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POST CORONAVIRUS DISEASE MUCORMYCOSIS:- A DEADLY ADDITION TO THE PANDEMIC SPECTRUM

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ABSTRACT

Mucormycosis, which was previously called zygomycosis, is a rare yet serious fungal infection that is very aggressive and potentially life-threatening. Mucormycosis is an emerging angioinvasive infection caused by the ubiquitous filamentous fungi of the Mucorales order of the class of Zygomycetes. Therefore, our ability to determine the burden of disease is limited. Based on anatomic localization, mucormycosis can be classified as one of 6 forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and uncommon presentations. Current epidemiological trends indicate a shift toward infections by Aspergillus spp., non-albicans Candida spp., and previously uncommon fungal pathogens that have decreased susceptibility to the available antifungal agents. The disease has a close link to diabetes, and conditions which compromise the immune system. Experts have said that an overuse during the COVID-19 pandemic of certain drugs which suppress the immune system could be causing the surge. These species exist as spores and thrive in dry, humid, and arid conditions. These transmit through the air and result in mild to severe infections in immunocompromised individuals. It diagnose by clinical examination, tissue biopsy, fungal culture etc. There are essentially two main treatment modalities – antifungal therapy and surgery. Besides these, adjunctive treatment approaches and controlling the underlying immunocompromising condition, have also been suggested.

KEYWORDS: Zygomycosis/Mucormycosis, Mucor, Covid-19, Amphotericin B.

INTRODUCTION

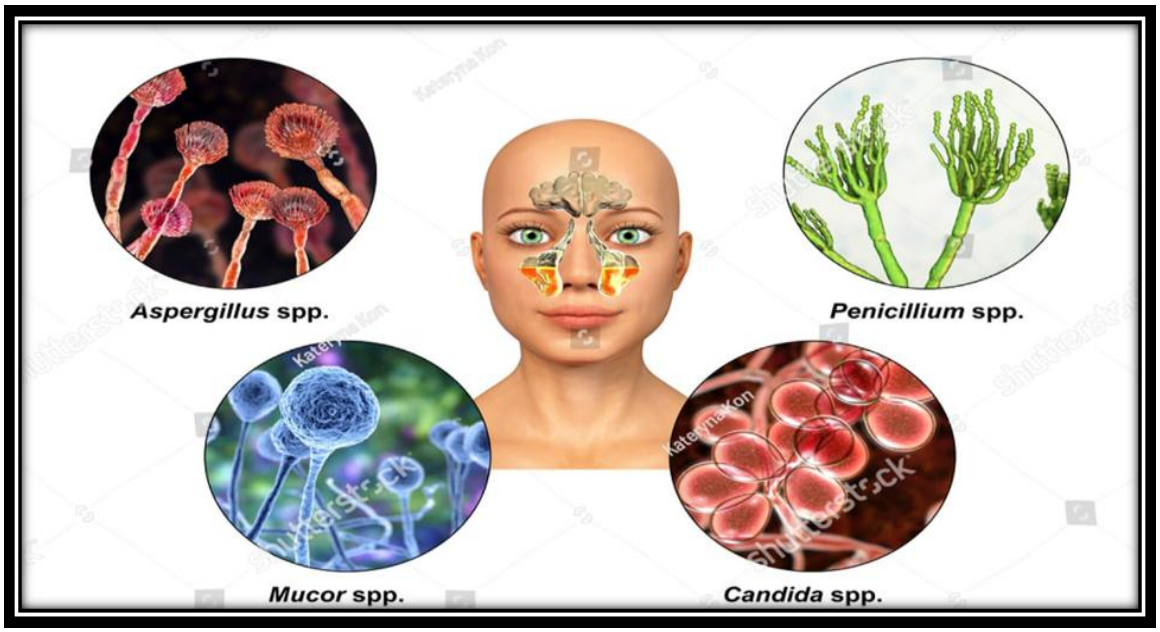

Fig. No. 01:- Anatomy of rhinosinusitis and microorganisms that cause sinusitis Staphylococcus aureus, Streptococcus pyogenes, Aspergillus fumigatus, and Pseudomonas aeruginosa.

