

ORIGINAL RESEARCH

Mucormycosis, Covid -19 & Diabetes “THE TROUBLESOME THREESOME”

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ABSTRACT

Background: Covid-19 infection time and again has been causing major morbidities and mortalities. Increased vulnerability of Covid-19 recovered patients was seen towards mucormycosis infection. Mucormycosis is an aggressive, angioinvasive fungal disease caused by fungi of order Mucorales. This increase in cases may be attributed to a weakened immune system, pre-existing comorbidities such as diabetes, overzealous use of steroids. We conducted a study on 25 cases admitted in mucor ward in a tertiary care setting to highlight this association and focusing on possible causes so that we can be prepared to handle any such catastrophe in future in a better way.

Methods and results: We did a retrospective study on 25 cases admitted in a tertiary care center catering to large population of Covid -19 patients with varying severity. Covid-19 associated mucormycosis(CAM) was found to be more common in males(76%).Diabetes mellitus was the most common underlying condition(72%).68% patients had received steroids and antibiotics , 28% patients had history of receiving Oxygen. In CAM predominant presentation was rhino-orbital mucormycosis. Unilateral orbit involvement was seen in (88%) cases.

Conclusion: As severe acute respiratory syndrome coronavirus-2 is highly susceptible to mutations and is causing series of waves, its association with opportunistic fungal infection is a serious concern. Incidences of mucormycosis were increased in Covid-19 patients due to immune modulation and coexistence of immunosuppressive conditions such as diabetes. Concurrent glucocorticoid therapy further heightens the risk. Early diagnosis and prompt intervention can help improve outcome.

Key Words: Covid-19, diabetes, Rhino-orbital mucormycosis, immunocompromised, Covid associated mucormycosis(CAM)

INTRODUCTION

Covid 19 has caused devastation all over the world¹. India witnessed a second wave in early 2021 which proved to be a major challenge to the already suffering health infrastructure

because of the pandemic. Along with claiming lives myriad of post- Covid complications like persistent weakness, breathlessness, anxiety and panic attacks added to the sufferings of people, then emerged one of the most dreaded aftermath of Covid - Rhino-orbital Mucormycosis^{2,3,4}.

Mucormycosis is a severe but rare disease that is caused by angioinvasive molds Mucormycetes. Immunocompromised individuals like those having diabetes, organ transplant patients, patients on steroids for a longer duration, and patients with hematological malignancies are at major risk⁵. Coronavirus (Covid- 19) causes an immuno-suppressed state thereby increasing the risk of secondary infections like mucormycosis also known as black fungus. Mucormycosis is ubiquitous and is found in soil, air, plants manure and in decaying vegetation. It is transmitted by coming in contact with fungal spores in the environment⁶. Various clinical manifestation depends upon the organ affected because it primarily causes progressive tissue necrosis and infiltration of vascular lamina leading to infarction and thrombosis..Because of high morbidity and mortality associated with Mucormycosis infection⁷and the fact that Covid-19 infection has still not gone and keeps on emerging as waves periodically, has prompted us to conduct a study to evaluate predisposing factors, clinical features, various diagnostic methods, treatment, and outcomes of Mucormycosis in post Covid-19 patients.

METHODS AND RESULTS

We did a retrospective study on 25 patients admitted to the mucor ward in a tertiary care center in Meerut (U.P.) from April –May 2021. All the patients were (RT-PCR) confirmed post Covid patients (14 days after recovery). The diagnosis of Mucormycosis was made based on clinical manifestations, radiological imaging, and confirmation was done by histopathological examination. We evaluated the patients clinical presentation, predisposing factors, lab and imaging findings, management, and other presenting complications.

The age of patients was between 45-60years and the majority of them were males (76%).Diabetes was the most common underlying condition (n=18, 72%).

17 out of 25 patients, (68%) had received steroids and antibiotics as a part of treatment for Covid-19. 7/25 patients (28%) had a history of receiving Oxygen during their hospital stay. Some patients had underlying comorbid conditions like hypertension (16%), chronic kidney disease (12%), Ischemic heart disease (12%), and Malignancy (4%). Common clinical features at presentation were headache, nasal block, ocular pain, black discharge from nose and swelling of lips. Sudden loss of vision was seen as a presenting feature in one of the patients. Unilateral involvement was found to be more frequent in comparison to bilateral (Unilateral in 88%.)

