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COVID-19 Associated Mucormycosis (CAM) - Risk Profile and Management Outcomes: A Single Centre Descriptive Study

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Abstract

Background and Objectives: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV- 2) has caused a global pandemic of Coronavirus disease (COVID- 19). Many patients with severe disease were treated with corticosteroids and broad-spectrum antibiotics. There has been a surge in cases of Covid-19 Associated Mucormycosis (CAM) in the last one year with cases reaching to epidemic levels in India. We aimed to study the clinical profile, risk factors, treatment outcomes and rate of recurrence in patients with CAM.

Materials and Methods: A total of 31 histopathologically proven cases of mucormycosis were treated in our hospital between April 15- July 31, 2021, of which 24 patients had history of past or present Covid-19 infection and thus were included in the study. All the patients were treated with surgical intervention and antifungal drug therapy and followed up for a period of three months after discharge. We conducted a single centre, descriptive study to identify risk factors, clinical presentation, treatment outcomes and rate of recurrence following treatment in patients with CAM.

Results: Of the 24 patients who were included in our study 20 (83.3%) patients had Covid-19 infection within last eight weeks and 4 (16.7%) patients had active Covid-19 infection. and were being treated for the same. The mean age of the patients was 52.3 (±10.89) years. 17 (70.8%) patients were males and 7 (29.2%) were females. The commonest predisposing factor was diabetes mellitus (87.5%) and corticosteroid therapy (83.3%%). During the study period, 3(12.5%) patients did not survive while recurrence of disease was seen in one patient during the follow up period.

Conclusion: *Mucor spp.* responsible for CAM is an angio-invasive fungus and is a colonizer of nasal cavity. Uncontrolled diabetes mellitus and treatment with corticosteroids appears to be the cause of sudden surge in CAM

Keywords: Covid-19, Covid-19 Associated Mucormycosis, Risk factors, Outcome

Introduction

Mucormycosis is a serious, opportunistic invasive disease caused by the fungi belonging to *zygomycetes* family which includes *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp., *Actinomucor* spp., and *Lichtheimia* spp. (formerly Absidia).[1] These fungi are common commensals in healthy individuals and cause infection primarily in the immunocompromised, patients with uncontrolled diabetes, defective

phagocytic function and elevated free iron level that supports fungal growth.

It is a rare disease, its incidence in the general population being previously cited as 0.005 to 1.7 per million population [2]. However, the incidence in India has been reported to be 0.14/1000 diabetic patients which is 80 times higher than that reported in other parts of the world.[3] The spectrum of disease ranges from locally invasive (Rhino-Orbital-Cerebral, Cutaneous) to systemic (Pulmonary, Gastrointestinal) and disseminated Mucormycosis.[4]

Recent Covid-19 pandemic, especially the later half, showed a surge of cases of mucormycosis, most of them presenting in the recovery phase of the illness. This infection with *Zygomycete spp*. as opportunistic infection in patients with COVID was particularly striking in the second wave of the pandemic as compared to the post COVID cohort of the first wave where Covid Associated Pulmonary Aspergillosis (CAPA) and candidemia was more common. [5]

Classical risk factors for mucor infection include overuse of steroids, poor glycemic control, diabetic ketoacidosis and increased serum free-iron.[5] Other possible risk factors suggested are non-judicious use of multiple antibiotics, overuse of zinc supplements, and poor mask hygiene. However, the exact cause of the surge is yet to be identified.[6] The unique nature of COVID-associated mucormycosis (CAM) cases is a predilection to rhino-orbital involvement. Whether COVID-19 infection is an independent risk factor of Rhino-Orbital-Cerebral Mucormycosis (ROCM) is a valid research question to be answered in the future.[7] As CAM is a progressive disease with poor outcome if diagnosed late, early diagnosis and treatment with a multidisciplinary team is necessary.

We conducted a single centre, descriptive study to identify risk factors, clinical presentation, treatment outcomes and rate of recurrence following treatment in patients with CAM.

