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Research Article

Alarming Rise of Mucormycosis After Second Wave of Covid: Who is At Risk?

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ABSTRACT

Introduction: Rhino-orbital Cerebral Mucormycosis (ROCM) is a rare invasive fungal infection that generally affects diabetic and immunocompromised individuals. There has been a recent rise in mucormycosis associated with SARS-CoV-2 infection even in non-diabetics. Diabetes, malignancy, transplant, chronic renal insufficiency and iron overload are established risk factors for the infection. This deadly disease demands prompt diagnosis and management to prevent mortality.

Aims and objectives:

1. To study the risk factors predisposing to mucormycosis in previously non-diabetic patients
2. To study the varied presentations and management of mucormycosis in non-diabetic patients

Material and methods: All the patients of mucormycosis who were admitted from May 2021 to December 2023 and who were previously non-diabetic were included in the study. Risk factors causing mucormycosis were studied. Various forms in which mucormycosis presents and their management were studied.

Result: Fifty SARS-CoV-2-positive patients were studied, and male predominance was observed with mean age being 64 years. All the patients had normal fasting and post-prandial blood glucose levels done within the last three months. 30 patients had recently been diagnosed with deranged blood sugar levels. Four patients were HCV positive; two were HBsAg positive, two were active cases of tuberculosis, two had recently diagnosed chronic renal failure, two patients had acute myeloid leukaemia, two had chronic lymphocytic leukaemia and two were known cases of Inflammatory bowel disease. Two patients had hypothyroidism, on thyroxine treatment for the past 4 years. In two patients, ferritin overload and vitamin D deficiency were found. Only 14/50(28%), received dexamethasone during covid-19 treatment. Ten patients out of 50(20%) had a history of oxygen support. All underwent debridement and received systemic liposomal Amphotericin B therapy. Two patients (4%) underwent skin debridement for cutaneous mucormycosis.

Conclusion: We hereby conclude that the recent surge in cases of mucormycosis was due to multiple factors apart from diabetes alone. We recommend restricted use of steroids (only guideline-based in critically ill patients) and strict monitoring for invasive mucormycosis in post-COVID-19 patients. Additionally, other risk factors that predispose the patients to mucormycosis such as Hepatitis, organ transplant, iron overload, hypothyroidism, and tuberculosis should also be kept in mind.

Keywords: COVID-19; Non-diabetics; ROCM; SARS-CoV-2; Mucormycosis; Risk factors

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Introduction

COVID-19 is a viral illness of the respiratory system that remains a serious public health concern globally. The condition causes typical symptoms such as fever, dry cough, exhaustion, and shortness of breath, and in extreme instances, it may progress to acute respiratory distress syndrome (ARDS)[1]. On the other hand, using corticosteroids to minimize lung damage and death in COVID-19 patients may expose them to opportunistic bacterial and fungal infections.[2]

Mucormycosis, a serious and frequently deadly invasive fungal illness, has gained public attention in reaction to an epidemic of cases in India. Thousands of cases of mucormycosis have been recorded in the aftermath of India's second wave of COVID-19 infections, drawing global attention to this devastating yet overlooked illness. Mucormycosis has been designated an epidemic in eleven Indian states and union territories under the Epidemic Diseases Act of 1897.

It is caused by pervasive environmental moulds with a worldwide distribution, such as Rhizopus, Apophysomyces, Mucor and Lichtheimia. Although the infection is normally innocuous to an immunocompetent host, it may be fatal in patients with weakened immune systems, such as those with haematological malignancies or poorly managed diabetes, or in those on steroids or other immunosuppressants. Structural breaches, such as traumatic cutaneous inoculation, may potentially cause mucormycosis. The disease manifests as a rapidly progressing angioinvasive infection, with the most common presentations being rhino-orbital-cerebral and pulmonary. There are multiple cases of mucormycosis in individuals diagnosed with coronavirus disease 2019 (COVID-19). [3-5] The most commonly reported form of mucormycosis is rhino-orbital-cerebral; symptoms include headache, nasal eschar, facial pain, and/or orbital swelling. Pulmonary mucormycosis infections have been found in COVID-19 patients who develop unexplained lung deterioration or complications. There have also been reports of gastrointestinal mucormycosis. [6-8] According to studies, mucormycosis symptoms normally appear 5 to 14 days after admission for COVID-19, however there have been cases when people were diagnosed with both conditions at the same time. [9-10]

