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A Review on Mucormycosis in a Clinical Microbiological Dilemma

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ABSTRACT:
Mucormycetes are a type of rare but opportunistic fungal pathogen that can cause serious and sometimes fatal fungal infections, including mucormycosis. During the second wave of the catastrophic COVID-19 epidemic, which occurred in India between April and June of 2021, mucormycosis, also known as black fungus, caused extreme disruption due to its abrupt and destructive surge that resulted in up to 50% mortality rate.People with diabetes who have recovered from COVID-19 infection have been found to be more susceptible to mucormycosis. However, in order to understand the pathophysiology and pathological components of this lethal infection and to find appropriate prophylactic and therapeutic measures, it is necessary to examine the exact cause and mechanism(s) driving its rise.
The indiscriminate use of zinc, steroids, and antibiotics as self-medication during the COVID-19 pandemic is thought to have contributed to gut microbiota dysbiosis, which has been linked to immune suppression and increased susceptibility to mycotic diseases in the risk group. Given this scenarios, this timely article makes an effort to consider and talk about a few probable contributing elements and mechanisms that might aid in understanding and explaining the mystery surrounding the unexpected, sharp, and lethal spike in mucormycosis infections during the second wave of the COVID-19 pandemic.

Keywords: Black fungus,COVID-19,Dysbiosis,Fungal infection,Gut Microbiota, Mucormycetes, Mucormycosis, SARS-CoV-2, Steroids.

INTRODUCTION:

Mucormycosis (also called zygomycosis) is a rare infection caused by organisms that belong to a group of fungi called Mucoromycotina. At one time these fungi were called Zygomycota, but this scientific name has recently been changed. Usually found in the soil, these fungi are associated with organic debris that is decomposing, such as old wood, compost piles, and leaves. Mucormycosis is a rare infection[1]. Although it happens infrequently in generally healthy individuals, the illness is more common in those with compromised immune systems. A susceptible individual comes into contact with the spores of mucormycosis in the environment.This contact can happen at the skin (spores can enter through cuts, abrasions or wounds) or respiratory mucosa (through inhalation). The fungus is ubiquitous, and the spores are commonly found in the surrounding environment. This disease is not contagious and cannot be transferred from person to person or between people and animals. [2]

Types Of Mucormycosis:

- Rhino-Orbito-Cerebral Mucormycosis (Rocm)
- Pulmonary Mucormycosis
- Gastrointestinal Mucormycosis
- Cutaneous Mucormycosis
- Disseminated Mucormycosi

HISTORY:

mucormycosis was described by Friedrich in 1885, as an infection from nonseptate, broad, branching hyphae typical of molds.Sluyter's description in 1847 of a case of pulmonary mucormycosis was the first instance of Mucorales infection in humans.

In 1943, the syndrome of acute orbital mucormycosis characterized by uncontrolled Hyper glycaemia , unilateral internal and external ophthalmoplegia, proptosis, and rapid death was first described by Gregory.[3]

BURDEN

Currently India is having the second largest Covid affected population in the world with more than 2.65 crore cases as on 24th May 2021. India is also the diabetes capital of the world with nearly 7.7% of adult population being diabetic. More than 6.5 Crore people in India are diabetic (this was 2016 global burden of disease data published in lancet in 2016). Covid-19 Associated Mucormycosis, Recent times has witnessed increased cases of Mucormycosis in India. These are Covid-19 associated mucormycosis and mostly they are seen in post covid diabetic population.[4]

According to the Central government a total of 40824 mucormycosis cases have been reported across the country out of which nearly 3229 patients have Yield to the disease. Nealry 28186 patients are still under treatment for the same, meaning that 31% patients have been cured till date. Very few case studies or case series have been published as of now related to Covid-19 associated mucormycosis and a review conducted in May 2021 suggested 101 cases worldwide which is only a fraction of actual cases. The article also mentions that nearly 80% are being observed in males and nearly 80% have pre-existing diabetes mellitus. The associated mortality was nearly 30%.Reports from various statesRecent times has witnessed increased cases of Mucormycosis in India. More than 1,000 cases of mucormycosis have been reported as of mid-May 2021, while the exact number of infections is unknown. AIIMS Delhi is home to 23 instances of mucormycosis, 20 of which are COVID-19 positive, and over 500 cases from other states. Reportedly, such cases are reported from Gujarat, Uttar Pradesh and Rajasthan too with associated mortality reported from Jabalpur in Madhya Pradesh and Thane in Maharashtra. Jabalpur reported three mucormycosis-related deaths between May 1 and May 10, 2021.About 10 people have lost vision while 40 others were undergoing treatment in Bhopal, Indore, Khandwa, Jabalpur, and Gwalior. From the eastern part of country, Odisha also reported its first case of COVID-19 related mucormycosis around 10 May 2021.[5]