Materials And Methods

This was a descriptive study of patients diagnosed with Mucormycosis. It was carried out at Parul Sevashram Hospital, Waghodia, Gujarat from April 15, 2021 to July 31, 2021 after getting approval from the institutional ethics committee. Written informed consent was obtained from all study participants.

Inclusion Criteria:

All patients aged 18 years and above, radiologically and microbiologically confirmed as cases of mucormycosis and who gave written informed consent for participating in the study were included.

Exclusion Criteria: 1. No past or present history of COVID-19 infection 2. Incomplete data 3. Refusal to give informed consent.

Case Definition:

CAM was defined as presence of all of the following four criteria:

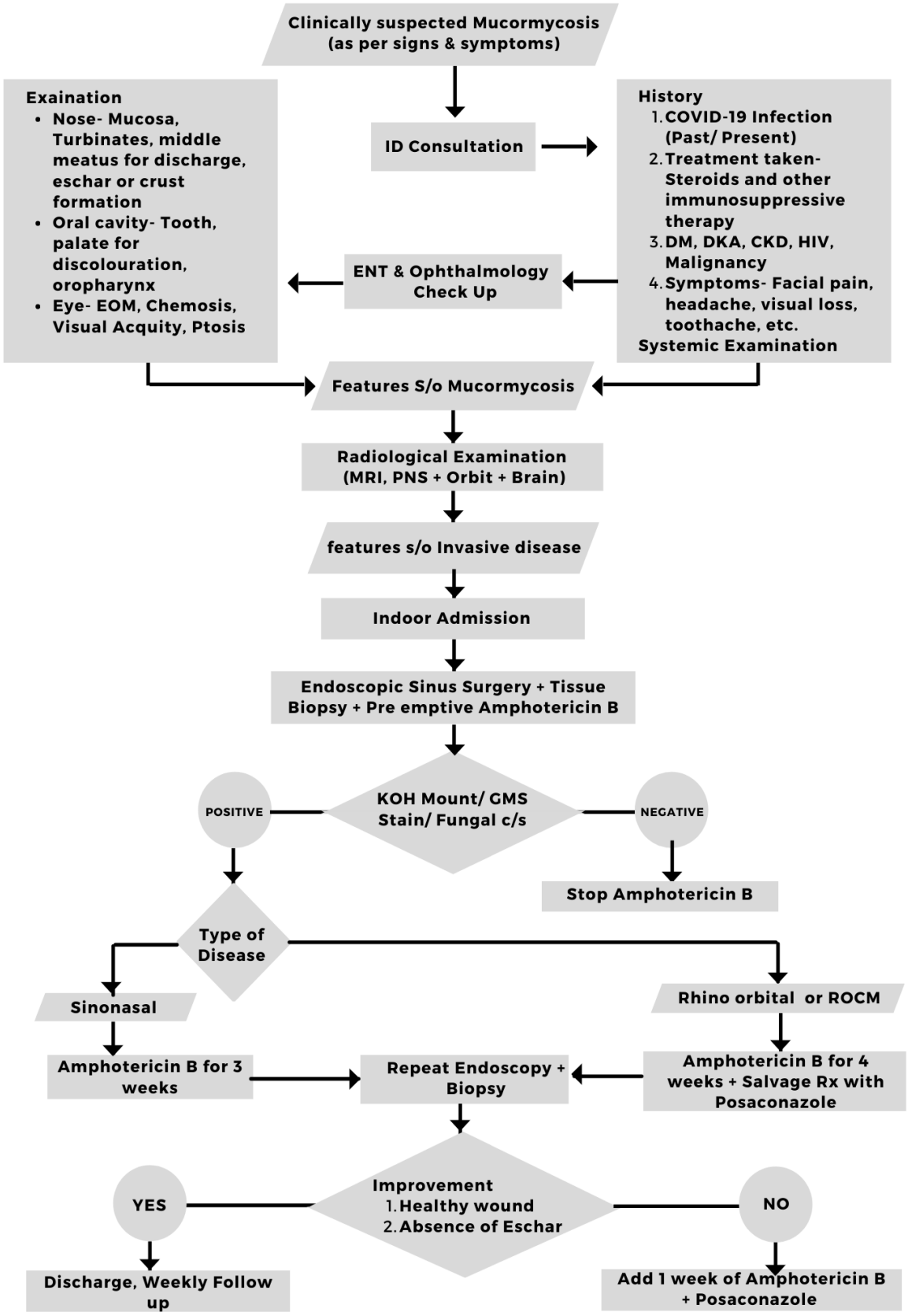
1. Symptoms and Signs (≥1 of the following):
    a. Headache
    b. Black or brown coloured nasal discharge
    c. Orbital swelling and pain
    d. Presence of black/brown exudate in oral cavity
    e. Hemifacial pain
    f. Nasal blockage
2. History of COVID illness within past 3 months - Diagnosed by either Reverse Transcriptase- Polymerase Chain Reaction (RT-PCR) or Rapid Antigen Test (RAT)
3. Radiological signs suggestive of locally invasive disease.
4. Microbiological diagnosis- Fluid/tissue from a sterile site or tissue biopsy from a non-sterile site showing broad, aseptate or pauci-septate, obtusely branching hyphae and/or fungal culture growing *zygomycetes* spp.