Prompt diagnosis is essential since treatment initiation is time-sensitive owing to the infection's fast growth; however, this is impeded by the scarcity of diagnostic tests available. The diagnosis is based on histology and tissue culture, although biopsy results take at least ten days. There are no serology tests or serum biomarkers available to aid in early diagnosis. Molecular approaches are in development, however they are not widely accessible.[11]

Even after a diagnosis is determined, treatment is difficult. Surgical debridement of diseased and necrotic tissue is required to provide the patient a chance of life; nevertheless, this may cause sight loss, severe disfigurement, or both. Many patients cannot get or afford good antifungal medication, which is another critical component of medical treatment. [12]

Amphotericin B, a nephrotoxic polyene antifungal that has been in use since 1958, is the cornerstone of antifungal therapy. Since liposomal formulations have less toxicity, they are generally too costly or inaccessible in many situations with limited resources. The few available alternatives, such isavuconazole and posaconazole, are too expensive and scarce for most people in the globe. In this study we have discussed some of the risk factors contributing to mucormycosis in non-diabetics and also the varied presentations and management of mucormycosis in these patients. This might help in early diagnosis of this deadly disease so that prompt diagnosis and effective management can be done.

Aims and objectives:

1.To study the risk factors predisposing to mucormycosis in previously non- diabetic patients

2. To study the varied presentations and management of mucormycosis in these patients

Materials and methods:

This was a retrospective study conducted from May 2021 to December 2023 at a tertiary health care centre.

All the patients of mucormycosis who were previously non-diabetic were included in the study. Patients who didn't give consent to participate in the study were excluded. Risk factors causing mucormycosis were studied. Various forms in which mucormycosis presents were studied. The patients had undergone complete general, otorhinolaryngological, ophthalmological examination, blood investigations and radiological imaging. Nasal wash microbiological examination was also done. All the patients underwent endoscopic debridement under general anaesthesia along with local debridement after confirmation of diagnosis. Biopsy taken from the appropriate disease site was sent for microbiological and histopathological evaluation. Liposomal amphotericin B was started in all the patients with proper monitoring of renal function tests. There was no mortality in any of our patients. All the patients are healthy with no disease recurrence till date.

Observation and Results

A total of 50 patients were included in our study. The age group varied from 20 years to 75 years. Mean age was 64 years. It was seen in 30 males and 20 females. All the patients had history of COVID-19 infection.

All the patients were non-diabetic. All the patients had previous records of normal fasting and post-prandial blood sugar levels, performed within 3 months of COVID-19 diagnosis. None of the patients were on insulin or any other oral hypoglycemic agents prior to COVID-19 infection.

Out of the total 50 COVID-19 positive patients, 36 patients were hospitalised (72%) and 10 patients (20%) had a history of oxygen therapy. Fourteen patients out of 50(28%) had a history of intake of corticosteroids. On further evaluation, we found that 30 patients out of 50 (60%) had recently diagnosed deranged blood sugar levels. Physician opinion was taken and regular

insulin was started, dose titrated according to the blood sugar levels. We found that some of these patients had some kind of undiagnosed immune-deficiency state in the body. Four patients were Hepatitis C positive, two were Hepatitis B positive, two were active cases of tuberculosis, two had recently diagnosed chronic lymphocytic leukaemia, two were diagnosed with acute myeloid leukaemia, two were renal transplant recipient patients (on dialysis) and two were known case of Inflammatory bowel disease who were taking corticosteroids for same the condition for past two years but their blood sugar levels were always in normal range. Two patients were case of hypothyroidism, on thyroxine treatment for past 4 years. In two patients, all the routine blood investigations were normal, triple viral marker test was also negative but on further evaluation, ferritin increased level and Vitamin D deficiency was found. (Table-1)

