

Original Article

A Hospital based Observational Study of Clinical spectrum and Outcome of Mucormycosis during the COVID Pandemic

Nandini Chatterjee¹, Jyotirmoy Pal², Indranil Khatua³, Pranabananda Pal⁴, Bibhuti Saha⁵, Debashish Bhattacharya⁶, Ajoy Chakraborty⁷

Background : Mucormycosis is a life threatening fungal disease caused by the filamentous fungi mucormycetes. Though a known entity for decades, it began to manifest in an unprecedented manner in the COVID scenario specially with the second wave in India. The objectives were to describe the demographic characteristics, clinical presentations, risk factors, therapy and in-hospital mortality of patients with Mucormycosis.

Material and Methods : We conducted a retrospective observational study for a period of six months from March 2021 to August 2021. The data was collected for cases of mucormycosis from multiple centres all over West Bengal and analysed. All consecutive individuals with confirmed mucormycosis were enrolled in this study. The data documenting demographic particulars, presentation, predisposing factors and comorbidities were recorded in a pre validated case report form. Details of investigation recording site and extent of disease, therapeutic intervention and outcome was mentioned. Statistical analysis was done using SPSS 21.0 for MS-Windows.

Results : The total number of cases from March to August 2021 was 263. There were 171 males and 92 females and the mean age of occurrence was 50.8±0.4 years. In West Bengal clusters of cases were being reported most commonly from the districts of North 24 Parganas, Kolkata, Jalpaiguri, Darjeeling and Hooghly. Some cases admitted here hailed from outside states like Bihar, Jharkhand, Odisha and Assam.

The majority of the cases 74.22% (196) were COVID Associated Mucormycosis (CAM) while only 25.78% were non COVID associated. Diabetes mellitus was associated in 78.7% and history of prolonged steroid therapy in 57.4% of cases. We encountered rhino orbital mucormycosis in 99.24% of cases and cerebral involvement in 47.3%. They were treated with Amphotericin B deoxycholate along with endoscopic debridement. The most common side effects of Amphotericin B Deoxycholate were hypokalemia (93%), hypomagnesemia (32%) and AKI (74%) of the cases. The number of patients discharged was 16.7% and 10 left against medical advice (LAMA). In hospital deaths were recorded to be 26.7%. Cause of death was commonly -AKI, septic shock and multiorgan failure.

Conclusion : Prevention is better than cure of this devastating disease which is difficult to diagnose and treat. Awareness about mucormycosis and careful clinical evaluation of post-COVID patients is mandatory in this era in order to rapidly diagnose and treat mucormycosis.

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Key words : COVID associated Mucormycosis, Diabetes mellitus, Rhino orbital.

CCOVID associated mucormycosis (CAM) is Mucormycosis in COVID-19 patients, often with comorbidities, in the later part of its clinical course. In India, prevalence of mucormycosis has been estimated as 140 per million population, which

Editor's Comment :

- Awareness about mucormycosis is important in the COVID era.
- Prevention is better than cure. Early diagnosis and prompt institution of therapy improves outcome markedly.

¹Professor, Department of Medicine, IPGME&R and SSKM Hospital, Kolkata 700020

²Professor, Department of Medicine, RG Kar Medical College & Hospital, Kolkata 700004

³RMO cum clinical Tutor, Department of ENT, NRS Medical College & Hospital, Kolkata 700014

⁴Junior Resident, Department of Medicine, IPGME&R and SSKM Hospital, Kolkata 700020 and Corresponding Author

⁵Professor STM, Department of Tropical Medicine, Kolkata 700073

⁶Directorate of Medical Education, Department of Health and Family Welfare, Government of West Bengal

⁷Director of Health Services, Government of West Bengal

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exceeds that in western countries by almost 70 times. There was a surge of mucormycosis cases during September–December 2020 which continued to enhance in the second wave of COVID-19 next year. CAM prevalence was found to be 0.27% among patients in hospital wards and 1.6% in ICU¹ and eleven states in India had declared it an epidemic.

Mucormycosis is a challenge to the medical fraternity as it is difficult to suspect, diagnose and treat. Awareness about this entity is of prime importance.

We undertook a retrospective observational study to characterize mucormycosis patients admitted in

various centres of West Bengal for a period of six months.

AIMS AND OBJECTIVES

The study objectives were to describe the demographic characteristics, clinical presentations, risk factors, therapy and in-hospital mortality of patients with Mucormycosis.

MATERIAL AND METHODS

We conducted the study from March 2021 to August 2021. The data was collected for cases of mucormycosis from multiple centres all over West Bengal and analyzed. Ethics committee approval was taken.