Workflow at our institute

The patients were managed based on our institutional mucormycosis management protocol which (Figure 1) incorporates a stepwise approach aimed towards early diagnosis and aggressive management of the condition. A suspected case of CAM was identified by infectious diseases team based on signs, symptoms and history of COVID within past 3 months. All the suspected cases were examined thoroughly by the ENT and Ophthalmology teams.

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

Figure 1: Workflow at our tertiary care centre



Volume 4, Issue 6; November-December 2021; Page No 1207-1218

A history of associated risk factors of mucormycosis was documented. All the suspected patients were admitted in a separate Mucor ward.

Following identification of suspected cases, radiological examination (MRI Brain + Orbit + PNS) was done to assess the disease extent (involvement of nasal cavity, paranasal sinuses, orbit and intracranial structures). If the radiological findings showed features suggestive of invasive disease, the patients were admitted and started on pre-emptive Amphotericin B. Intravenous liposomal or deoxycholate Amphotericin B was commenced based on feasibility. All the patients underwent FESS (Functional Endoscopic Sinus Surgery) where tissue biopsy was collected for histopathological examination, KOH mount, Gram stain, fungal culture and pyogenic culture.

All patients with limited sino-nasal mucormycosis were administered liposomal amphotericin B at 3-5 mg/kg/day for 3 weeks for a targeted cumulative dose of 4-5 g OR Amphotericin B Deoxycholate at 1 mg/kg/day (maximum 60 mg/day) for 3 weeks. For Rhino-Orbital and Rhino-Orbito-Cerebral mucormycosis (ROCM), 5 mg/kg of liposomal amphotericin B was administered for four weeks followed by Posaconazole salvage therapy for eight weeks. Daily complete blood count, serum electrolytes and renal function test were monitored. Patients underwent emergency endoscopic debridement, orbital decompression, maxillectomy and/or mandibulectomy based on the extent of disease. All the patients underwent weekly nasal endoscopy to rule out disease recurrence and assess the need for repeat debridement till discharge.

All discharged patients were followed up weekly for a period of three months to look for any recurrence. Patients with documented recurrence received full dose of Amphotericin B for 3 weeks OR Posaconazole for 8 weeks and any surgical intervention if needed.

Statistical Analysis: Data was compiled in MS Excel and analysed using SPSS ver 20.0. Descriptive statistics are presented as mean and standard deviation for quantitative variables and as frequencies with percentages for qualitative data. Associations between variables were explored for hypothesis generation using Chi square test for qualitative variables and unpaired t-test for quantitative variables.