Order Mucorales –Mucormycosis :

(a) Rhizopus arrhizus (old name R. oryzae)
(b) R. microspores var. rhizopodiformis
(c) Mucor racemosus
(d) Rhizomucorpusillus[6]

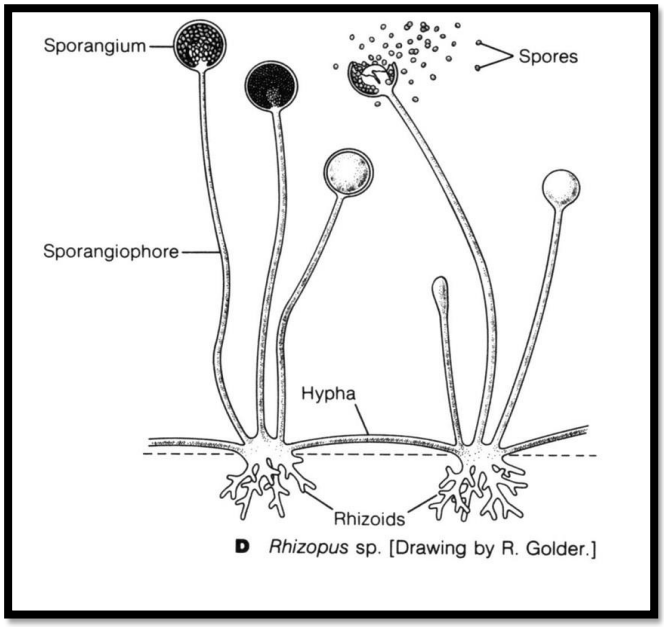

Fig. 1. Parts of Rhizopus Species.

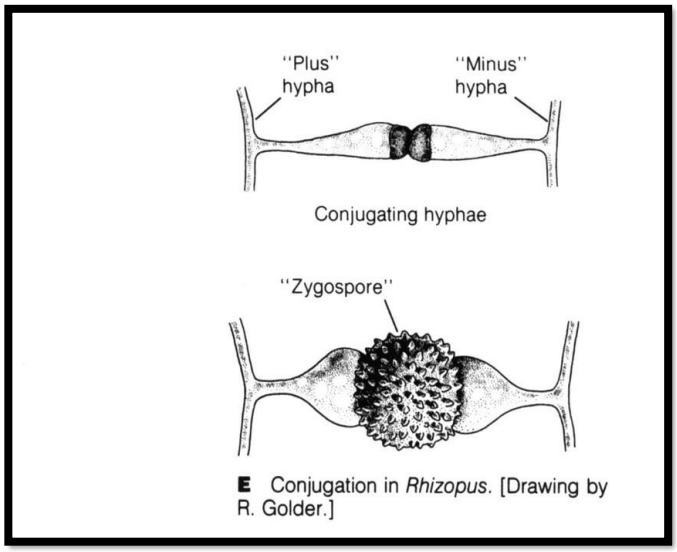

Fig. 2. Sexual Reproducation in Rhizopus Species.

Mucormycetes, the group of different types of fungi can cause mucormycosis. The most common causative agents are Rhizopus species and Mucor species. Other causative fungi are Lichthemia, Rhizomucor, species, etc. Belonging to the scientific order Mucorales, these mucormycetes live throughout the environment. The main way that humans get infected is through inhaling sporangiospores; contaminated food or traumatic inoculation are also occassionally used.They are more common in soil with decaying organic material, compost piles animal dung, and also present in the air. [7]

RISKFACTORS

Population at risk- All those who have lowered immunity are at an increased risk as this is an opportunistic infection. The list can include people who have the following. [8]

