

RESEARCH ARTICLE

AN EPIDEMIC IN A PANDEMIC: EMERGENCE OF MUCORMYCOSIS POST COVID-19 RECOVERY- CASE SERIES ON A MULTI DISCIPLINARY APPROACH

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ABSTRACT: INTRODUCTION: Mucor mycosis is an Angio invasive mycosis with high morbidity and mortality rates that predominantly occurs in immunocompromised patients. It is commonly reported in immunocompromised patients such as those suffering from uncontrolled diabetes mellitus, blood dyscrasias, malnutrition, neutropenia, iron overload, organ transplant, and immunosuppressive therapy. Diagnosis of Mucor mycosis is made by performing Rapid fungal stains, fungal culture and Histopathological examination of the biopsy / nasal scrapings obtained from the affected site. **CASE PRESENTATION:** We have reported seventeen (17) cases of Mucor mycosis at our hospital in the past 25 days which is between 10/05/2021- 04/06/2021. Out of Out of these seventeen (17) cases, fourteen (14) cases were affecting only the paranasal sinuses causing Acute Invasive Fungal Sinusitis. Three (3) were diagnosed as Rhino- Orbital type. Among the three Rhino-orbital cases, two (2) were Rhino-Orbito- cerebral type (ROCM). Unfortunately, one (1) case succumbed while rest others are undergoing treatment. **DISCUSSION:** A common observation found among all was rampant use of steroids for treating COVID-19 disease and poor glycemic control. Majority of patients were either known diabetic or were diagnosed with Diabetes Mellitus during the course of their current illness. **CONCLUSION:** COVID-19 causes Mucor mycosis through multiple mechanisms. COVID-19 causes alteration of iron metabolism leading to "Hyperferritinemic syndrome" which provides free iron in circulation favoring growth of mucor. Also autopsies conducted indicated widespread severe vascular endothelial injury in COVID-19 than patients died of influenza A, H1N1.

KEYWORD: Covid-19, Mucormycosis, Pandemic, H1N1

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INTRODUCTION :

Mucor mycosis is an Angio invasive mycosis with high morbidity and mortality rates that predominantly occurs in immunocompromised patients. It was first described by Paultauf in 1885. Mucor mycosis is an acute opportunistic infection caused by saprophytic fungus of class Phycomycetes order Mucorales and family Mucoraceae, found in soil, bread molds, and decaying fruits and vegetables. Fungi grow best at warm temperatures and moist climate. The growth of fungi is more prevalent among tropical countries than those in temperate zones. The common temperature for fungal growth is 15-30 degree Celsius with a pH range of 3-7. Fungi require either high sugar or high salt medium. More commonly Asian and African countries are affected by fungal infections and diseases followed by cold countries. The diseases caused by fungal infections are called as fungal sinusitis or in the present context Fungal rhinosinusitis.

Fungal rhinosinusitis (FRS) comprises a spectrum of disease processes, which vary in clinical presentation, histologic appearances, and biological significance. FRS can be acute (aggressive; symptoms <30days), subacute (symptoms 30–90days), and chronic (indolent; symptoms >90days). FRS is most commonly classified as non-invasive or invasive based on whether fungi have invaded into tissue. Non-invasive Sino nasal fungal diseases include: saprophytic fungal infestation, fungal ball, and allergic fungal rhinosinusitis. The invasive forms of FRS include: acute, chronic, and chronic granulomatous. While non-invasive FRS is a serious condition requiring surgical and medical intervention, invasive forms of disease more often result in significant morbidity and mortality, particularly if left untreated.^[7]

Most common species associated with Mucor infections causing sinusitis are Rhizopus, Rhizomucor, Absidia and Cunninghamella. The term rhino cerebral Mucor mycosis (RCM) is used if

the facial, palatal, orbital, paranasal sinus or cerebral regions are involved and the patients generally present with signs and symptoms primarily located in these regions.^[1] The three subtypes of RCM are rhinomaxillary, rhino-orbital and rhino-orbit cerebral Mucor mycosis.

Acute fungal sinusitis is commonly reported in immunocompromised patients such as poorly controlled diabetes mellitus, blood dyscrasias, malnutrition, neutropenia, iron overload, organ transplant, and immunosuppressive therapy.^[2] Early diagnosis and treatment of Mucor mycosis is extremely important due to the aggressive course of the disease.^[3] Control of underlying disease need to be established, metabolic abnormalities corrected and antifungal therapy should be combined with surgical debridement of all necrotic tissue.^[2] Diagnosis of mucormycotic is made by performing Rapid Fungal stains, Fungal culture and Histopathological examination of the biopsy / nasal scrapings obtained from the affected site.