In the majority of the patients (n=19, 76%) predominant presentation was rhino orbital Mucormycosis followed by a rhino-orbital cerebral presentation (n=5) 20%. Nasal endoscopy showed a change in the normal appearance of the nasal mucosa. MRI was done in patients with the suspected intracranial disease, and orbital involvement and in patients presenting with seizures and orbital apex syndrome.

MRI findings in patients with the rhino–orbital involvement were mucosal thickening in sinuses, non-enhancement of turbinate (Black turbinate sign), Involvement of orbital fat and involvement of masticator spaces (retro antral region) (Fig 1-3).

Histopathological examination of the affected tissue showed broad aseptate hyphae and branching at right angles (Fig 4-5).

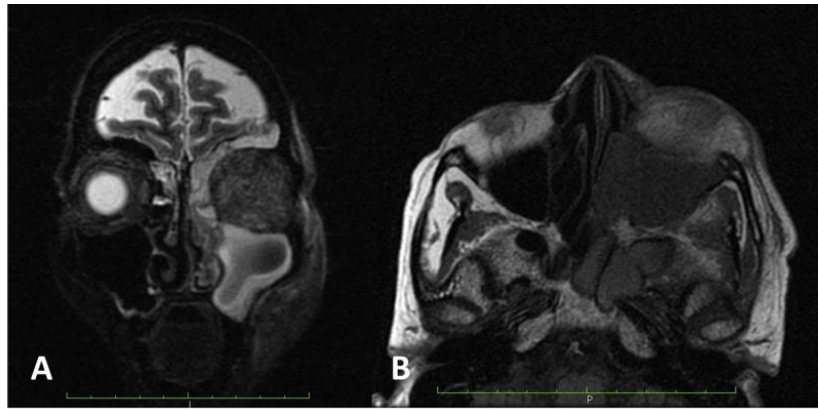


Fig. 1 T2W coronal (A) and T1 W axial (B) MRI reveals mucosal thickening in left maxillary sinus and frontal sinuses



Fig. 2 CEMRI Axial (A) and sagittal (B) reveals enhancing soft tiassue thickening in involving the extraconal fat of left orbit (A) and (B) and enhancing thrombus in left ophthalmic artery (B)

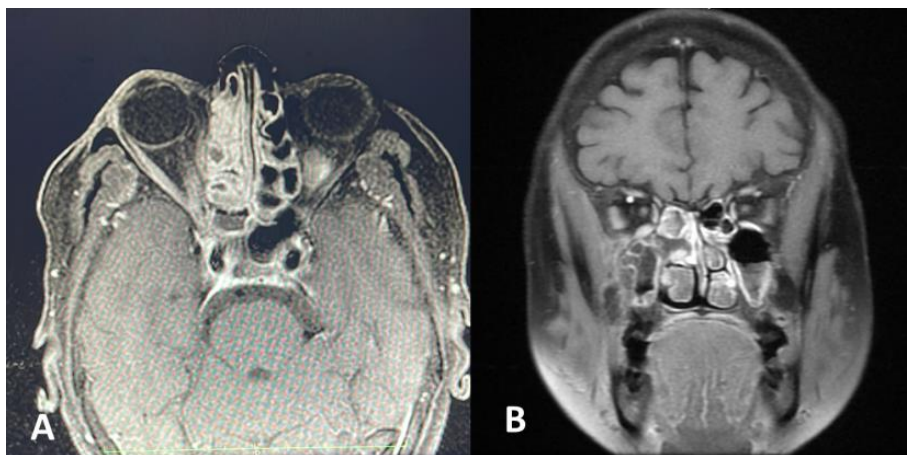


Fig. 3 CEMRI Axial (A) and Coronal (B) reveals enhancing mucosal thickening in ethmoid sinus involving the extraconal fat of right orbit (A) and right maxillary sinus and nasal turbinate (B)