Mucormycosis also called as Zygomycosis and Phycomycosis was first described by Paultauf in 1885. Mucormycosis is the disease caused by the many fungi that belong to the fungal family "Mucorales". Fungi in this family are usually found in the environment – in soil, for example and are often associated with decaying organic material such as fruit and vegetables.

Rhino-orbital-cerebral-mucormycosis (ROCM) is caused by molds of the order Mucorales. In this, there are a few subgroups like Rhizopus, Mucor, Rhizomucor which are most commonly involved in this infection.

These fungi are angioinvasive i.e, they invade the surrounding blood vessels and destroy them resulting in tissue necrosis and death. These molds live throughout the environment and their spores are present in the air. They get lodged in the nasal cavity and adjoining sinuses. The member of this family most often responsible for infections in humans is called Rhizopus oryzae. In India though, another family member called Apophysomyces, found in tropical and subtropical climates, is also common.

Fungi in the Mucorales family are considered opportunistic, meaning they usually infect people with an impaired immune system, or with damaged tissue. Use of drugs which

suppress the immune system such as corticosteroids can lead to impaired immune function, as can a range of other immunocompromising conditions, like cancer or transplants. Damaged tissue can occur after trauma or surgery.

WHAT IS MUCORMYCOSIS ?

- Mucormycosis or black fungus is an aggressive and invasive fungal infection caused by a group of molds called mucormycetes.
- Mucormycosis is the general term that indicates any fungal infection caused by various genera of the class *Zygomycetes*.
- Another term used in medical and lay publications that means the same is phycomycosis.
- These forms of mucormycosis usually occur in people who have health problems or take medicines that lower the body's ability to fight germs and sickness. Mucormycosis can also develop on the skin after the fungus enters the skin through a cut, scrape, burn, or other type of skin trauma.

ETIOLOGY OF MUCORMYCOSIS

- The fungal species that are most frequently isolated from patients with Mucormycosis are *Apophysomyces, Cunninghamella, Lichtheimia, Mucor, Rhizopus,* and *Rhizomucor*.
- The etiology of these infections differs considerably in different countries, but *Rhizopus* spp is the most common cause of these infections in most parts of the world.
- These species exist as spores and thrive in dry, humid, and arid conditions. These transmit through the air and result in mild to severe infections in immunocompromised individuals.
- The species present in the order Mucorales display only a small number of distinguishable morphological characteristics that can be used to distinguish between themselves.
- The Mucoralean fungi are defined by usually abundant and rapidly growing mycelium and other anamorph structures.
- The mycelium is unsepted or irregularly septed, and the anamorphic sporangiospores produce multi-spored sporangia.
- Structures like chlamydospores, arthrospores, and yeast cells are rare in these species. The sporangia consist of the variously shaped columella.
- Some species might exhibit appendages that enable them to switch between the filamentous multicellular state and the yeast-like state.