- Post COVID-19 recovered population

- Uncontrolled hyperglycaemia with or without diabetes mellitus
- Immunocompromised patients
- Organ transplant
- Stem cell transplant
- Iron overload (COVID-19, Bone-marrow transplantation, hemochromatosis
- Intravenous drug abuse
- Skin injury due to surgery, burns, or wounds
- Tuberculosis
- Patients living with Human immunodeficiency virus
- Chronic kidney disease
- Hepatitis-B and other Chronic Liver diseases • Chronic alcoholics and smokers
- Cancer Chemotherapy
- Prolonged ICU stay
- Immunosuppressive therapy as part of COVID-19 treatmentDiabetes, especially ketoacidosis
- Long term use of systemic steroids
- Old age
- Organ or stem cell transplantation
- Iron overload
- Any types skin Disease
- Broad-spectrum antibiotics
- Intravenous drug abuse
- Fungal endothelial interactions [9]

CLINICAL FEATURES

The general early warning signs and symptoms for mucormycosis are:

- Pain and redness around eyes and/or nose (PNS)
- Fever
- Headache
- Coughing
- Shortness of breath Acute Haemorrhage (Bleeding from the palate/gums, Hemoptysis, Blood in vomit/stools)

(1) Rhinocerebral Mucormycosis

Rhino ocular cerebral Mucormycosis (ROCM) is the most common form, and it is often seen in patients with diabetic ketoacidosis or with uncontrolled diabetes mellitus . A study from India reported that 88% of the patients with ROCM had diabetes mellitus. A similar finding was reported from the United States, where 83% of the patient had diabetes mellitus. Most commonly, it spreads from nasal mucosa to turbinate bones, paranasal sinuses, orbit and palate with eventual extension into brain where massive invasion of blood vessels causes major infarct.[10,11]

- Nasal congestion
- Nasal discharge
- Localized pain
- Facial swelling or numbness

- Headache or orbital pain
- Loosening of maxillary teeth
- Jaw involvement

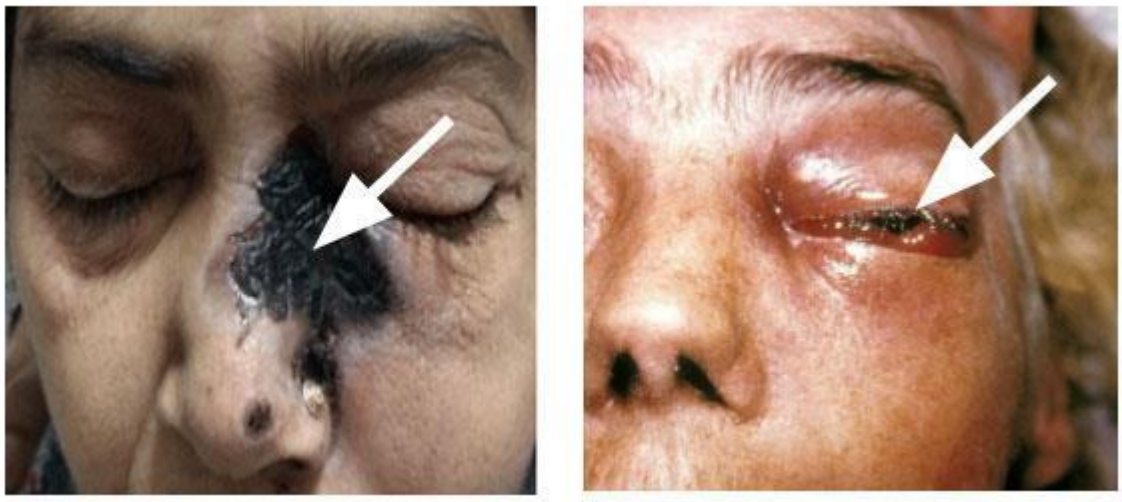

Fig. 3. *Rhinocerebral Mucormycosis*

In COVID 19 settings the most common presentation is either rhino orbital or Rhinoorbito-cerebral (ROC) Mucormycosis. The patients can be categorized as Possible (Suspected), Probable, and Proven (Confirmed). [12]