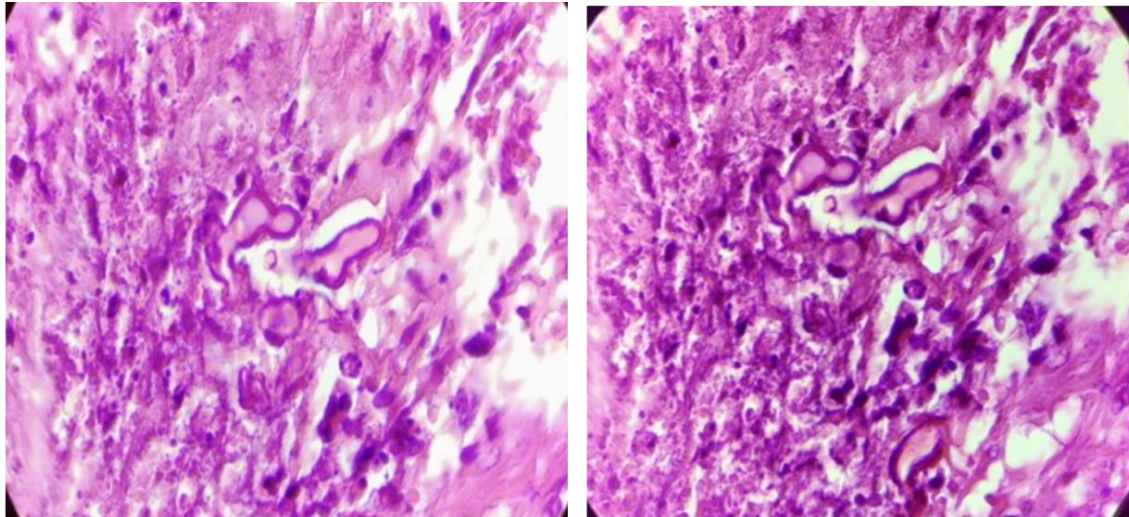


Fig 4.A and B shows numerous broad aseptate fungal hyphae(H&E 40 x)

All these patients underwent routine blood workup, including complete blood count, fasting blood glucose levels, C-reactive protein. Treatment of underlying metabolic disorders was also done. Every alternate day kidney functions and serum electrolytes were monitored. Ophthalmic evaluation was done in all patients. They were treated with surgical debridement of the nose and paranasal sinuses, along with IV amphotericin B. Posaconazole was given to 3 patients in addition to amphotericin B. Despite aggressive multidisciplinary management morbidity in Mucormycosis patients was noted to be high, good prognosis being seen only in patients with limited anatomic disease.

DISCUSSION

The unprecedented rise in Mucormycosis cases was seen during Covid 19 pandemic in India^{3,8}. Covid still continues to cause significant fatalities worldwide. Our study highlights this unfortunate but definite correlation between Covid- 19 and Mucormycosis infection. Sars – CoV-2 infection causes immune dysregulation by reducing the number of T-lymphocytes (CD4+T and CD8+T) cells and also causes alteration of neutrophil to lymphocyte ratio^{9,10}. The use of steroids as a part of a therapeutic regimen further suppresses the immune response¹¹. Steroids also raise blood glucose levels thus causing insulin resistance. They not only exacerbate hyperglycemia in patients with diabetes mellitus but also causes diabetes in patients without documented hyperglycemia even before the initiation of glucocorticoid therapy^{12,13}. In India which is already the diabetic capital of the world and where only a quarter of patients on treatment are euglycemic the prolonged use of steroids created a fertile environment for Mucorales to thrive¹¹.

Even in the precovid era, we had the highest burden of Mucormycosis globally, our tropical and humid climate supports the high load of mucor spores in the air. They can enter the host either through inhalation, percutaneous inoculation, or ingestion¹⁴.

The cooperative interplay of the innate and adaptive immune systems protects the body against any infection. Epithelial damage is often seen in patients of diabetes which promotes the binding of a fungal ligand (Co+H) to host receptors glucose regulator proteins (GRP 78) and induces endothelial cell-mediated fungal endocytosis. Hyperglycemic patients with diabetes and also in patients on prolonged steroids as part of Covid-19 treatment, increase GRP78 amplifies susceptibility towards mucormycosis¹⁵. Also, neutrophil response towards *Rhizopus* hyphae is impaired in hyperglycemia as well as by Covid-19 infection which further increases the risk of these patients to Mucormycosis¹⁶. This explains the deadly triad

of diabetes, Covid-19 infection, and Mucormycosis(CAM)..Further, the use of oxygen therapy in intensive care units in severely sick patients,increased the exposure to moisture thereby increasing susceptibility to fungal infections.

CONCLUSION

As the pandemic still continues and in view of unpredictable nature of SARS CoV2 preventive strategies must include managing the comorbid condition in a high-risk group, judicious use of steroids and antibiotics, understanding the pathogenesis early, and prompt treatment to reduce morbidity and mortality as far as possible, would be key to survival.

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