Results: A total of 31 histopathologically confirmed cases of Mucormycosis were admitted at our institute during the study duration. Seven patients were excluded from our study as they had no history of prior Covid-19 infection. Of the 24 patients who were included in our study 20(83.3%) patients had Covid-19 infection within last 4 - 6 weeks while 4(16.7%) had active COVID-19 infection and were being treated for the same. The mean age of the patients was 52.3±10.89 years. 17(70.8%) patients were males and 6(29.2%) were females. All the patients were admitted in a dedicated Mucor ward. None of these patients were vaccinated against COVID-19. (Table 1)

The mean duration of onset of mucormycosis was 15.21±5.50days after the onset of Covid-19 infection. 21(87.5%) patients had diabetes which was the most frequent co-morbidity. In patients with diabetes, mean blood glucose was 268.9(±103.6) mg/dl with mean glycated haemoglobin (HbA1C) of 8.84% (±2.43) at admission. One patient presented with diabetic ketoacidosis. 20(83.3%) patients had history of steroid exposure in the form of either dexamethasone or methylprednisolone while being treated for Covid-19 infection. 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 them gave history of receiving anti-IL6 therapy or monoclonal antibodies. There were no cases of malignancy, organ transplant or HIV/AIDS with mucormycosis in our study.

In patients with CAM, 19(79.2%) had headache, 21(87.5%) had nasal symptoms in form of rhinorrhoea & nasal obstruction, 17(70.8%) had facial pain and swelling, 12(50%) had orbital swelling, 2(8.3%) had visual loss, 2(8.3%) had cutaneous symptoms and 3(12.5%) patients gave history of tooth ache. Examination demonstrated proptosis in 12(50%), ptosis in 4 (16.7%), facial palsy in 1(4.2%) and palatal discoloration was seen in two patients. (Table 1)

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

Table 1. Baseline Clinical Characteristics of Study participants and among survivors and non survivors

Parameters	All patients (n=24)	Survivors (n=21)	Non-Survivors (n=3)	P value[a]
Age (years)	52.3±10.89	51.09±10.77	60.67±7.59	0.619
Gender (%)				0.865
- Male	17 (70.8%)	15 (71.4%)	2 (66.7%)	
- Female	7 (29.2%)	6 (28.6%)	1 (33.3%)	
Comorbidities				
-Diabetes Mellites	21(87.5%)	18 (85.7)	3 (100%)	0.484
-Hypertension	10 (41.7%)	8 (38.1%)	2 (66.7%)	0.754
-Cardiovascular disease	1 (4.2%)	0	1(33.3%)	0.247
-Chronic kidney disease	1 (4.2%)	1(4.8%)	0	0.699
COVID-19 Infection				
-Active	4 (16.7%)	2 (9.5%)	2 (66.7%)	0.098
-Past Infection	20 (83.3%)	19 (90.5%)	1 (33.3%)	
Mean duration of onset of Covid-19 to mucor diagnosis	15.21±5.50	15.10±5.86	16.0±2.0	0.7965
H/O Corticosteroid Use				
Yes	20 (83.3%)	17 (80.9%)	3 (100%)	0.408
No	4 (16.7%)	4 (19.1%)	0	
Symptoms				
Headache	19 (79.2%)	16 (76.2%)	3 (100%)	0.8493
Facial pain and swelling	17 (70.8%)	17 (81%)	0	0.0273
Nasal symptoms	21 (87.5%)	19 (90.5%)	2(66.7%)	0.8155

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

Eye swelling	12 (50%)	9 (42.9%)	3 (100%)	0.2170
Visual loss	2 (8.3%)	1 (4.8%)	1 (33.3%)	0.5766
Cutaneous Symptoms	2 (8.3%)	2(9.5%)	0	0.5766
Toothache	3 (12.5%)	3(14.3%)	0	0.4840
Signs				
Proptosis	12 (50%)	9 (42.9%)	3 (100%)	0.2170
Ptosis	4 (16.7%)	2 (9.5%)	2 (66.7%)	0.0977
Facial palsy	1 (4.2%)	1 (4.8%)	0	0.6994
Palatal discolouration	2 (8.3%)	2 (9.5%)	0	0.5766