MODE OF TRANSMISSION OF MUCORMYCOSIS

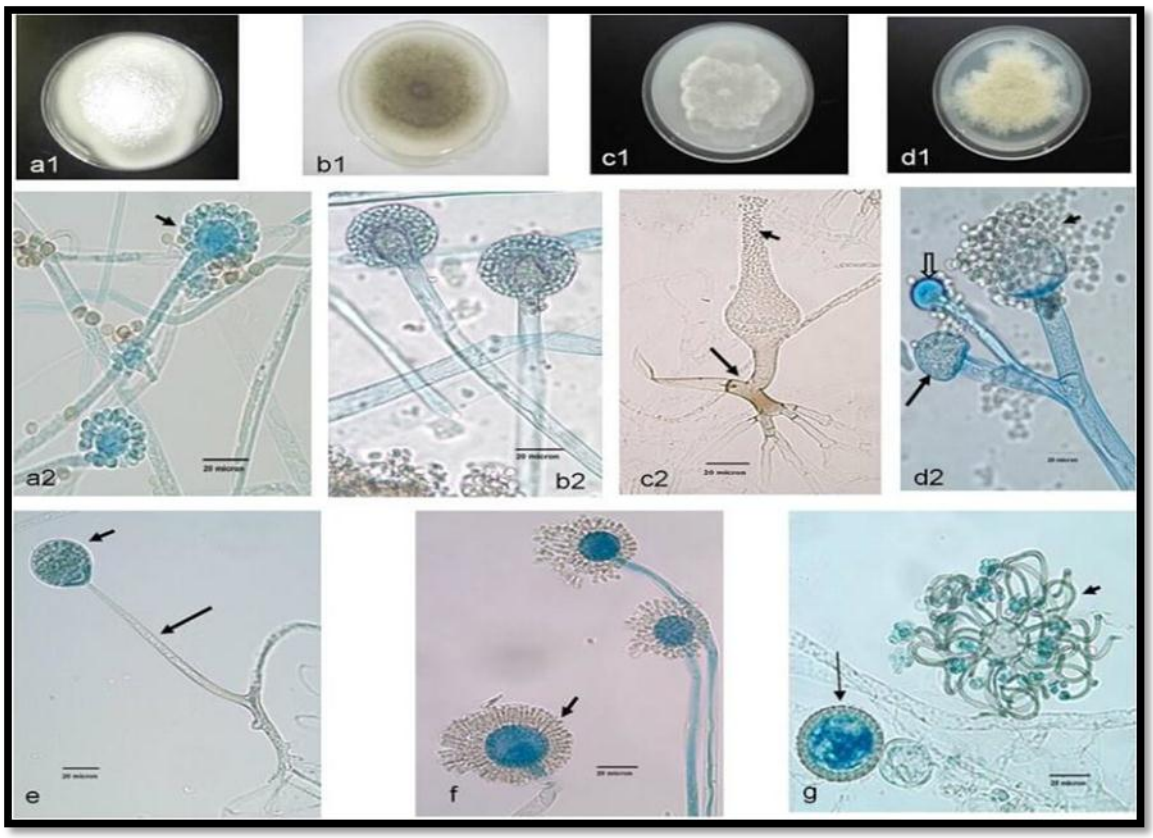

Figure 02: Unusual Mucormycetes. (a2, b2, c2, d2, and e to g) Lactophenol cotton blue mount preparations. (a1, b1, c1, and d1) Potato dextrose agar (PDA) medium plates. (a1) Cunninghamella bertholletiae colony surface on a PDA medium plate. (a2) C. bertholletiae sporangiophores in terminal swellings called vesicles, with sporangioles (short arrow). (b1) Colony surface of Rhizomucor pusillus on a PDA medium plate incubated at 30°C for 96 h. (b2) R. pusillus sporangiophores with globose sporangia. (c1) Saksenaea vasiformis colony surface on a PDA medium plate incubated at 30°C (48 h). (c2) S. vasiformis sporangiophore arising from a "foot cell"-like hyphal element (long arrow), flask-shaped sporangium, and liberated sporangiospores (short arrow). (d1) Actinomucor elegans colony surface on a PDA medium plate incubated at 30°C (96 h). (d2) Actinomucor elegans branched sporangiophores, sporangium (long arrow), columella (block arrow), and various sporangiospores (short arrow). (e) Unbranched Apophysomyces elegans sporangiophore (long arrow) with a pyriform sporangium (short arrow). (f) Syncephalastrum racemosum sporangiophores with merosporangia (short arrow). (g) Cokeromyces recurvatus sporangiolating vesicle (short arrow) and zygospores (long arrow). Bars, 20 µm.