Inclusion criteria : All consecutive individuals with confirmed mucormycosis who gave informed consent, were enrolled in this study.

We defined a case of mucormycosis as those individuals with clinical and radiological features indicating disease with the demonstration of fungi in the tissue by direct microscopy (broad ribbon like aseptate hyphae) and histopathology with or without positive culture.

Patients underwent all routine investigations followed by contrast enhanced MRI of sinuses, orbit and brain and CT Scan of thorax. Tissue biopsies were taken from debrided material and sent for smear/stain, culture, and histopathology.

Microscopy was performed using the KOH mount method. Culture was done in Sabouraud Dextrose Chloramphenicol Agar (SDCA).

The tissue samples submitted for histopathological examination were examined using Gomori's methenamine silver stain.

All participants had received treatment at the discretion of the treating physician.

The data were recorded in a pre validated case report form documenting demographic particulars, presentation, predisposing factors and comorbidities.

Details of investigation, recording site and extent of disease, therapeutic intervention and outcome were mentioned.

The data were analysed using SPSS 21.0 for MS-Windows with the help of descriptive statistics. The chi-square test (or Fischer's exact test) and Mann-Whitney test were used as appropriate for categorical as well as continuous variables as appropriate. A p-value <0.05 was considered as significant.

RESULT

The total number of cases from March to August 2021 was 263. There were 171 males and 92 females

and the mean age of occurrence was 50.8 ± 0.4 years. In West Bengal clusters of cases were being reported most commonly from the districts of North 24 Parganas, Kolkata, Jalpaiguri, Darjeeling and Hooghly. Some cases admitted here hailed from outside states like Bihar, Jharkhand, Odisha and Assam (Table 1).

The majority of the cases (196) 74.22% were COVID Associated Mucormycosis of which (125) 47.52% were post COVID and (71) 26.7% were suffering from COVID-19 at the time of mucor infection. The mean duration of development of COVID -19 and mucormycosis was 21.7 days (5-35 days). Of these patients 59% had required oxygen support. Non COVID Mucormycosis was seen in 25.78% of the cases.

Sl No	District	Case
1	North 24-Parganas	38
2	Kolkata	30
3	Jalpaiguri	19
4	Darjeeling	19
5	Hooghly	14
6	Purulia	12
7	Bihar	12
8	Paschim Medinipur	12
9	Bankura	12
10	South 24 Parganas	10
11	East Midnapore	11
12	Nadia	7
13	Howrah	8
14	Jhargram	6
15	Alipurduar	6
16	Murshidabad	6
17	Paschim Barddhaman	6
18	Dakshin dinajpur	6
19	Purbo Barddhaman	4
20	Malda	4
21	Birbhum	4
22	Others	17

Diabetes mellitus was the single most important accompanying disease for mucormycosis patients, being present in 78.7% (207) of the patients. More than half of the patients had history of steroid intake 57.4% (151). There were 3 post renal transplant patients in our series, while 4 patients had cancer. Other comorbidities found were ischemic heart disease (97), Hypertension (89), COPD (20) Chronic Kidney Disease (28) and Chronic liver Disease (9) (Table 2).

We encountered Rhino Orbital Mucormycosis (ROCM) in 99.24% of cases, cerebral involvement in 47.3% and pulmonary involvement in 0.76% cases (2 Cases). One case of penile cutaneous mucormycosis was diagnosed.

Common symptoms were headache /orbital pain (90%), nasal blockade and discharge, blurring or dimness of vision and loosening of teeth. Unilateral Swelling of eye was the commonest sign seen in 62%

Comorbidities	N = 263 (%)
Diabetes mellitus	207 (78.7)
Ischemic Heart Disease	97 (46.8)
Hypertension	89 (33.8)
Chronic Kidney Disease	28 (10.6)
COPD	20 (7.6%)
CLD	9 (0.03%)
Renal Transplant	3 (0.01%)
Malignancy	2 (0.007%)

followed by facial swelling, palatal ulcer, loss of ocular motility and loss of vision.

Of the investigations, the markers of inflammation like CRP, Ferritin and D Dimer were universally raised. The commonest radiological findings were diffuse mucosal involvement in nasal, maxillary and ethmoid sinuses in nearly 64%, orbital involvement in 42%. Orbital apex was involved in 18%. In the CNS, cavernous sinus was most commonly involved in 45% of cases. Cerebral infarction was found in 15 patients. Cerebral involvement was predominantly found in CAM patients.