The aim of this case report is to present cases with mucormycosis seen post COVID -19 in order to draw attention to its existence in our environment and to emphasize the need for early diagnosis and treatment as it can get life threatening

CASE PRESENTATION:

We have reported seventeen (17) cases of Mucor mycosis at our hospital in the past twenty five (25)days which is between 10/05/2021- 04/06/2021. Out of these seventeen (17) cases, fourteen (14) cases were affecting only the paranasal sinuses causing Acute Invasive Fungal Sinusitis. Three (3) were diagnosed as Rhino- Orbital type. Among the three Rhino-orbital cases, two (2) were Rhino-Orbito- cerebral type (ROCM) Unfortunately, one (1) case succumbed while rest others are undergoing treatment.

Table 1. Acute Fungal Sinusitis

Limited to Paranasal Sinuses	Limited to paranasal sinuses and orbit	Spread to brain (cerebrum)
14	3	2

During the current ongoing pandemic of COVID-19 across the globe, India was fighting the battle with the popular “double mutant strain” namely, B.1.617 and its variants currently known as delta strain. It was a VOC- Variant of concern possessing a mutation L452R which was also present in the dominant strain of California and E484Q which was first detected in South Africa and Brazil. This wave of pandemic differed significantly from the last wave in various aspects. The strain of COVID 19 virus affected the young and middle-aged population along with the elderly. The infectivity of the strain was very high so that the entire families were infected with one index case in the family. The percentage of population with moderate to severe illness was higher than the last time. In this wave, a large number of patients were developing hypoxia due to the illness reaching the lungs and required hospitalization. Hypoxia was causing rapid fall in oxygen saturation which pointed towards a necessity of hospital bed. The proportion of beds required was definitely higher than the availability and in anticipation of lack of beds steroids were prescribed and used in large numbers. Oral and parenteral steroids were used.

As the COVID-19 peak subsided a little, The ENT and Ophthalmology departments of the hospital saw a sudden surge of patients in the Outpatient department who had recovered from COVID 19 and after eighteen to twenty days of the disease were experiencing headache, facial pain, eyesight related problems and other symptoms suggestive of Opportunistic infection of the local area of head and neck post COVID 19 infections.

The common chief complains that patients presented with are headache, facial pain, facial

swelling, hypoesthesia and anesthesia in areas around eyes and decreased vision. The uncommon symptoms are difficulty in opening mouth, drooping of eyelids, double vision and weakness of limbs. The course of disease was rapid and very aggressive.

The common observations seen among all of these patients during History- taking were 1. persistent hyperglycemic state presenting as uncontrolled diabetes or new onset of diabetes 2. use of steroids for treating the COVID-19 disease as there was significant lung involvement. Some of these patients were admitted to some health-care facility for their treatment whereas others had either video consulted or had self-medicated themselves for COVID-19 on the basis of floating prescriptions as they could not approach a doctor.

Physical examination performed by nasal endoscopy revealed extensive crusting inside nasal mucosa variable in early cases, localized over middle turbinate or nasal septum. In extensive cases, crusting was present all over the nasal cavity. Sensitivity over nasal mucosa was significantly decreased. Often the tissue for examination could be taken without giving any topical anesthesia.

Sometimes only purulent discharge was present inside middle meatus and gets difficult to differentiate from usual sinusitis. Besides crust and ulceration, slough, destruction of turbinates and nasal septum exposing underlying bone and cartilage were also present. One or more symptoms were observed in all of these cases.

Based on the history and clinical presentation, provisional diagnosis of acute fungal sinusitis was made. The biopsies and /or nasal scrapings collected during the procedures were immediately sent to the laboratory for performing fungal stain, fungal culture and histopathological examination. At the same time, all the patients were requested for Gadolinium enhanced MRI scan of PNS , orbit and brain.

The rapid fungal stain performed using 10% Potassium Hydroxide revealed broad aseptate hyphae with obtuse angle branching suggestive of opportunistic infection by *Mucor* species in all of the seventeen samples. The advantage of performing a meticulous fungal stain is early diagnosis and early initiation of treatment of the patients. Critical call alert was sent to the treating physician within no time for initiating rapid action for these patients. After performing the fungal stain, the samples were sent for fungal cultures and Histopathological examination.