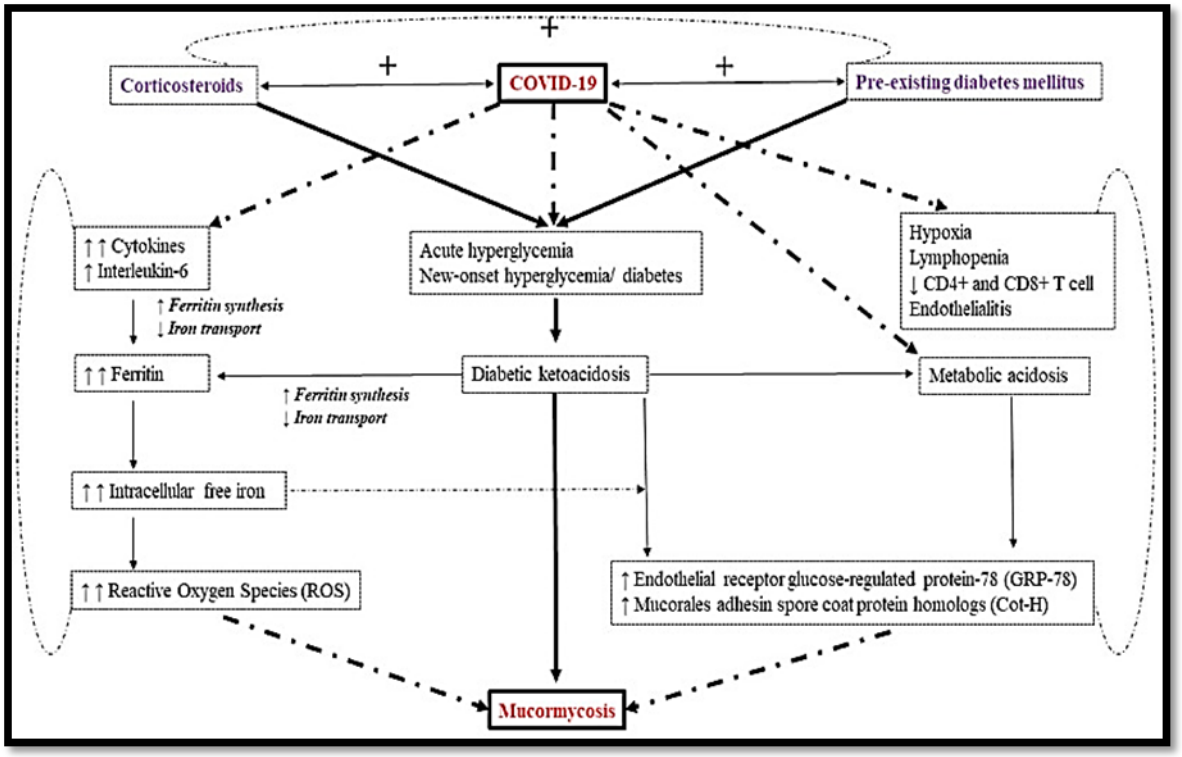

Fig. No. 3:- Postulated interaction of diabetes, corticosteroid and COVID-19 with mucormycosis.

- Mucormycosis is acacquired by immunocompromised individuals, mostly by the inhalation of fungal spores from the environment
- The primary mode of transmission of Mucorales is the inhalation of sporangiospores. Other modes of transmission include ingestion of the spore or inoculation of conidia from wounds or trauma.
- Nosocomial outbreaks of infections can also occur; however, these are quite rare. Nosocomial infections are associated with contaminated bandages, medical equipment, and ventilation.
- The mode of transmission of the fungi from one individual to the other depends on the site of infection and the severity of infection.
- Rhinocerebral mucormycosis transmits mostly via the inhalation of spores or droplets, whereas cutaneous mucormycosis transmits via close personal contact.

TYPES OR FORMS OF MUCORMYCOSIS

The following are some of the types of mucormycosis that are observed in immunocompromised humans.

- **Rhinocerebral (Sinus and Brain) mucormycosis**

Fig. 4.

Rhinocerebral mucormycosis is an infection in the sinu ses that can spread to the brain. The infection begins in the nasal cavity and slowly moves to the adjacent paranasal sinuses.

The fungi then attached themselves to the surface of the sinus and began reproducing as the humid condition of the nose facilitates growth and invasion of the organism.

The disease is most acute, but it can become chronic as the fungus grows rapidly and aggressively. This form of mucormycosis is most common in people with uncontrolled diabetes and in people who have had a kidney transplant.

The progression of the diseases continues as a result of different virulence factors. It is initiated by the invasion of blood vessels and damage to the endothelial cells resulting in ischemia and tissue necrosis.

- **Pulmonary (Lung) mucormycosis**

Fig. 5.

Pulmonary mucormycosis is an uncommon form of mucormycosis but can result in life-threatening opportunistic infections. The infection proceeds from the entry of the organism via inhalation. The organism reaches the lung spaces where it adheres to the endothelial cells to result in tissue damage.

The infection is more frequent in immunocompromised patients with transplants and hematological malignancies. It is the second most common mucormycosis infection accounting for about 25% of total mucormycosis infections.

It has a high mortality rate of 40-70%, especially in cases with rapid local progression and angioinvasion.

Diagnosis of the disease is based on intrapulmonary imaging with lobar and segmental consolidation.