Clinical presentation: Forty eight patients out of 50(96%), which were included in the study presented with rhino-orbito mucormycosis (ROM)(Figure-1). These patients presented with unilateral facial pain, numbness, swelling, nasal discharge and with or without- proptosis, vision loss and palatine mucosa eschar. None of the patients had cerebral symptoms. On clinical examination, crusting was found on one side (20 patients) or both sides (28 patients) of nose. Ophthalmic examination was also done. Diminution of vision and proptosis was seen in 10 patients. Palate was examined in all the patients. Palate mucosa was found to be normal in 30 patients (60%). 16 patients (32%) had unilateral palatal perforation. Four (8%) patients had central palatal perforation involving hard palate and had irregular mucosa of palate.

Two patients (4%) had cutaneous mucormycosis with necrosis involving unilateral side of face.

Diagnosis: A wet KOH mount was sent for all the patients. CT scan nose and paranasal sinus with orbit was done. Contrast enhanced MRI of nose, paranasal sinuses and orbit and brain (Figure-2) was also done in all the patients to know the exact extent of the disease.

Management: All the patients were managed by systemic antifungal therapy. Liposomal Amphotericin B was given in all the patients at the dose of 5mg/kg body weight. Adequate hydration was maintained. Blood investigations including renal function tests, serum creatinine were monitored regularly. All the patients were subjected to endoscopic debridement under general anesthesia and the tissue removed was sent for histopathological examination (Figure-3). The patients in which palatal perforation was present were managed by palatal debridement (20) and inferior maxillectomy (16). Bilateral inferior maxillectomy(4) was done in patients in which there was central palatal necrosis involving both mucosa and bone and there was loosening of teeth on both sides. TRAMB (Transcutaneous Retrobulbar amphotericin B) and orbital exenteration was done in 10 (20%) patients who presented with diminution of vision and in which intraconal compartment of eye was involved in MRI. This helped in relieving pain and reduced the spread of disease. No intracranial involvement was noticed in MRI. Cutaneous mucormycosis was managed by endoscopic debridement along with skin debridement. Primary local flap closure was not done due to risk of secondary infection. Medical management was also done as shown in table. Patients were followed up every week for 4 weeks. All the patients are healthy with no disease recurrence. There was no mortality in any of our patients. (Table- 2 and 3)

Figure-1: Rhino-orbito mucormycosis

Table-1: Risk factors predisposing to mucormycosis

Sr. No.	Risk Factors	Number of patients
1	Hepatitis B	2
2	Hepatitis C	4
3	Hypothyroidism	2
4	Inflammatory bowel disease	2
5	Tuberculosis	2
6	Renal transplant	2
7	High Ferritin and Vit D deficiency	2
8	Recent deranged blood sugar level	30
9	Acute Myeloid leukaemia	2
10	Chronic Lymphocytic leukaemia	2

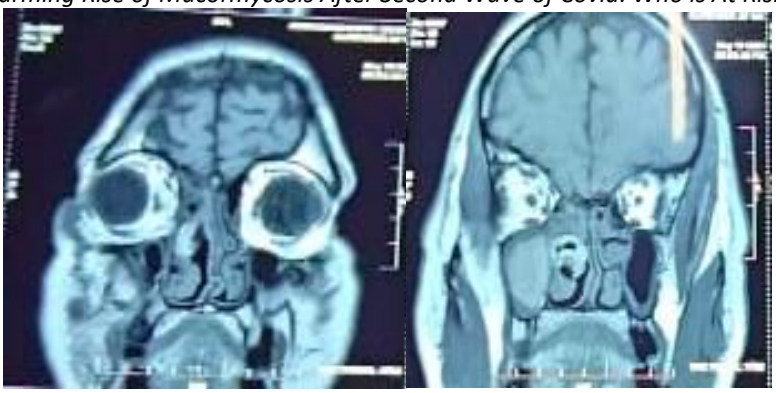

Figure-2: MRI: Proptosis of right eye globe with retro orbital fat stranding and mild pre septal edema along with mucosal thickening in right maxillary sinus? Thick secretions ? fungal etiology