The fungal cultures obtained were processed on Sabraud's Dextrose Agar. Ten (10) out of seventeen (17) samples showed positive growth of *Mucor* species within a week's time. On gross examination culture showed growth of fluffy, cottony white, gray or brown hyphae filling the culture container within 24-96 hours. Coarse hyphae had grown with brown to black sporangia. Identification of genera was made on the presence of aseptate hyphae and the structure of sporangiophore. Lactophenol Cotton Blue was used to visualize the microscopic preparation. We could identify *Mucor* species as aerial unbranched and branched sporangiophores arising randomly from mycelia. Sporangia were large and spherical.

Histopathological examination in ten (10) patients on microscopic examination revealed thrombosed blood vessels and blood clots. The necrotic tissue and thrombosed blood vessels are infiltrated by broad hyphae with "floppy" twists and folds that are basophilic on hematoxylin and eosin stain. The outer hyphal walls are slightly refractile with uneven thickness. Septations were absent or erratic but hyphal folding mimicking septations is noted. Hyphal branches form variable angles. On gross examination the tissues received in formalin reveal multiple grey, soft brown tissue pieces with bone.

Images of the *Mucor* species identified in lab Figure 1-4

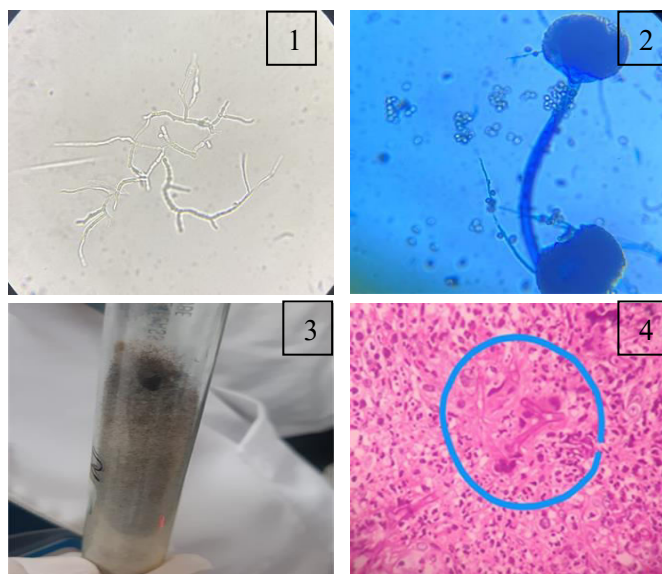


Figure.1 KOH stain of tissue biopsy sample suspected to be suffering from mucormycosis Figure. 2 LCB mount from the fungal culture processed on the tissue biopsy Figure. 3 Histopathological examination of tissue biopsy suspected of mucormycosis Figure. 4 Culture tubes showing Fluffy cottony white growth at the bottom with older colonies exhibiting black spores on the surface

Other laboratory investigations performed for these patients :HbA1C was requested for all of the patients to estimate the long term glycemic control of the patients.

The diabetes was promptly controlled by the suitable preparations of Inj. Insulin. Immediate Anti-fungal treatment was started with Liposomal Amphotericin B or with Posaconazole Inj. : 300mg bid on day 1 and then 300 mg /day for 6-8 weeks.

Administration of Liposomal Amphotericin B is done by first giving a preload of Normal Saline. A test dose of 1 mg in 100 ml D5 over 01 hour. If there is no reaction, a premedication of Inj. Avil 01 amp. Iv stat with Tab Paracetamol 500 mg stat. Followed by a full dose of 3-5 mg/kg/day in 250 ml D5 over 4-6 hours followed by 500 ml of Normal

Saline. Daily monitoring of Serum Creatinine, Electrolytes and Magnesium is performed.