- **Gastrointestinal mucormycosis**

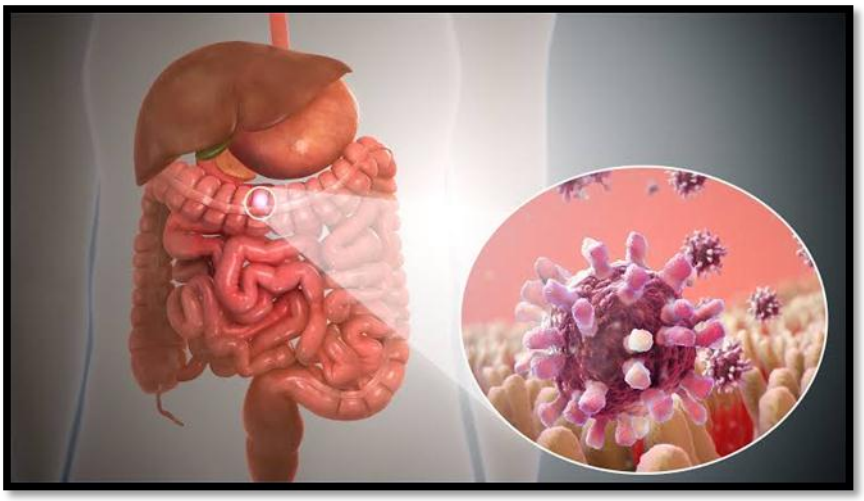

Fig. 6.

This form of mucormycosis is most 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 that lower the body's ability to fight germs and sickness.

Gastrointestinal mucormycosis is very rare and is observed only in about 2 to 11% of the total cases of mucormycosis. The organs involved in the infection are the stomach and intestine, but in some cases, the infection can spread to other regions of the intestinal tract.

The infections are mostly mild, but in some cases, these can be fatal. The infection begins with the ingestion of spores with food or other substances that finally make way into the gastrointestinal tract.

Aggressive antifungal treatments and medical therapy with surgeries can be used as a method of treatment.

- **Cutaneous (Skin) mucormycosis**

Fig. 7.

Cutaneous mucormycosis results from the entry of the pathogen through trauma or cuts on the skin as a result of surgery, natural disaster, or inoculation of soil and other contaminated sources.

The infection can spread quite rapidly on the skin to inner layers like the subcutaneous layer, fascia, and bone.

It can be classified as primary and secondary mucormycosis, where the primary infections include infections where the organism infects the individual via direct inoculation. Secondary mucormycosis involves the dissemination of organisms from other locations, commonly a rhinocerebral infection.

most commonly affected areas in the case of cutaneous mucormycosis are legs and arms, including other rare cases in the scalp, face, back, thorax, breast, neck, and groin.

- **Disseminated mucormycosis**

Fig. 8.

Disseminated mucormycosis occurs when the infection spreads through the bloodstream to affect another part of the body. The infection most commonly affects the brain, but also can affect other organs such as the spleen, heart, and skin.

It is the rarest form of mucormycosis that is usually only observed in neutropenic patients with hematologic tumors or post-transplant patients. The cases are quite rare but have an extremely high mortality rate of about 90% as the infection tends to be invasive.

The direct inoculation of the fungi is a common mode of transmission where the fungi can infect cutaneous, subcutaneous, fat muscles, and skeletal tissues.

In severe cases, the organism can even reach deep organs and result in localized infections at multiple sites.

6. Isolated renal mucoromycosis

Fig. 9.

Isolated renal mucoromycosis in immunocompetent individuals is a rare infection with devastating outcomes.

Isolated involvement of the kidney with mucormycosis has been reported and is presumed to occure via seeding Of the kidney duringand episode of fungemia.

Almost all patients with all renal mucoromycosis have risk factor of fungemia including an intravenous cathetor intravenous drug uses or aids.

