Type of Manuscript: Review
Mucormycosis Associated With COVID-19: A Review (Coronavirus: Mucormycosis Cases Spike In COVID-19 Recovered Patients)

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Abstract- *With the onset of the second wave of coronavirus, many new symptoms and associated challenges have come to the surface. A recent report has also identified a rise in the cases of mucormycosis in COVID-19 patients, who are either hospitalised or recovering.Severe coronavirus disease (COVID-19) is currently managed with systemic glucocorticoids. Opportunistic fungal infections are of concern in such patients. While COVID-19 associated pulmonary aspergillosis is increasingly recognized, mucormycosis is rare. We describe a case of probable pulmonary mucormycosis in a 55-year-old man with diabetes, end-stage kidney disease, and COVID-19. The index case was diagnosed with pulmonary mucormycosis 21 days following admission for severe COVID-19. He received 5 g of liposomal amphotericin B and was discharged after 54 days from the hospital. We also performed a systematic review of the literature and identified seven additional cases of COVID-19 associated mucormycosis (CAM). Of the eight cases included in our review, diabetes mellitus was the most common risk factor. Three subjects had no risk factor other than glucocorticoids for COVID-19. Mucormycosis usually developed 10–14 days after hospitalization. All except the index case died. In two subjects, CAM was diagnosed post-mortem. Mucormycosis is an uncommon but serious infection that complicates the course of severe COVID-19. Subjects with diabetes mellitus and multiple risk factors may be at a higher risk for developing mucormycosis. Concurrent glucocorticoid therapy probably heightens the risk of mucormycotic. A high index of suspicion and aggressive management is required to improve outcomes.*

Keywords- Zygomycotic Mucorales Tocilizumab Dexamethasone Diabetes CAPA

Fig: (Black fungus) Mucormycosis

I. BACKGROUND

Coronavirus disease 2019 (COVID-19) is a new disease entity caused by a novel coronavirus (SARS-CoV-2) first documented in China in December 2019 and subsequently causing a worldwide pandemic. While the pathophysiology of the virus is still under investigation, new symptomatic manifestations and complications of the disease continue to be identified and described in medical literature. Mucormycosis and orbital compartment syndrome are rare, time sensitive conditions that must be recognized and treated promptly to avoid mortality and morbidity. Herein I present a case of rhino-orbital-cerebral mucormycosis in a patient who presented to the Emergency Department with altered mental status, proptosis, and COVID-19 infection.[1,2,3,4,5]

II. INTRODUCTION

The pandemic coronavirus disease 2019 (COVID-19) continues to be a significant problem worldwide. While several treatment options have been evaluated, none except systemic glucocorticoids have been shown to improve survival in COVID-19. Unfortunately, the widespread use of glucocorticoids can lead to secondary bacterial or fungal infections. Invasive pulmonary aspergillosis complicating the course of COVID-19 is widely recognized,[6] however, mucormycosis is uncommonly suspected or diagnosed.

Herein, we report a case of pulmonary mucormycosis in a patient with severe COVID-19. We also perform a systematic review of literature to identify cases of COVID-19 associated mucormycosis (CAM) and describe their clinical features, risk factors, and outcome.[7]Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is continuing to spread worldwide with a high proportion of infected individuals needing respiratory support and ICU treatment.[8] Viral infections can cause acute respiratory distress syndrome (ARDS), consequently leading to susceptibility for secondary pulmonary infections. Over the past few weeks, a number of studies have reported on secondary pulmonary aspergillosis complicating severe COVID-19 . Here, we report the first case of a critically ill COVID-19 patient who was diagnosed with pulmonary mucormycosis.[9,10,11,12,13,14]

Mucormycosis:

Mucormycosis, previously known as zygomycosis, is a severe fungal infection caused by a group of molds called mucormycetes. It is prevalent in people who are suffering with a health condition or take medicines that weaken the body's immune system, making it unable to fight germs and viruses. The infection usually affects the sinuses, brain or lungs and therefore can be quite common in people suffering or recovering from COVID-19.[15] Mucormycosis is an infection caused by fungi belonging to the order Mucorales.[16] Rhizopus Oryza is the most common organism isolated from patients with mucormycosis and is responsible for ∼70% of all cases of mucormycosis.[17,18] The major risk factors for mucormycosis include uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns,malignant hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis.[19,20,21] Because of the increasing prevalence of diabetes mellitus, cancer, and organ transplantation in the aging US population, the number of patients at risk for this deadly infection is dramatically increasing.[22] Unfortunately, despite disfiguring surgical debridement and adjunct antifungal therapy, the overall mortality rate for mucormycosis remains >50%, and it approaches 100% among patients with disseminated disease or those with persistent neutropenia.[23] Clearly new strategies to prevent and treat mucormycosis are urgently needed, and such strategies can be facilitated by clear understanding of the pathogenesis of the disease. Invasive fungal infections caused by the members of Mucorales (mucormycosis) are relatively rare but have increased in the last years.[24] These aggressive and highly destructive infections occur predominantly in immunocompromised hosts, especially in patients with haematological malignancies or those receiving hematopoietic stem cell transplantation. Diabetic patients with ketoacidosis and patients with transfusional/dyserythropoetic iron overload are unique risk groups. The difficulties in diagnosis and subsequent antifungal treatment, partly due to a highly intrinsic resistance to many of the commonly used antifungal drugs[25,26] still leads to high mortality rates in certain patient groups.[27] Compared to other fungal pathogens, such as Aspergillus fumigatus or Candida albicans, only little is known so far on fungal properties leading to successful infection and host immune response to the various representatives of the Mucorales.

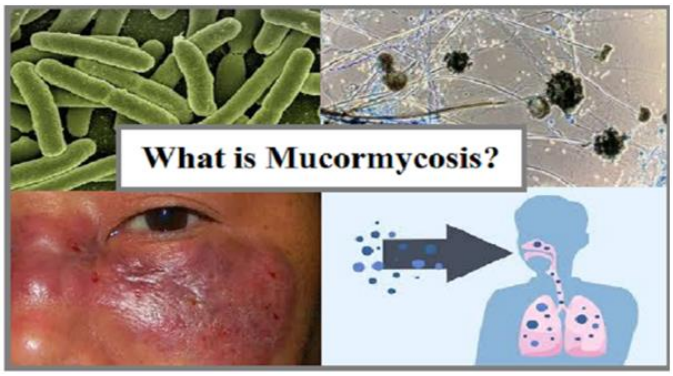

Fig: Mucormycosis

Types of Mucormycosis:

1. **Gastrointestinal mucormycosis:** This type of infection is more common in young children than adults, especially premature and low birth weight infants less than 1 month of age, who have had antibiotics, surgery, or medications. Due to this body's ability to fight germs and sickness gets lowered.
2. **Rhinocerebral (sinus and brain) mucormycosis:** This type of infection occurs in the sinuses and can spread to the brain. Most commonly it is found in people with uncontrolled diabetes and in people who have had a kidney transplant.
3. **Disseminated mucormycosis:** This type of infection spreads through the bloodstream to affect another part of the body. Most commonly, the infection affects the brain, but also can affect other organs like the spleen, heart, and skin.
4. **Pulmonary (lung) mucormycosis:** This is often the foremost common type of infection in people with cancer and in people who have had an organ transplant or a stem cell transplant.
5. **Cutaneous (skin) mucormycosis:** As the name suggests, this infection occurs after the fungi enter the body through a break in the skin like after surgery, a burn, or other types of skin trauma. It is said that this is the most common type of mucormycosis among people who do not have weakened immune systems.