The dose of usual Amphotericin: Test dose: 1 mg IV x1 infused over 20-30 min followed by loading dose of 0.25-0.5 mg/kg IV infused over 2-6 hour. A maintenance dose of 0.25-1 mg/kg IV q Day OR up to 1.5 mg/kg IV QID (may increase gradually by 0.25 mg-increments/day)

These patients were taken up for Radiodiagnosis. Contrast enhanced Magnetic Resonance Imaging was performed which not only helped in confirming the diagnosis but also determined the extent of the disease. All MR scans were performed on 3T Philips MR scanner. Routine imaging sequences dedicated to paranasal sinuses and orbits were obtained. Coronal T1 weighted images with and without fat saturation, Axial and coronal T2 weighted images with and without fat saturation and post contrast axial and coronal T1 weighted images. Additional sequences for evaluation of intracranial extent were performed. FLAIR, DWI and post contrast 3D T1 weighted in axial plane were performed. The diagnosis of invasive fungal disease was confirmed on the basis of loss of normal contrast enhancement in Sino nasal region and/or extra sinus extension of the disease into surrounding space. Figure 5 and Figure 6

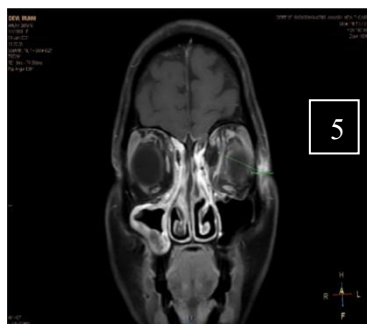


Figure.5 Sagittal view showing Left Orbit Mucor infection. Figure.6 Sagittal view showing non-Enhancing nasal Cavity and Inferior Turbinate

Of the total seventeen diagnosed cases, surgical debridement of necrotic tissues of nasal wall and palate was performed in eight cases (8) keeping in

mind patient's comfort and avoiding any morbidity to the patient. Timely Debridement is of utmost importance as it helps to reduce fungal burden and achieves adequate source control as Amphotericin B may have poor penetration due to the ongoing thrombosis.

Orbital exenteration had to be performed in three [3] patients. Reconstruction by prosthesis will be assessed and planned once the patients will be completely disease free.

Proposed staging of Rhino orbitocerebral Mucormycosis published by Indian Journal of Ophthalmology Table 2.

Table 2. Staging of Rhinorbitocerebral Mucormycosis

StaGe	Site	Treatment proposed
Stage 1	Nasal mucosa	FESS and Anti-fungal
Stage 2	Stage 1 + Paranasal sinuses	FESS and Anti-fungal+ SOS Maxillectomy
Stage 3	Stage 2 + Orbit	FESS and Anti-fungal+ TRAMB/ Exenteration
Stage 4	Stage 3 + CNS	FESS and Anti-fungal +Exenteration+ Craniotomy and debridement

DISCUSSION:

As we have seen the second wave of COVID-19 pandemic caused more severe and serious illnesses, more hospitalizations and more admissions in Intensive care units (ICUs). Due to the associated co-morbidities in these patients and the virulent nature of the virus, many of the patients developed severe bacterial and fungal infections. [8]. Mucormycosis emerged as one of the life threatening infections, others being oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis, blood stream candida infections etc.

Mucor the fungus is ubiquitous, occurring naturally in the environment, the body surfaces and orifices. The spores inoculate the paranasal sinuses and the nasopharynx with subsequent spread to the orbit and to the intracranial cavity in persons with decreased cellular and humoral defenses.

The sudden resurgence of Mucormycosis needed urgent attention and prompt interventions. Besides initiating antifungals and prompt surgical interventions, it was important that emphasis should be laid on correcting the underlying risk factors. In patients with Diabetes and Diabetic ketoacidosis, most common site is ROCM, in neutropenic patients the site is pulmonary and in malnourished patients, gastrointestinal location is most common. In this epidemic we have mostly isolated cases affecting Paranasal sinuses and Rhino-orbital type leading to Acute Invasive Rhino-sinusitis.

CONCLUSION:

Though the exact etiology of sudden increase in the cases of Mucor mycosis is yet to be delineated, many causes and factors are held responsible for the same. There is an increased incidence of infection in diabetic patients, especially diabetic ketoacidosis. Hyperglycemia depletes the immunity of the body. Phagocytosis of leukocytes, neutrophils chemotaxis, and local inflammatory response is depressed in patients with diabetes mellitus. Rhizopus is found to thrive in the ketone-reductase system, glucose-rich medium, and low oxygen tension typical of diabetes. Iron is required for the growth of bacteria and fungi. The use of iron chelator (deferoxamine) makes the iron available in an appropriate form for fungal growth, thus increases fungal virulence.^[7] COVID-19 causes alteration of iron metabolism leading to "Hyperferritinemic syndrome" which provides free iron in circulation favoring growth of mucor.^[4] Also autopsies conducted indicated widespread severe vascular endothelial injury in COVID-19 than patients died of influenza A, H1N1.^[5]

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