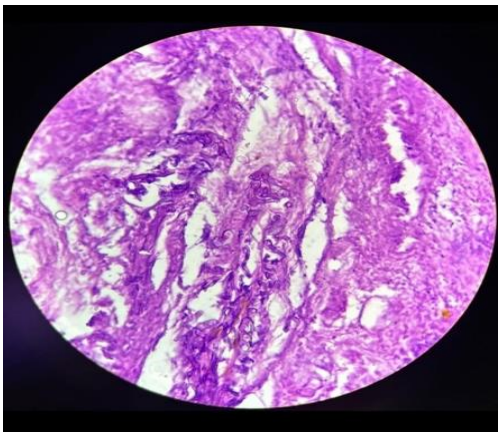

Figure-3: Irregular branching with pauciseptate hyphae in tissue

Table-2: Medical management of predisposing diseases to mucormycosis

Sr. No.	Disease predisposing to Mucormycosis	Management
1.	Hepatitis B	Lamivudine + debridement + Systemic Ampho-B
2.	Hepatitis C	Elbasvir and Grazoprevir + debridement + Systemic Ampho-B
3.	Hypothyroidism	Eltroxine + debridement + Systemic Ampho-B
4.	Inflammatory bowel disease	Corticosteroids + debridement + Systemic Ampho-B
5.	Tuberculosis	Anti-tubercular treatment for 6 months + debridement + systemic Ampho-B
6.	Renal transplant	Dialysis + debridement + systemic Ampho-B
7.	Hyperferritinemia and Vit D deficiency	Iron chelation therapy and Vit B12+ Vit D supplements+ debridement+ Systemic Ampho-B
8.	Deranged blood sugar level	Regular insulin+ debridement + Systemic Ampho-B

Table-3: Surgical management of mucormycosis according to sites involved

Site involved	Management
Nose and Paranasal sinus (48)	Endoscopic Debridement-24 patients
Palate (20)	Palatal debridement-10 patients Inferior Maxillectomy:- Unilateral-8 patients Bilateral- 2 patients
Ocular(10)	TRAMB with orbital exenteration
Cutaneous involvement(2)	Skin debridement

Discussion:

In humans, mucormycosis ranks third in terms of significant causes of invasive fungal infections, after Aspergillus and Candida species. Increasing numbers of individuals with COVID-19 infection have been documented to have mucormycosis; however, not much data is presented for such patient's risk factors, clinical features and management.[13] We present fifty cases of invasive mucormycosis in previously nondiabetic patients with SARS-CoV-2 infections.

This study reported male predominance for mucormycosis (60%) compared to females(40%). Studies conducted by Singla et al. and Anas et al. came to a similar conclusion. In the former, 68.8% of men and 31.30% of females were found to have mucormycosis, while in the latter, 83.3% of males and 16.6% of females were the ones who were diagnosed with mucormycosis.[14-15] A protective function of oestrogen in females as a preventative factor against mucormycosis may be related to the fact that men are more likely to be affected than females. [16] In addition, the age group commonly affected by mucormycosis was between 20 years to 75 years. Mean age was 64 years. This finding was similar to that seen in study by Chaganti et al.[17]