[a] P< 0.05 was considered as statistically significant

Baseline investigations showed high leucocyte count at admission in 18(75%) patients. No significant difference was found in mean leucocyte counts between survivors and non survivors. HbA1C and random blood sugar (RBS) levels of non-survivors at admission was significantly higher than survivors. (Mean HbA1C - 11.60±2.095 and 8.5±2.25 and respectively; p = 0.035 and mean RBS - 395±113.03 and 250.86±91.3 respectively; p = 0.0205). (Table 2)

Cross sectional Imaging (MRI) demonstrated Sino-nasal, Rhino-orbital and ROCM in 12(50%), 9(37.5%) and 3(12.5%) patients respectively. Maxillary and ethmoid sinuses were involved in 75% and 79.2% cases respectively, whereas sphenoid and frontal sinus involvement was comparatively less common (66.6% and 45.8% respectively). (Table 2)

Table 2: Laboratory, Radiological and Microbiological Characteristics of Study participants and among survivors and non survivors

Laboratory parameters (Mean±SD)	All patients (n=24)	Survivors (n=21)	Non-Survivors (n=3)	P value[a]
Hemoglobin (g/L)	10.76±1.43	10.72±1.44	11±1.65	0.762
WBC Count(cells/cumm.)	12174.5±3872.3	11795.7±3955.7	14826.7±1975.7	0.212
Platelet Count (10^5/MM^3)	2.45±0.95	2.55±97488.2	1.79±0.38	0.209
RBS (mg/dl)	268.9±103.6	250.9±91.3	395±113.03	$0.0205^{\pm}$
HbA1C (%)	8.84±2.43	8.5±2.25	11.6±2.095	$0.035^{\pm}$
Sr. Creatinine (mg/dl)	1.13±0.58	1.05±0.56	1.67±0.45	0.083
Sr.Potassium(mmol/L)	3.88±0.65	3.83±0.68	4.2±0.25	0.415
Disease Spread (on imaging)				
PNS Involvement				

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

-Maxillary Sinus	18 (75%)	17 (80.95%)	1 (33.3%)	0.2850
-Ethmoid Sinus	19 (79.2%)	17 (80.95%)	2(66.7%)	0.5687
-Sphenoid Sinus	16 (66.7%)	14(66.7%)	2(66.7%)	1.000
-Frontal Sinus	11 (45.8%)	10 (47.6%)	1(33.3%)	0.6423
Orbital Spread	9 (37.5%)	8 (38.1%)	1(33.3%)	0.8734
Intracranial Spread	3 (12.5%)	1 (4.8%)	2 (66.7%)	0.0358
Disseminated	0	0	0	NA
Microbiological Diagnosis				
Microscopy	21 (87.5%)	19 (90.5%)	2 (66.7%)	0.054
Culture	10 (41.7%)	8 (38.1%)	2 (66.7%)	0.098
HPE	24 (100%)	21 (100%)	3 (100%)	NA

[a] P< 0.05 was considered as statistically significant

Microscopy was positive in 21(87.5%), histopathology in 24 (100%) and fungal culture in 10 (41.7%) cases. (Figure 2)