Epidemiology and Pathogenesis:

Diabetics in ketoacidosis are disproportionately affected. In the largest single series to date of 126 patients with rhinocerebral mucormycosis,70% were diabetic.[28] Rhizopus organisms have an active ketone reductasesystem and thrive in high glucose, acidotic conditions.Diabetics also havedecreased phagocytic activity because of an impaired glutathione pathway. The exact mechanism of increased susceptibility of diabetics remainsunknown. Hyperglycaemia or acidosis alone does not permit fungalgrowth in vivo, although acidosis without hyperglycaemia has been reported with invasive mucormycosis.[29]Normal serum inhibits Rhizopus growth, whereas serum from patients in diabetic ketoacidosis stimulatesgrowth.[30,31,32]Boelaert and colleagues have shown that dialysis and iron overloadpatients treated with deferoxamine B (DFO), an iron and aluminum chelator, are more susceptible to mucormycosis. Of 59 dialysis patients withmucormycosis reported through 1991, 46 (78%) were receiving DFO.[33]

Manifestation of disease:

Mucormycosis may have an acutely fulminant course or a slowerindolent invasive course. When the source of immunocompromise isgreat, the rapidity of progression is great, whereas in cases of no or mildimmunocompromise, indolent invasive clinical pictures emerge.Dooley and colleagues described an indolent invasive course in adiabetic patient without granulomatous response who developed sphenoidal ocular syndrome.[34] The diagnosis was not made until 7 weeks afterpresentation, when hyphal elements were found at the third sphenoidotomy. Despite cavernous sinus involvement and carotid artery thrombosis, institution of amphotericin B was curative. Others also have reportedindolent mucormycosis, some of which progressed to carotid involvement.[35,36,37]Cases reported as fungus balls caused by mucormycosis lack fungalculture data or are diagnosed after invasive disease is treated. In any casethey are quite rare. The presence of mucor as a fungus ball in a diabeticpatient warrants surgical removal. The patient probably should be coveredperioperatively with amphotericin B to prevent the development of invasion with the trauma and mucosal breaks that occur with surgery.[38,39,40]Likewise, saprophytic cases may occur. The spores are ubiquitous. Ifa patient has an asymptomatic sporulating mass on a crust within thesinonasal cavity and has no symptoms of invasive disease, particularly noanaesthesia, and there is no source of immunocompromise, then no furthertherapy is required beyond cleaning of the sporulating crust. If the patientis immunocompromised, then follow-up examination is most prudent,although institution of antifungals is not required unless there is someclinical evidence of invasion.Rare cases of allergic fungal sinusitis associated with Mucor specieshave been reported.[41]

The link between Mucormycosis and COVID-19:

SARs-COV-2 virus seems to target the body's immune system. Therefore, the association between the deadly virus and mucormycosis is the state of weakened immune responses in patients. According to doctors and medical professionals, many COVID-19 patients have been exposed to strong drugs ranging from antiviral to steroids, which has led to a diminishing rate of immune system in individuals suffering or recovering from the deadly virus. Additionally,the steroids can also impact the blood glucose levels, especially in those who already have diabetes. These medications in turn promote the growth of fungal infections.[42,43,44,45]

Current situation of mucormycosis in India:

The Central government on Sunday released an advisory for screening, diagnosis and management of mucormycosis or ‘black fungus’ infection that is being widely reported among COVID-19 survivors in the country. According to the Union Health Ministry, mucormycosis is a fungal infection that mainly affects people who are on medication and reduces their ability to fight environmental pathogens. Sinuses or lungs of such individuals get affected after fungal spores are inhaled from air and it may turn fatal if not cared for. The Health Ministry and ICMR that have been in the frontline of the government’s battle against the pandemic have prepared guidelines to prevent or manage the disease.