1. A patient who has symptoms and signs of rhino-orbital or ROCM in the clinical setting of concurrent or recently treated COVID-19, diabetes mellitus, use of systemic corticosteroids, mechanical ventilation, or supplemental oxygen to be considered as Possible ROCM. [13]
2. A patient with clinical symptoms and signs of rhino-orbital or ROCM supported by CT scan, or contrastenhanced MRI, diagnostic nasal endoscopy findings, the patient to be considered as Probable case.
3. A probable case with microbiological confirmation of tissue sample on direct microscopy (KOH mount) or culture or histopathology with special stains is to be taken as confirmed case. [14]

Clinical Progression

Stage 1: Infection of nasal mucosa and sinuses
Stage 2: Orbital Involvement - Superior orbital fissure syndrome; and Orbital Apex Syndrome
Stage 3: Cerebral Involvement - spread through Opthalmic artery; Superior Orbital Fissure /Cribriform plate. [15]

2. Pulmonary Mucormycosis

The mucormycetes may present as pulmonary disease through inhalation of sporangiospores. The patients are severely immunocompromised by virtue of an absolute lack of circulating neutrophils, secondary to hematologic malignancy like leukemia, lymphoma, profound immunosuppression or bone marrow transplantation. [16]

- Chest pain
- Hemoptysis

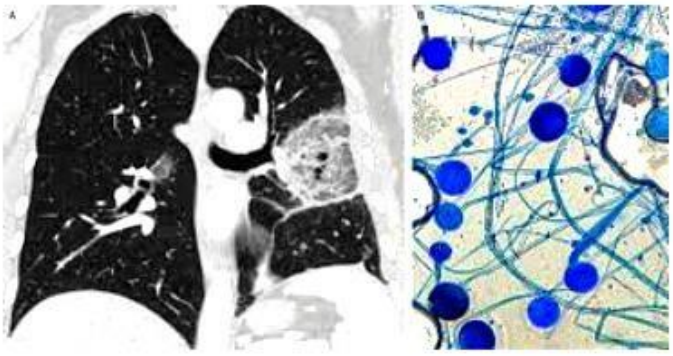

Fig.4 ***Pulmonary Mucormycosis***

3. Cutaneous Mucormycosis

In their early stages, lesions resemble ecthyma gangrenosum; cotton-like growth may be seen over surface of tissues, a clinical sign known as 'hairy pus'. The cutaneous type of mucormycosis can be either primary infection or secondary to the disseminated form. [17] • Ulcers

• Black infected area with pain, redness and warmth around the wound

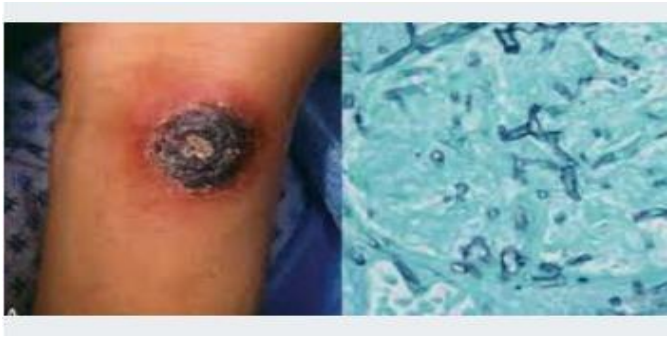

Fig. 5 ***Cutaneous Mucormycosis***

(4) Gastrointestinal Mucormycosis

The gastrointestinal mucormycosis occurs rarely accounting for ~7% of all cases of mucormycosis, most often involving stomach. It is primarily found among patients suffering from extreme malnutrition and is believed to be acquired by ingesting food contaminated with fungal spores. [18]

- Abdominal pain
- Nausea and vomiting
- Gastrointestinal bleeding.