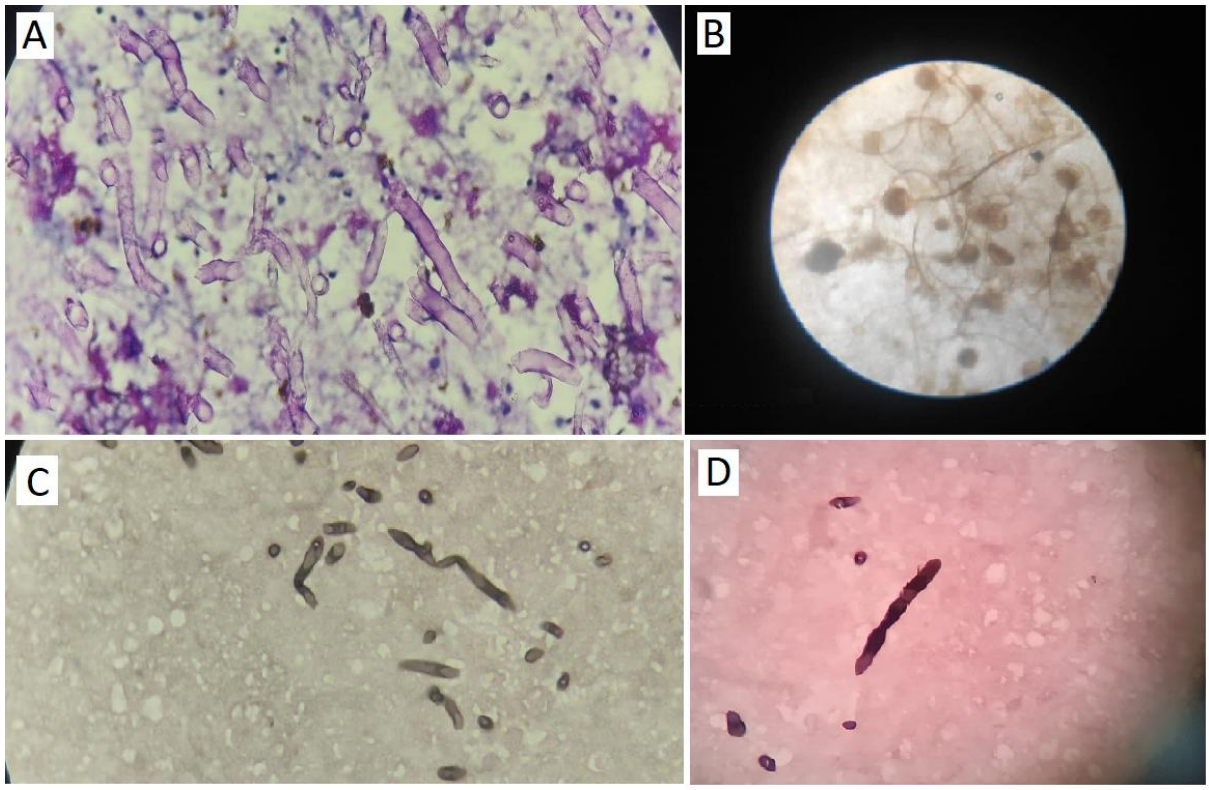


Figure 2: A. Histopathological section-non septate hyphae branching at broad angles B. KOH preparation of nasal scrapping C. PAS Stain D: GMS Stain

Patients at our centre were started on either deoxycholate or liposomal formulation of amphotericin B based on feasibility. 10(41.7%) patients received deoxycholate amphotericin B and 14 (58.3%) patients received

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

liposomal amphotericin B. No significant difference was found with respect to mortality between the two groups. Oral Posaconazole was given to 14 patients (58.3%). (Table 3)

Table 3: Treatment, adverse effects of treatment and outcome in patients with CAM

Treatment	All patients (n=24)	Survivors (n=21)	Non-Survivors (n=3)	P value[a]
Deoxycholate Amphotericin	10 (41.7%)	8 (38.1%)	2 (66.7%)	0.098
Liposomal Amphotericin	14 (58.3%)	13 (61.9%)	1 (33.3%)	0.098
Oral Posaconazole	14 (58.3%)	12 (57.1%)	2 (66.7%)	0.754
FESS with Debridement	24 (100%)	21 (100%)	3 (100%)	NA
Orbital decompression	1 (4.2%)	1 (4.8%)	0	NA
Maxillectomy	4 (16.7%)	3 (14.3%)	1 (33.3%)	NA
Adverse effects of Amphotericin B				
Hypokalemia	16 (66.7%)	13 (61.9%)	3 (100%)	0.518
Hypomagnesemia	4 (16.7%)	3 (14.3%)	1 (33.3%)	0.408
Leucopenia	10 (41.7%)	9 (42.9%)	1 (33.3%)	0.754
Chills/Febrile episode	15(62.5%)	12(57.1%)	3(100%)	0.426
Raised Creatinine	14 (58.3%)	12 (57.1%)	2 (66.7%)	0.754
Treatment Outcome				
Discharge	21 (87.5%)	NA	NA	NA
Death	3 (12.5%)	NA	NA	NA
Recurrence	1	1	0	NA

NA- Not applicable. [a]P< 0.05 was considered as statistically significant.