Therapy was given with Amphotericin B Deoxycholate at a dose of 1mg/kg/day in our Government set ups for 4-6 weeks followed by Posaconazol tablet orally. Debridement was done in addition to medical management in 67% of cases and orbital exenteration was performed in 8 patients while maxillectomy was done in 5 patients. One patient underwent penile resection. The outcome of open surgery was dismal with mortality in 60% of the cases.

The most common side effects of Amphotericin deoxycholate were hypokalemia in 93% hypomagnesemia in 32% and Acute Kidney Injury in 74% of the cases (Table 3).

The number of patients discharged was 16.7%, 10 left against medical advice (LAMA). In-hospital deaths in CAM were recorded to be 26.7%. Cause of death was -Acute Kidney Injury, septic shock and multiorgan failure.

Complications of therapy	(%)
Hypokalemia	93
Acute Kidney Injury	74
Hypomagnesemia	32
Agranulocytosis	10
Allergic reaction	4
Hypotension	2

DISCUSSION

According to a Government of India advisory, many states in India had made mucormycosis a notifiable disease in May 2021. A study by Patel et al reported that 6% of hospitalized COVID patients incurred systemic fungal infection. There was a doubling of mucormycosis cases during September–December 2020 in comparison to 2019. CAM prevalence was found to be 0.27% among patients in hospital wards and 1.6% in ICU². Gujarat Maharashtra, Andhra Pradesh, Madhya Pradesh and Telangana were topping the list of states with mucormycosis though eleven states had declared it an epidemic.

This fungus belongs to the genus Mucorales order of the class of Zygomycetes. The fungi have broad,

aseptate, ribbon like hyphae with branching at wide angles. *Rhizopus arrhizus* is the most common subtype worldwide, *Apophysomyces variabilis* common in Asia and *Lichtheimia* species is more frequent in Europe. In our country, *Rhizopus* and *Apophysomyces* are the common isolates^{3,4}.

Demonstration of fungal hyphae with characteristic morphology on direct microscopic examination enables rapid diagnosis, enabling clinicians to start antifungal treatment right away. Fungal culture is positive in approximately one third to half of the cases, hence histopathology helps to confirm in most cases. Species identification however requires a positive culture. Angioinvasion is the histopathological hallmark of diagnosis. Giant cell invasion, thrombosis, infarction and eosinophilic necrosis of the underlying tissue are characteristic findings⁵.

In our series the total number of cases from May to August 2021 was 263. There was male preponderance. Diabetes mellitus was identified as an important risk factor, 99% cases being Rhino-orbito-cerebral-mucormycosis (ROCM). Very low number of pulmonary cases were found. Several pulmonary mucormycosis cases also might have remained undiagnosed because of challenges in obtaining diagnostic respiratory samples among critically ill COVID-19 patients.

This pattern has also been seen in a series by Patel et al and others. Post-pulmonary tuberculosis and chronic kidney disease have been found to be emerging risk factors based on studies in the Indian population². The disease can affect the Nose, Sinus, Orbit, CNS, Lung, Gastrointestinal Tract, Skin, Jaw Bones, Heart, Kidney, and Mediastinum.

Reported literature states that the Asian continent shows abundance of Rhino-orbito-cerebral-mucormycosis (ROCM) and high frequency of diabetes as the predisposing factor, whereas haematological malignancies and transplantation are the major risk factors in the United States and European countries with pulmonary mucormycosis being the commonest site⁶.

It is important to note that mucormycosis prevalence had increased greatly in COVID times and more so in India (70 times the the world figures) as the hot and humid weather is conducive to fungal growth. Widespread use of cowdung manure may also be a factor. The predisposing factors are different in Europe USA than Asia where diabetes is predominating and mortality pattern is also different as indicated by different studies⁷⁻⁹ (Table 4).

Apparently healthy individuals can get skin-soft

TABLE 4 — *The predisposing factors*

	Pre -COVID	Pre-COVID	Pre-COVID	CAM	CAM
Study	Prakash <i>et al</i> 2019 India	WEBB <i>et al</i> 2018 USA	Skiada A <i>et al</i> 2011 Europe	Patel <i>et al</i> 2021 India	Chatterjee <i>et al</i> 2021 India, West Bengal
Prevalence	14 Cases/Million	0.3 Case /Million	0.12 Cases/Million	0.27% in Admitted COVIDPTS	–
Commonest Predisposing Factors	Diabetes Mellitus 57% Post Pulmonary TB CKD	Stem Cell /Solid Organ Transplant 2-15% Hematological Cancer	Hematological Cancer 38-62% Transplant HSCT/SOT	Diabetes Mellitus Steroid Therapy	Diabetes Mellitus 78.7% Steroid Therapy 57.4%
Commonest Presentation	ROCM Pulmonary	Pulmonary ROCM	Pulmonary ROCM	ROM/ROCM	Rom/ Rocm
Mortality	46%	57%	52-76%	45.7%	26.7%

tissue mucormycosis following traumatic injuries in natural disasters like tornado, tsunami, and roadside accident. Healthcare-associated mucormycosis from contaminated ventilation systems, air conditioners, and ongoing construction in hospitals have been postulated as a risk factor of mucormycosis in the past. However, we could not estimate the burden of Mucormycetes spores in the hospital environment¹⁰.