Sign and symptoms of mucormycosis/black fungus:

- Pain and redness around eyes and/or nose
- Fever
- Headache
- Coughing
- Shortness of breath
- Bloody vomits
- Altered mental status[46]

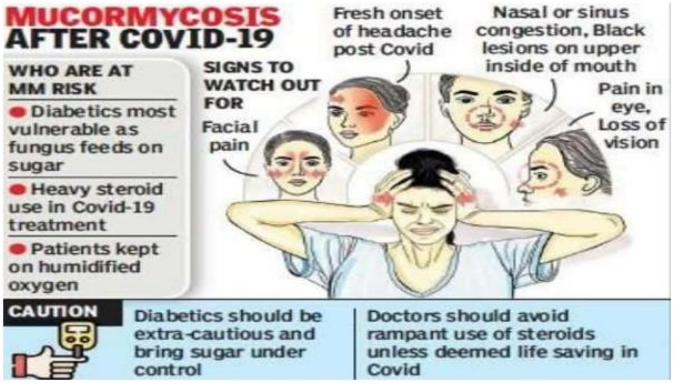

Fig: Mucormycosis after covid-19

Dos:

- Control hyperglycaemia.
- Monitor blood glucose level after COVID-19 recovery and also in diabetics.
- Use steroid judiciously – correct timing, correct dose and duration.
- Use clean, sterile water for humidifiers during oxygen therapy.
- Use antibiotics/antifungals judiciously.[47]

Don`ts:

- Do not miss warning signs and symptoms.
- Do not consider all the cases with a blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on immunomodulators.
- Do not hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDITOF), for detecting fungal aetiology.
- Do not lose crucial time to initiate treatment for mucormycosis.[47]

Prevention mucormycosis/black fungus:

- Use masks if you are visiting dusty construction sites.
- Wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure.
- Maintain personal hygiene, including thorough scrub bath.
- In fungal spores, it is difficult to avoid breathing because the fungi that cause mucormycosis are common in the environment. There is no vaccine to prevent mucormycosis. There are some ways for people who have weakened immune systems to lower the chances of developing mucormycosis.
- Therefore,it is important to protect yourself from the environment. It is noted that these actions are recommended and not proven to prevent mucormycosis.
- Try to avoid going into areas where there is a lot of dust like construction or excavation sites and wear masks.
- It will be better to avoid direct contact with water-damaged buildings and flood water after hurricanes and natural disasters.
- Avoid activities that involve close contacts with soil or dust, like yard work or gardening. If it is not possible then wear shoes, long pants, a long-sleeved shirt, wear gloves, etc.
- Antifungal medication: If there is a high risk of developing mucormycosis and other mold infections in a person then to prevent it, the healthcare providers may prescribe medications. Here to note is that still doctors, and scientists are learning about which transplant patients are at the highest risk and the best way to prevent fungal infections.[48]

Suspect the fatal infection of mucormycosis:
(in COVID-19 patients, diabetics or immunosuppressed individuals)

- Sinusitis – nasal blockage or congestion, nasal discharge (blackish/bloody), local pain on the cheekbone or one-sided facial pain, numbness or swelling
- Blackish discolouration over the bridge of nose/palate
- Toothache, loosening of teeth, jaw involvement
- Blurred or double vision with pain; fever, skin lesion; thrombosis & necrosis (eschar)
- Chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms[49]

Predispositionsof Mucormycosis:

- Uncontrolled diabetes mellitus
- Immunosuppression by steroids
- Prolonged ICU stays
- Co-morbidities – post-transplant/malignancy
- Voriconazole therapy[50]

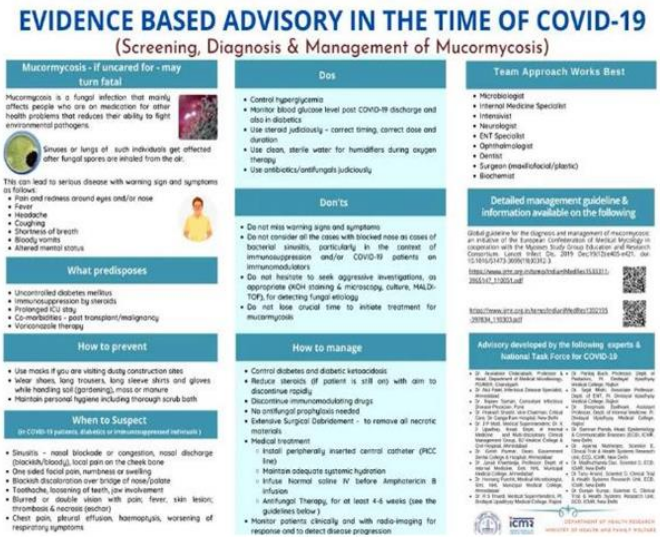

Fig: Evidence based advisory in the time of covid-19

Management of mucormycosis:

- Control diabetes and diabetic ketoacidosis.
- Reduce steroids (if the patient is still on) with the aim to discontinue rapidly.
- Discontinue immunomodulating drugs.
- No antifungal prophylaxis needed.
- Extensive Surgical Debridement - to remove all necrotic materials.[51]

Medical treatment for mucormycosis:

- Install peripherally inserted central catheter (PICC line).
- Maintain adequate systemic hydration.
- Infuse normal saline IV before Amphotericin B infusion.
- Antifungal therapy, for at least 4-6 weeks (follow guidelines).
- Monitor patients clinically and with radio-imaging for response and to detect disease progression.[52]

Mucormycosis consult by:

- Microbiologist
- Internal Medicine Specialist
- Intensivist Neurologist
- ENT Specialist
- Ophthalmologist
- Dentist Surgeon (maxillofacial/plastic)
- Biochemist[53]

Black Fungus Cases Surge Across Gujarat, Maharashtra; Experts Detail Symptoms & Treatment:

COVID- induced black fungus or cases of mucormycosis are on the rise among COVID-19 survivors. Health officials in Gujarat and Maharashtra have alarmed this can lead to causing blindness or other serious issues. At least eight COVID-19 survivors have succumbed to this fungal infection in Gujarat. Black Fungus has been seen as a post-coronavirus complication seen in COVID-19 survivors and has been on the rise in Gujarat, even crossing the 100-mark. The State governments have also set up separate wards for the treatment of Black Fungus. Cases of mucormycosis are serious but it is a rare fungal infection that can additionally weaken COVID-19 patients. This is so because black fungus can be a fatal or further cause of diseases not only for transplant recipients but people in ICUs or those who have long-term immunodeficiency concerns.[43]Dr Tatyarao Lahane who heads the Directorate of Medical Education and Research (DMER) said to PTi that mucormycosis is a serious fungal infection that is found among people with a low level of immunity as well as among those suffering from chronic diabetes, or those who have gone through a kidney transplant among others. Dr Lahane also said the fungal disease is already known but the cases are increasing because of COVID-19 related complications, wherein the use of steroids elevates the sugar level in blood while some medicines result in suppression of immunity of patients.

"Though this fungus is present in the environment, people with suppressed immunity as well as who have received steroids during COVID-19 treatment are more susceptible to it. COVID-19 patients with co-morbidities are also vulnerable and can catch the infection early."

III. CONCLUSION

In conclusion, COVID-19 is considered an explanation for severe immunosuppression which may increase the danger to develop opportunistic infections. Early detection of symptoms for mucor like cheek swelling, blackening etc got to be reported immediately. Furthermore, if a CT scan finds a mucormycosis fungus, then there's a gold standard treatment and also removing dead tissue through surgery. Clinical suspicion and prompt treatment are fundamental to realize the cure of the disease. However, there are no reports of mucormycosis associated with COVID-19. Our patient was diagnosed with rhinoserebral mucormycosis after COVID-19, wedon't know whether the cause of death was invasive mucormycosis. More studies are necessary to determine if these two pathologies are related.

IV. ACKNOWLEDGEMENT

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V. ABBREVIATIONS

CAM:	COVID-19 associated mucormycosis
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus-2
ICU:	Intensive care unit
ARDS:	Acute respiratory distress syndrome
DFO:	Deferoxamine B
ICMR:	Indian Council of Medical Research
KOH:	Potassium hydroxide
MALDITOF:	Matrix-assisted laser desorption/ionization time Flight mass spectrometer
PICC:	Peripherally inserted central catheter
DMER:	Directorate of Medical Education and Research

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