There were serious adverse reactions following administration of amphotericin B. Hypokalemia was seen in 16 (66.7%) patients, febrile episode with chills in 15(62.5%), leucopenia in 10(41.7%), hypomagnesemia in 4(16.7%) and raised creatinine was seen in 14 (58.7%) patients. All patients

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

underwent FESS with debridement and samples were sent for histopathological diagnosis and confirmation. Additionally, four patients underwent maxillectomy and in one patient orbital decompression was done. During the entire duration of study, 3(12.5%) patients succumbed; 2 patients died due to progressive disease and 1 patient died due to severe comorbid conditions. 21(87.5%) patients were discharged after completion of therapy. All discharged patients were called for weekly follow up for a period of 12 weeks (Table 3). Recurrence of disease was seen in one patient during follow up for which the patient underwent surgical debridement with mandibulectomy and was administered oral Posaconazole for 8 weeks. The patient is coming for regular follow up till date without any recurrence.

Discussion:

India has the highest global burden of mucormycosis with a prevalence of 140 per million population.[8] According to latest reports from Central Government, 47,572 cases of CAM have been reported across the country out of which 4437 (9.3 %) have succumbed [9], thus showing a high case fatality. In a recent multicentre study, 187 cases of CAM were reported, with incidence of 0.27% among hospitalized cases. The caseload of Mucormycosis was found to be 2.1 folds higher than the previous year [10].

It is known by now that diabetes and Covid-19 share a bidirectional relationship leading to poor outcomes.[16] Diabetes is a pro-inflammatory state that leads to increased viral replication of SARS COV-2 causing severe infection. [11,12] SARS COV-2 has direct pathogenic effect on pancreatic islet cells leading to reduced insulin secretion. It also induces insulin resistance due to transient hyperinflammatory state. [13] Diabetes is also associated with endothelial dysfunction [14,15] which enhances tissue invasion of *Mucorales spp*. through endothelial adhesion and angio-invasion, both being critical for manifestation of locally invasive disease. [16,17] The most common risk factor associated with CAM in our study was also diabetes mellitus. 87.5% patients had diabetes mellitus with mean blood sugar of 268.9±103.6 mg/dl and mean HbA1C of 8.84±2.43 %. We also found that higher blood sugar and HbA1C levels at admission were associated with greater mortality probably because of extensive disease.

The 2nd most common risk factor associated with CAM was use of corticosteroids. 83.3% patients had history of use of corticosteroids during Covid-19 infection, but details of dose and duration of steroids used were available for very few study participants. Dexamethasone and equipotent systemic and inhalational steroids were approved for treatment of patients with Covid-19 infection on supplemental oxygen.[18,19] Their effect on CAM is multipronged. Firstly, they lead to immunosuppression and secondly, cause drug induced hyperglycemia and worsening of glycemic control in diabetics. It has been documented earlier that the usage of steroids for at least three weeks or more is a risk factor for CAM. [20, 21] But in a case report by Hoang et al. it was seen that CAM can develop even after a short duration of steroid use. [22] In India, steroids are available as over-the-counter medicines and hence, their improper and prolonged use leading to increased susceptibility to CAM cannot be ruled out.

Another significant observation was absence of history of COVID -19 vaccination in all the patients who presented with CAM. Vaccination against COVID-19 may result in less severe disease requiring lower doses of corticosteroids for lesser duration, if at all required. No such observation has been reported by any previous study.