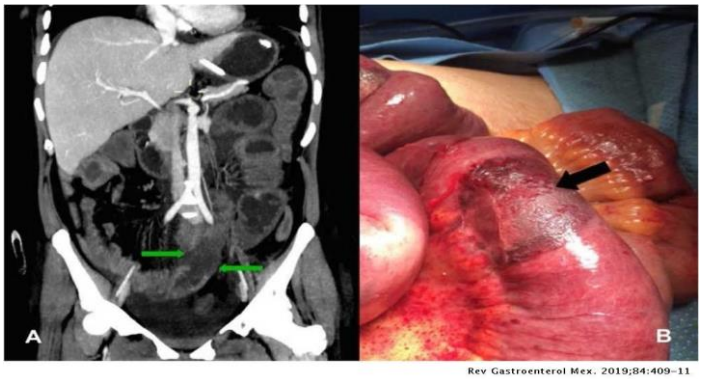

Fig.6 ***Gastrointestinal Mucormycosis***

(5) Disseminated Mucormycosis

The mucormycetes may become widely disseminated affecting lungs, kidney, gastrointestinal tract, heart and brain however lungs being the most commonly involved site. The clinical syndromes most frequently reported include pneumonia, stroke, subarachnoid hemorrhage, brain abscess, cellulitis or gangrene of a skin structure. [19]

- In this form, the infection spreads to other areas of the body and becomes widespread (disseminated)
- If infection is disseminated to the brain and patients can present with altered sensorium or coma
- Other areas that can be affected include the heart, kidney, spleen, skin, and other organs.

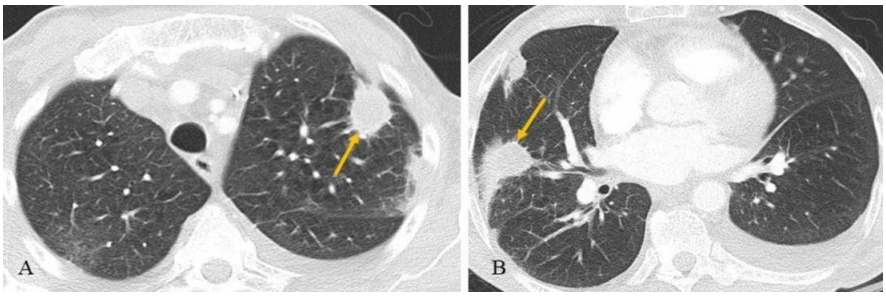

Fig. 7 ***Disseminated Mucormycosis***

DIAGNOSIS:

Mucormycosis diagnosis is Difficult. The laboratory diagnosis of mucormycosis is slightly Challenging because of rapid and fulminating course of disease and doubtful significance of isolates, which are usually encountered as laboratory contaminants. Therefore, detection of fungus in tissues is supplemented to establish reliability of cultural isolate . The detection of circulating antigen such as galactomannan and β-D-1,3glucan provides no help for mucormycosis diagnosis. [20]

Radiodiagnosis

It has been established that CT and particularly MRI are most helpful in enabling an early detection of orbital, sinus, meningeal, intraparenchymal, cerebral lesions as well as intracranial vascular occlusion, even before clinical signs develop. [21]

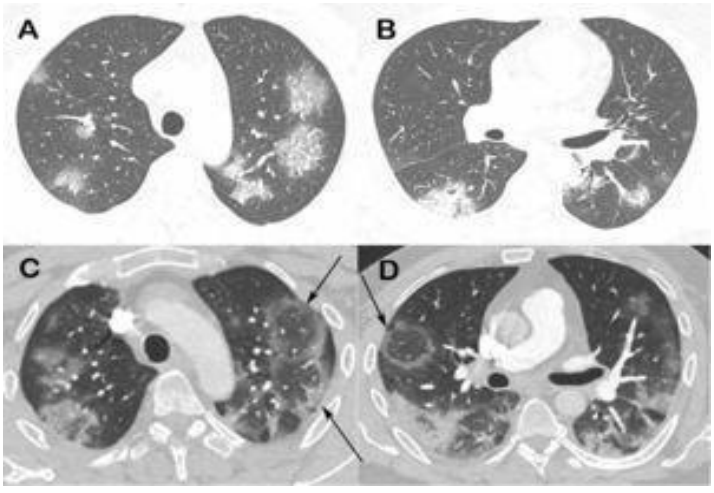

Fig.8 *Chest computed tomography images of a 48-year-old man with confirmed COVID19 pneumonia. mages obtained at the levels of the upper (a) and lower (b) lobes two days after symptom onset show bilateral round and oval ground-glass opacities. Enhanced images (c and d) obtained at the same levels as Fig. 9a and b, three days later show multiple reversed halo signs (arrows) in both lungs.* [22]