In Indian patients with COVID-19, DM was seen in 11-23% of the hospitalized patients. New onset DM was seen in 20.6% of patients with mild to moderate COVID-19. The virus is said to damage the pancreatic islet cells producing new onset DM, worsening of pre-existing DM or DKA. The cytokine storm indirectly fuels this by resulting in insulin resistance. Corticosteroids also precipitate hyperglycemia and DKA. Hyperglycemia leads to glycosylation of transferrin and ferritin which affects the capability of transferrin to chelate iron. There is increase in free iron levels helped by an acidic environment allowing mucor to multiply. There is a dysfunction of cellular immunity with impaired chemotaxis, phagocytosis and oxidative /nonoxidative damage performed by neutrophils and mononuclear cells^{11,12}.

In our series 78.7% of patients had DM and steroid therapy was documented in 57.4% cases.

The most common symptoms were fever, nasal discharge, and headache but the loosening of maxillary teeth and jaw involvement were very peculiar feature in our patients and its presence should be considered a point of suspicion in post COVID patients. Diagnosis was confirmed by histopathology in our patients as culture identified the etiologic agent in only 44.1% cases. In our series, the peak was seen between days

twelve to twenty one days with 56% patients developing ROCM symptoms within 14 days from the diagnosis of COVID-19.

Liposomal Amphotericin B had been used in most series with a survival rate of 67% in comparison to deoxycholate that was 60%¹³. Survival was increased to 70% when surgery was combined with deoxycholate¹⁴. In our study Amphotericin B Deoxycholate was used for 4-6 weeks followed by posaconazole oral therapy and the percentage of hypokalemia (93%) hypomagnesemia (32%) and AKI (74%) of the cases was higher than the series by Patel *et al* where liposomal variety was used.

Surgical debridement/de-bulking of necrotic lesion is a very important component of mucormycosis therapy. Surgical debridement improves drug penetration to the infected site and improves the outcome. In our series open surgery had poorer outcome (mortality 60%) than endoscopic debridement in conformation to other studies¹⁵.

Mortality of mucormycosis infection varies between 20 to 50% depending on site of infection and nature of comorbidity. It is nearly 70-90% for cases of disseminated Mucormycosis. Our figure of 26.7% was much less probably because of reporting bias, patients being lost to follow up or the fact that most patients had rhino orbital involvement with better prognosis. Also hospitalized patients are better monitored which leads to better outcome¹⁶.

The overall mortality rate of mucormycosis is high (overall 47%) with the highest mortality in HSCT (76%) recipients. Observed mortality is in patients with hematological malignancy (52%), pulmonary mucormycosis (56%), patients with disseminated

mucormycosis (58%), and diabetic patients (44%)^{17,18}.

A recent multicenter study published from India also reported high mortality of 52% at 90 days follow up, mainly as some patients had left the hospital before initiation of therapy and 14% left against medical advice after initiation of therapy¹⁹.

Limitations of our study were many. Patients were lost to follow up. Confirmation by culture or species identification was not possible and sensitivity patterns could not be studied. Patients received amphotericin B deoxycholate which was an alternative choice due to cost factors. Comparison of CAM and Non CAM was not done.

We also do not have data on the duration of amphotericin B use, timing of surgery, or duration of sequential antifungal therapy, which are critical factors that have a bearing on mucormycosis outcomes.

CONCLUSION

There was a surge of cases during the second wave of COVID-19 that was much higher than the first wave and research is ongoing as to what was the critical factor determining this steep rise. The combination of the delta variant of COVID (that causes more severe disease) along with sudden overwhelming use of steroids after the RECOVERY Trial and COVID Induced hyperglycemia could have been the deciding factors. It is of prime importance to be aware of this entity as prompt clinical suspicion, early diagnosis and treatment improves outcomes. However prevention by proper glycemic control, logical use of immunosuppressants optimal management of COVID-19 and mass vaccination, is vital.

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