Many researchers noted rhino-orbital mucormycosis as the most common type seen in post Covid-19 patients as was seen in studies conducted by Mishra et al.[23] and Pal et al.[6] (59.4% and 60 % cases of rhino orbital mucormycosis respectively). In contrast, we observed that the radiological pattern of CAM was predominantly sino-nasal disease (12 out of 24 - 50%), followed by rhino-orbital disease (9 out of 24-37.5%). This difference could be because of early reporting to hospital by most patients and prompt initiation of therapy in our study.

Medical management was done in all patients with either liposomal or deoxycholate amphotericin B. Both above formulations are claimed to have similar efficacy, but the latter has poor adverse effect profile. Adverse events in the form of hypokalemia, hypomagnesemia, febrile episode/chills, raised creatinine and leucopenia were observed. Similar observations were made by Pal et al.[6] Hence, effective monitoring of patients with regular blood

Volume 4, Issue 6; November-December 2021; Page No 1207-1218

investigations is necessary. In all patients on Amphotericin B treatment, blood urea, creatinine, electrolytes, and blood counts should be monitored regularly to prevent therapy related adverse events.

3(12.5%) patients did not survive. This was similar to a study conducted by Mishra et al.[23] Others have found mortality to be greater than 30%. Pal R et al. [24], Kumari et al. [25] and Patel et al. [10] reported 34%, 30% and 38.3% mortality respectively. Prognosis of disease is known to improve in cases of sino-nasal disease when diagnosed and treated early and mortality reported is less than 10%, [26]. This could be one reason why the mortality was lower in our study. Other causes could be early initiation of therapy and surgical debridement. All patients were followed up for a period of three months after discharge to look for any recurrence of disease. Recurrence of disease occurred in only one patient who underwent surgical intervention and medical management. We could not find any literature on rate of recurrence in CAM for comparison.

Multiple cases of Candidemia and COVID associated Pulmonary Aspergillosis were reported following the first wave. Although the risk factors associated with CAM were present during both the first and second waves of COVID pandemic, mucormycosis was reported with higher frequency in COVID and post COVID phases of illness in the second wave of the pandemic in India. This shows that additional risk factors may facilitate manifestation of overt mucormycosis and are hitherto unknown. The second wave of COVID 19 was attributed to B.1.617 variant of SARS-CoV-2, also called a 'double mutant' or the 'delta' variant [27-29]. This variant was found to have higher infectivity with greater virulence as compared to the earlier variants and was consequently associated with greater mortality.[30] Various hypotheses have been suggested to explain the pathogenesis of COVID-19 associated mucormycosis (CAM). Uncontrolled diabetes, impaired immune response, acidosis, hyperferritinemia and glucocorticoid therapy were suggested as primary risk factors. Over expression of Glucose Related Protein 78 (GRP78), which is utilized by SARS CoV2 and Mucorales for endothelial translocation, may help facilitate tissue invasion by Mucorales. (31) Besides these factors, we suggest that empiric use of broad-spectrum antibiotics reduced the normal nasal flora and promoted growth of fungi. Severe denudation of the nasal mucosa may facilitate tissue invasion and subsequently angioinvasion. Further molecular research is required to unravel mechanisms involved in the pathogenesis of CAM.

Limitations: This was a single centre study with a small sample size and may not be representative of the whole population. We did not have any control group of mucormycosis patients without Covid-19 infection as comparator.

Strengths: To our knowledge, this is the first study where all CAM patients were followed up for a duration of 3 months after discharge to document and manage recurrence of the disease.

Conclusion:

CAM is a serious, opportunistic, and locally invasive disease that is rapidly life threatening. A high index of suspicion with prompt diagnosis and multidisciplinary management is imperative to achieve favourable outcomes. Close follow up of patients with CAM is warranted due to possibility of recurrence despite adequate management.

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Volume 4, Issue 6; November-December 2021; Page No 1207-1218

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Volume 4, Issue 6; November-December 2021; Page No 1207-1218

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Volume 4, Issue 6; November-December 2021; Page No 1207-1218