequent co-morbidity followed by Diabetes with Hypertension among 18% and only Hypertension among 6%, 2% had coronary artery disease with Diabetes with Hypertension

and 10% did not have any co-morbid conditions as depicted in figure:2.

Table 1:

Co-morbidities	No (%)
Diabetes	66(66%)
Diabetes, Hypertension	18(18%)
Hypertension	6(6%)
Diabetes, Hypertension with Coronary artery disease	2(2%)

Table: 1 show that diabetes was considered to be most common comorbidity associated with mucormycosis. In patients with diabetes, mean blood glucose was 232.63 (±82.81) g/dl with mean glycated haemoglobin (HbA1c) of 9.06% (±2.19) at admission. There were no patients with diabetic ketoacidosis in our study.

The majority of the patients, 89% had history of steroid exposure in form of either dexamethasone and methylprednisolone. The duration and amount of exposure could not be determined as it varied due to physician preference and intake of OTC (over the counter) steroid by the patients. None of our patients received anti- IL6 therapy or monoclonal antibodies. There were no cases of malignancy, organ transplant or HIV/AIDS with Mucormycosis in the present study.

Clinical presentation

In Patients with CAM 51% had nasal symptoms in form of rhinorrhoea & nasal stuffiness, block and 49% had eyes symptoms in form of redness or eye pain, oedema associated with facial swelling, matting of eye lashes, ptosis, proptosis as depicted in figure: 3.

On admission, all patients presented with CAM. All the patients with Rhino orbital involvement are admitted and given Amphotericin Intravenous injections 3 doses, intraorbital injections inpatients with orbital apex involvement, Posaconazole for 60 days, All patients recovered and discharged. No deaths were reported during the hospital stay.

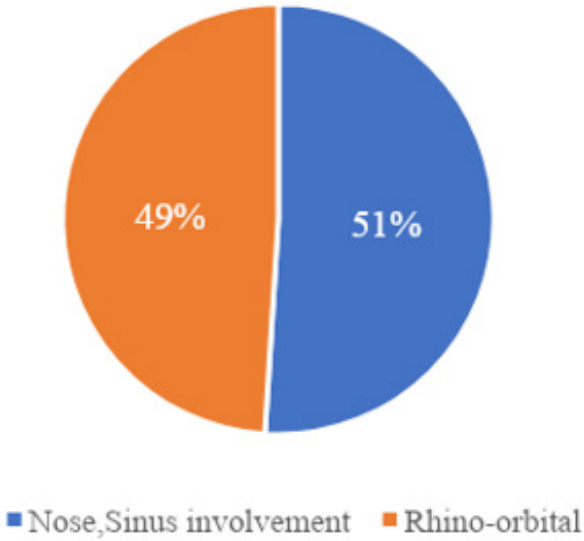

Figure 3: Distribution of patients based on clinical presentation

Contrast Enhanced Commuted Tomography/ MRI Paranasal Sinuses revealed 49 % with Rhino-orbital involvement. Among the Nose and Paranasal sinuses, (Maxillary and Ethmoid sinus) were predominantly involved in 51 % cases. We had one patient with Maxillary, frontal and Ethmoid sinus and one patient with maxillary, sphenoid and ethmoidal sinus involvement and 3 patients with rhino orbito cerebral involvement

There were no patients with pulmonary or disseminated Mucormycosis. The diagnosis of Mucormycosis was confirmed with microscopy 85%, histopathology 80% and by culture in 27% cases.

Treatment and outcome

In all the Patients endoscopic debridement of sinuses was done along with intra orbital wash with Lyposomal Amphotericin B was done to patients with orbital involvements following which liposomal Amphotercin B was given intra orbitally for 3 days along with IV Amphotercin B followed by Posaconazole for 60 days with glycaemic control. Exenteration was required for 8 eyes who presented late with orbital apex involvement.

Discussion

Around 14,872 cases of CAM have been notified in India as of May 28, 2021[4]. The present surge in Mucormycosis cases is possibly due to the high

burden COVID-19 in the country. The mean duration of onset of Mucormycosis was 16.18 (±11.36) days after the onset of COVID-19.

In the present study, it was observed that mucormycosis was predominantly seen in males (72%) as compared to females. Similar findings were reported systematic review done by **Singh AK et al in 2021**[6] study where mucormycosis was predominantly seen in males (78.9%).

In the present study, Diabetes was associated in our study with 84% similarly in a study done by **Y. Mishra, M. Prashar, D. Sharma et al. in 2021**[7]**,** it was reported to be 87.5%.Similar findings were reported systematic review done by **Singh AK et al in 2021**[6] study, where Pre-existing DM accounted for 80% of cases, while concomitant DKA was present in nearly 15% of people with mucormycosis and COVID-19.