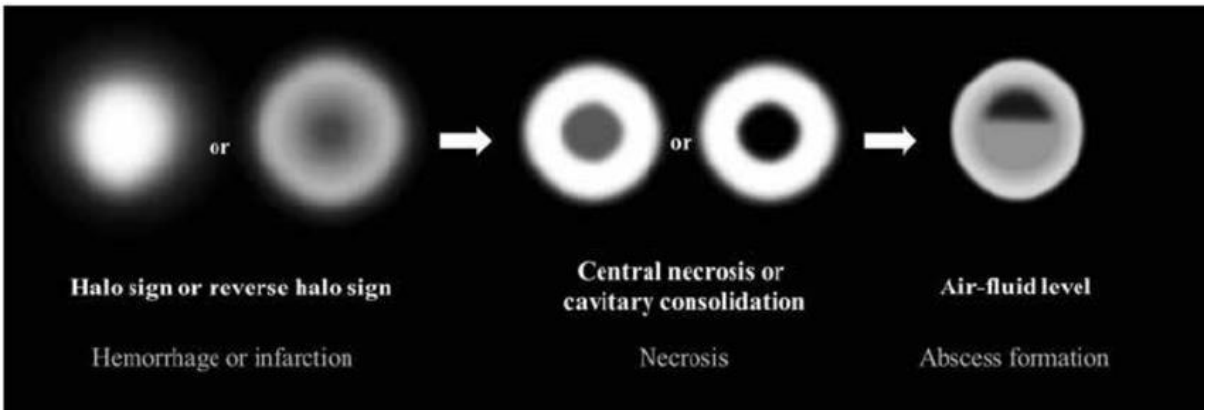

Fig.9 *Initially, the halo sign on CT which represents focal consolidation with adjacent ground-glass opacity, develops due to hemorrhage caused by the angioinvasive characteristics. Thereafter, the reversed-halo sign may be seen. After disease progression, internal infarction causes central ground-glass opacity with peripheral consolidation. Necrotic or cavitary consolidation or masses may develop due to necrosis followed by abscess formation with an internal air-fluid line.* [23]

Nasal Endoscopy

Black eschar present in meatus which is painless on removal with no or minimal bleeding. [24]

Nasal Endoscopic Examination

- Black Necrotic tissue and eschar Blood tests **Blood tests**
- CBC (Look for neutropenia / monocytopenia, Raised ESR)
- FBS, PPBS, HBA1C
- LFT, RFT with electrolytes
- HIV, HBsAg

Radiographic imaging

- X-Ray PNS (Para Nasal Sinuses) and OPG (Ortho-Pantomogram) – can be normal
- CECT of PNS and Orbit – Erosion and thinning of hard tissues, mucosal thickening of sinuses, enlargement of masticatory muscles
- Contrast MRI – Optic neuritis, intracranial involvement, CST, Infratemporal fossa involvement
- Nasal endoscopic examination (if available): Black necrotic eschar tissue Radiographic Examination: X- Ray PNS and OPG may be normal
- Contrast enhanced CT scan with 3D Reconstruction findings and MRI with contrast for assessment of disease extent HRCT Chest - Reverse halo sign: nodule (≤3 cm)/ mass (>3 cm) or consolidation with surrounding groundglass opacity halo, central necrosis and air-crescent sign. [25]

Biopsy

Nasal cavity for ROCM, if palatal involvement then biopsy from oral cavity, Transbronchial biopsy and BAL (for Pulmonary). CT guided FNAC can be considered in some cases of Pulmonary Mucormycosis. [26]

Histopathology

Broad ribbon-like, thin-walled, primarily aseptate or pauci septate hyphae that have irregular diameters; with non-dichotomous irregular branching and accompanying tissue necrosis and fungal angioinvasion. (Grocott Methenamine Silver GMS and Periodic Acid-Schiff PAS stainsLaboratory Investigations: CBC, ESR, FBS, PPBS, HbA1C, LFT,

RFT with electrolytes, HIV, HbSAg, CSF (if indicated)

Biopsy: Oral cavity: Biopsy from deeper portion of extracted tooth socket/exposed bone

Nasal Cavity: Nasal endoscopy and crust sampling

Checklist of sentinel signs and symptoms to be monitored in admitted Covid-19 patients or post-Covid follow up:

1. Nose and sinuses Mucor infection (relatively early disease). Early detection at this stage can enable early treatment and minimize complications. [27]

- Headache and nasal obstruction especially if persistent and severe and not responding to pain medicines
- Nasal crusting and nasal discharges which could be brownish or blood tinged
- Pain or loss of sensation over face
- Discoloration of skin of face/localised facial puffinace
- Loosening of teeth/discoloration or ulceration of palate or bridge of nose
- Erythematous to violaceous to black necrotic eschar in nasal cavity Sinusitise [28]

PREVENTION:

Use of steroids and broad-spectrum antibiotics in COVID-19, coupled with uncontrolled hyperglycaemia has found to have increased the incidence of mucormycosis. Mucormycosis can be seen in both active COVID-19 patients and in postrecovered individuals. Case fatality rates of mucormycosis according to previously reported data are as high as 50-70% and hence, prime importance should be laid on preventing the occurrence of this disease and eliminating all the risk factors leading to the infection in future. Per reports, prevalence of CAM is more among patient with diabetes. Hyperglycaemia affects the immunity and also provides favourable environment for the growth of fungi. [29]

Primary Prevention

- Proper usage of masks (universal)
- Avoid activities that involve contact with soil or dust, such as dusting or yard work or gardening
- Hand-hygiene is a good way to avoid transferring infection from hands to the respiratory mucosa
- Proper wound care (Surgical dressing, usage of antiseptic, debridement)
- Strict glycaemic control and regular blood glucose monitoring
- Strict adherence to Anti-Diabetic medications
- Post COVID follow up and daily blood glucose monitoring in previously nondiabetics as well
- Diet and Lifestyle modifications for preventing Diabetes
- Cessation of smoking and alcohol
- Avoidance of self-medication

- Compulsory Health education to patients suffering from Covid-19 and those who have been discharged from either home isolation or facility-based treatmen Information dissemination, Risk communication and Health education to public on early warning signs and symptoms
- Mass chemoprophylaxis is currently not recommended
- Currently no vaccine is available for prevention of Mucormycosis
- PNS endoscopy in post COVID-19 patients who are at increased risk of development of mucormycosis (such as uncontrolled diabetics) for two months
- Judicious use of antibodies/ antifungals and steroids Early detection of mucormycosis as well as risk factors/ associated comorbidities can help prevent severe form of disease, disability, invasive treatment and death.
- Stress on universal case definition, methods of diagnosis and treatment
- Continued education of treating physicians, surgeons, oral and dental surgeons, pathologists, radiologists, and microbiologists regarding mucormycosis
- An Integrate Disease Surveillance Program (IDSP) based surveillance system to identify the burden of disease in the country. [30]

DOS

- Control hyperglycemia
- Monitor blood glucose level post COVID-19 discharge 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.

DONTS

- Do not miss warning signs and symptoms
- Do not consider all the cases with 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 etiology
- Do not lose crucial time to initiate treatment for mucormycosis. [31]

HOW TO MANAGE

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

Medical treatment

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 (see the guidelines below) Monitor patients clinically and with radio-imaging for response and to detect disease progression.

TREATMENT

Mucormycosis therapy can be divided in four concomitant approaches. These are Rapid correction of underlying predisposing factor of the host like diabetic ketoacidosis Surgical debridement of necrotizing tissue if this is feasible Antifungal therapy Consideration of adjunctive therapy such as hyperbaric oxygen.

The combination of surgical debridement and antifungal drugs is required for an ideal treatment of mucormycosis.

It should be preferably done under general anesthesia taking adequate healthy tissue for debridement. Simultaneously management of underlying risk factor, if any, is also essential.

Surgical debridement is the mainstay of therapy for cutaneous mucormycosis and topical amphotericin B is a useful adjunct in concentration of 5 mg/ml, which is applied with a gauge.

In case of posaconazole, it should be kept in mind that the drug becomes effective after a fortnight or so. There is no oral chemoprophylactic agent available for this fungal disease.