We found that recently diagnosed diabetes, irrational use of steroids and prolonged oxygen therapy were the most attributed risk factors for mucormycosis, accounting for 60%, 28% and 20% patients, respectively. Our findings were consistent with those of Gupta et al. and Patel et al., who found that an elevated sugar level (73.7% patients) and an irrational use of steroids led to prolonged oxygenation treatment (90% patients) as a result of an extended stay in the intensive care unit. [18-19] Recently diagnosed diabetes (Hyperglycaemia) can be due to COVID-19 which affects beta cells of the pancreas and leading to secondary diabetes.[20] Hyperglycaemia impairs the ability of the human body to fight infection by interfering with innate and adaptive immunity by reducing number of dendritic cells in circulation, increasing apoptosis of Natural Killer cells and neutrophilic dysfunction and hence increasing susceptibility to developing mucormycosis.[21-22]. The World Health Organization (WHO) recommends dexamethasone 6 mg daily for 7–10 days for management of severe and critical COVID-19. Corticosteroids have been recommended in the treatment of severe and critical cases of COVID-19 by the WHO after the publication of data from the Oxford RECOVERY trial demonstrated mortality benefit.[23] But these have been used off label for treatment of moderately ill patients also. Glucocorticoids inhibit host immunity through multiple effects, most notably by causing a variety of functional abnormalities in T lymphocytes, polymorphonuclear cells, monocytes and macrophages. Glucocorticoids at high doses have been associated with mucormycosis, especially in patients treated for cancer and those with solid organ transplants.[24] The possibility of mucormycosis in cases of COVID-19 treated with dexamethasone warrants heightened consideration among clinicians. Further, several studies have shown that individuals with severe COVID-19 develop lymphopenia, T cell dysregulation and other immune and cytokine dysregulation. Because Mucorales specific T cells CD4+ and CD8+ are active against mucorales by producing cytokines that could directly damage hyphae, SARS-CoV-2 immune dysregulation could contribute to the risk of development of mucormycosis. Other risks for mucormycosis include the strain on health care system from the sudden surge of SARS-CoV-2 cases. There are numerous reports of rationing medical supplies and the need for improvised supplies in some cases.[25] Hospitals where care demand has exceeded capacity have reported insufficient resources to provide the care of critically ill patients, such as sterile water for the humidification of oxygen. Because non-sterilized water may become colonized with fungus when used for delivery of humidified oxygen, it could add to risk of the development of mucormycosis. [26] Oxygen therapy was given to 10 of our patients. Apart from these, other risk factors in our study predisposing to mucormycosis were Hepatitis B, Hepatitis C, Hypothyroidism, Inflammatory bowel disease, Tuberculosis, Renal transplant and Vitamin D deficiency and high ferritin level. All these are immunocompromised conditions, therefore increasing susceptibility to mucormycosis. Increased ferritin level promotes growth of Mucorales, since iron is required for cell growth and development of humans as well as infective agents.[27-28]

ROM (Rhino-Orbital Mucormycosis) typically originates in the nasal or oral mucosa, spreads to the paranasal sinuses and enters the orbit via the ethmoid and maxillary sinuses or via the nasolacrimal duct. Intracerebral extension(Rhino-Orbital Cerebral Mucormycosis) may occur from the orbit via orbital apex, orbital vessels, or via cribriform plate.[29] In our study 96% patients presented with rhino-orbito mucormycosis (ROM). Mucormycosis resulted in high involvement of nasal mucosa & paranasal sinus(96%). This finding was consistent with the findings found in study by Kumar S et al.[30] Other sites involved were palate(40%) and eye(20%). In addition cutaneous mucormycosis was noticed in only 4% patients.

The initial test in the diagnosis of invasive ROCM is a non-contrast CT scan of the paranasal sinuses. MRI with contrast can be obtained if intraorbital or intracranial spread is suspected. Imaging findings of focal bony erosions or spread out of the paranasal sinuses suggest the diagnosis. Intravenous Liposomal Amphotericin B is the antifungal of choice. Prognosis of invasive ROCM is poor with reported mortality from intracerebral and intraorbital complications exceeding 50%.[31] Nevertheless, there was no fatality in our instances since the disease was diagnosed in a timely manner and the treatment was successful. The treatment consisted of intensive surgical debridement in conjunction with systemic antifungal medication and treatment of associated risk factors.

Conclusion:

Mucormycosis after second wave of COVID is mainly seen amongst immunocompromised and diabetic patients and may present as post COVID-19 complication. The possible pathogenesis of ROCM post COVID 19 in previously non diabetics include immunosuppression caused by unregulated usage of dexamethasone, immune dysregulation caused by COVID-19 and excessive burden on hospitals due to increased demand and limited resources, with the use of same face masks for oxygenation due to limited supply and use of unsterilized water for humidification and presence of other predisposing risk factors such as hypothyroidism, tuberculosis, vitamin D deficiency and hyperferritinemia. So, we recommend that strict monitoring of signs and symptoms of invasive mucormycosis should be done in post COVID patients even in those who are immunocompetent and non-diabetic. Still more research is needed to understand the possible mechanisms.

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