In the present study among patients with diabetes, mean blood glucose was 232.63 (±82.81) g/dl with mean glycated haemoglobin (HbA1c) of 9.06% (±2.19) at admission. Similarly in a study done by **Y. Mishra, M. Prashar, D. Sharma et al. in 2021**[7], it was reported to 242.63 (±84.81) g/dl & mean glycated haemoglobin (HbA1c) of 9.06% (±2.19) at admission.

Diabetes is the most frequent co-morbidity in Mucormycosis in about 73.5% in India [8]. However, in western countries diabetes is associated with 17% cases of Mucormycosis[9] Incidence of Mucormycosis is around 1.6 cases/1000 patients with diabetes[10].

History of corticosteroid intake for the treatment of COVID-19 was present in 89% of the patients whereas it was 76.3% in **Singh AK et al study done in 2021**[6]**.**

In the present study, Commonest organ involved with mucormycosis was nose and sinus were 51 % followed by Rhino-orbital involvement (49%). Maxillary and Ethmoid sinuses were predominantly involved.

Singh AK et al study done in 2021[6]**, found that** Commonest organ involved with mucormycosis was nose and sinus (88.9%), followed by rhino-orbital (56.7%) and ROCM type (22.2%).

Prognosis is improved in cases of Sino-nasal disease with early surgical debridement and mortality has not been reported in the present study whereas it was 12.5% in **Y. Mishra, M. Prashar, D. Sharma et al. in 2021**[7] **to** be less than 10% in a study done by **Nithyanandam S, Jacob in 2003**[11]In contrast it was 30.7% in Singh **AK et al study done in 2021**[6]**.**

The mortality appears to be less in our case possibly due to early diagnosis with early surgical debridement. However, we did not have any patients with pulmonary and disseminated Mucormycosis disease. Moreover, we did not have any patients with hematological malignancy or organ transplant.

There are numerous reasons for the emergence of Mucormycosis in COVID 19. In our study diabetes was the most common comorbidity. Diabetes mellitus and COVID-19 share a bidirectional relationship with adverse outcomes. Diabetes is a proinflammatory state which leads to deficient control of SARS-CoV-2 replication and severe COVID 19 infections [12]. SARS-CoV-2 infection leads to decreased insulin secretion due to direct pathogenic effect on pancreatic islet cells. It also induces insulin resistance due to transient hyper-inflammatory state[13]. Subsequently, a state of hyperglycemia is produced leading to the growth of invasive mucormycosis.

Corticosteroids are considered essential therapy in patients with COVID 19 on supplemental oxygen[14]. Though traditionally, usage of prednisolone or equivalent 1 mg/kg for 3 weeks or more is considered a risk factor for Mucormycosis [15], certain case reports have shown occurrence of Mucormycosis after a short course of steroids [16]. The effect of corticosteroids in CAM is multifaceted.

First, they can lead to immunosuppression since they impair migration, phagocytosis and phagolysosome formation in the macrophages. Secondly, they lead to drug induced hyperglycemia and worsening of glycemic control in patients with diabetes.Moreover, in countries like India where it is available as Over the counter drugs, improper and prolonged steroid use could lead to increase susceptibility to Mucormycosis.[17]

SARS-CoV-2 infection causes endothelial dysfunction due to direct viral invasion and host inflammatory response causing apoptosis and pyroptosis of endothelial cells[18]. Diabetes

is a chronic inflammatory state associated with endothelial dysfunction[19]. Endothelial adhesion and angioinvasion are critical for invasion of Mucorales[5].

Thus, patients with diabetes with COVID-19 infection are at high risk for invasive Mucormycosis. Overall, hyperglycemia in patients with diabetes and COVID-19 on steroids contributes to risk of Mucormycosis .

India has high burden of Mucormycosis among patients with COVID-19 in the world[20]. The incidence has sharply risen during the second wave of COVID-19 with over 14,872 cases of mucormycosis till date[4].

Limitations:

It was a single centre study with limited cases of Mucormycosis and may not represent the full picture of the current state of the world. Moreover, we explored attributability of diabetes and COVID19 in the risk of Mucormycosis and did not have enough data for other risk factors like malignancy, neutropenia, HIV or organ transplant. We did not have a control group of patients without COVID-19 with Mucormycosis.

However, our study provides useful insights for demographic and clinical profile of CAM and its relation with diabetes.

Conclusion:

Mucormycosis is an angioinvasive fungal disease with significant morbidity and mortality. The disease has risen dramatically due to interplay of COVID 19 pandemic, uncontrolled diabetes and inappropriate corticosteroid use leading to pathogenic invasion and adverse outcomes. The treatment involves early detection, surgical debridement and antifungal drugs for better survival.

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Declaration of competing interest: The Authors declare there is no conflict of interest

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