Cytokines such as interferon-γ and granulocyte-macrophage colony-stimulating factors (GM-CSF) have also been used to treat mucormycosis [8, 26] Fluconazole, voriconazole, echinocandins (caspofungin, anidulafungin, micafungin) or 5 flurocytosine is not active against mucormycosis. [34]

FIG Treatment of COVID associated mucormycosis(fungal infection study forum recommendation)

Medical management:

1. Mucormycosis should be treated with Injectable antifungal Amphotericin-B for 2- 3 weeks on clinical suspicion & as per severity even while awaiting diagnostic and culture reports.
2. Duration of pre operative Amphotericin therapy may be considered as per clinical severity and early need for surgical intervention. [35]
3. Oral antifungal: Overlap with Injectable for 3-4 days before step down and to be continued 1 week after endoscopic biopsy is negative.
4. Liposomal Aamphotericin-B is preferred in cases having renal complication due to Amphotericin-B and in case of cerebral parenchymal involvement. First line antifungal therapy: Inj

Amphotericin B Deoxycholate (C-AmB):

- Dose: 1.0-1.5 mg/kg once per day, IV: infused over 4 - 6 hours
- Half-life: Biphasic: Initial 15 to 48 hr, Terminal 15 days
- Disadvantages: Highly toxic, poor CNS penetration
- Install peripherally inserted central catheter (PICC line)
- Pre-infusion administration of 500 to 1,000 mL of normal saline To avoid infusionrelated immediate reactions:
- Premedicate with NSAID and/or Diphenhydramine
- Acetaminophen with Diphenhydramine
- Hydrocortisone
- Dosage: 5 mg/kg per day and in CNS Mucormycosis, the dose is 7.5–10 mg/kg per day
- Advantages: Less nephrotoxic, better CNS penetration than AmB or ABLC
- Disadvantage: Expensive

- Contraindication: Hypersensitivity Inj Amphotericin B lipid complex (ABLC):

Dosages: 5 mg/kg/day - Advantages and Supporting Studies: Less nephrotoxic than AmB deoxycholate Disadvantage: Expensive, Possibly less efficacious than LAmB for CNS infection Second line- AZOLE Derivatives (Step Down or Salvage Therapy): Step-down therapy: Posaconazole and Isavuconazole are broad-spectrum azoles that are available in both parenteral and oral formulations. For patients who have responded to Amphotericin B, Posaconazole or Isavuconazole can be used for oral step-down therapy. Amphotericin B should be continued until the patient has shown signs of improvement; this usually takes several weeks. Salvage therapy: Posaconazole or Isavuconazole may be used as salvage therapy for patients who do not respond to or cannot tolerate Amphotericin B. The IV formulation of Posaconazole or Isavuconazole should be used in patients who have to be switched from Amphotericin B before they have had a favorable response and in patients who have an inability to absorb oral medications. A. Isavuconazole: Isavuconazole should be given as a loading dose of 200 mg (equivalent to 372 mg of the prodrug isavuconazoniumsulfate) IV or orally every 8 hours for the first six doses followed by 200 mg IV or orally every 24 hours thereafter. Because the IV formulation of isavuconazole is highly water soluble and does not contain the SBECD vehicle, there are no known concerns about administering the IV formulation to patients with renal impairment. B. Posaconazole: Dosage: Posaconazole (both IV and delayed-release formulations) is given as a loading dose of 300 mg every 12 hours on the first day, followed by a maintenance dose of 300 mg every 24 hours thereafter. Oral formulation should be taken with food. The IV formulation should be avoided in patients with moderate or severe renal impairment conclusionThe epidemiology of mucormycosis is evolving. In light of COVID-19 disease, diabetes mellitus still remains the main underlying risk factor for developing this disease. In developed countries most common underlying diseases are haematological malignancies. [36]

Conclusion:

The epidemiology of mucormycosis is evolving. In light of COVID-19 disease, diabetes mellitus still remains the main underlying risk factor for developing this disease. In developed countries most common underlying diseases are haematological malignancies.An unholy trinity of diabetes, rampant use of corticosteroid in a background of COVID-19 appears to increase mucormycosis. All efforts should be made to maintain optimal glucose and only judicious use of corticosteroids in patients with COVID-19 .Diagnosis of mucormycosis remains challenging. Histopathology, direct examination and culture remain mainstay, although newer tools like molecular methods are improving. Newer molecular platforms are being investigated and new fungal genetic targets are being explored. More such needed rapid methods that do not require invasive procedures, such as serology-based point of care hopefully will be evaluated and used in the near future.

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