SYMPTOMS OF MUCORMYCOSIS

The symptoms and signs depends on the type of mucormycosis, which in turn depends on the site of action. These are briefly highlighted below-

1) Rhinocerebral Mucormycosis

• Fever, reddish and swollen skin over nose and sinuses, Headache
• Black patches on the nose and upper inner side of nose
• Nasal or sinus congestion, Facial pain
• Visual problems

2) Pulmonary Mucormycosis

• Fever, Cough, Chest pain
• Shortness of breath
• Hemoptysis may occur in the presence of necrosis
• Dyspnea, Cavitations

3) Gastrointestinal Mucormycosis

• Abdominal pain, Nausea, Vomiting
• Gastrointestinal bleeding
• Hematochezia
• Massive gastrointestinal haemorrhage

4) Cutaneous Mucormycosis

• Pain, Redness, Swelling
• Blackened skin patches
• Blistering, Ulceration

5) Disseminated Mucormycosis

- Headache, fever
- Brain infection can lead to mental disorders and even coma

6) isolated renal mucoromysis

- Fever, Flank pain

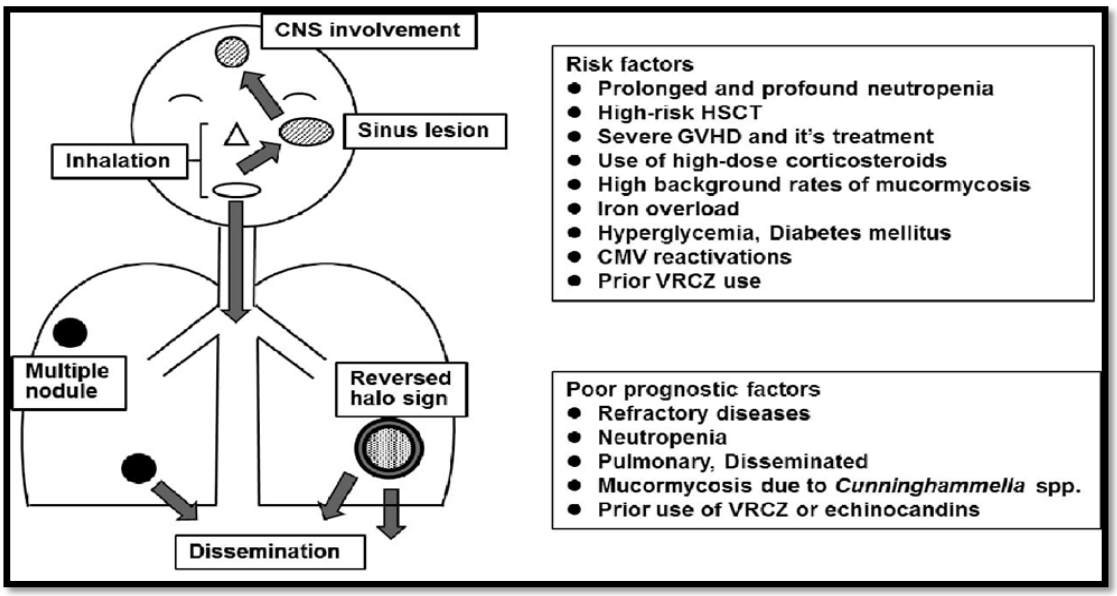

Fig. No 10:- Clinical manifestations, risk and prognostic factors of mucormycosis.

RISK FACTORS

MUCORMYCOSIS AND COVID-19

- Mucormycosis has been increasingly observed as a form of secondary fungal infection in COVID 19 patients.
- The most common form of mucormycosis in COVID 19 patients is pulmonary mucormycosis, closely followed by rhinocerebral mucormycosis.
- The incidence of mucormycosis with COVID 19 isn't unusual as the disease tends to affect the immune status of the patients, resulting in increased chances of mucormycosis.
- Similarly, glucocorticoids and remdesivir are some of the only drugs that have been beneficial in COVID 19; however, the use of glucocorticoids can increase the risk of secondary infections.
- The use of concurrent immunomodulatory drugs and the immune dysregulation as a result of the viral infection further add to the increased risk of the infections.
- The correlation between COVID 19 and mucormycosis has still not been recognized completely due to the underdiagnosis of these infections.

- Some of the factors that help prevent the infections from turning severe include the control of hyperglycemia with early treatment with appropriate antifungal agents.

WHY IS IT OCCURRING IN COVID 19 PATIENTS?

Mucormycosis can occur any time after COVID-19 infection, either during the hospital stay or several days to a couple of weeks after discharge. "The COVID-19 causes favourable alteration in the internal milieu of the host for the fungus and the medical treatment given, unwittingly also abets fungal growth. COVID-19 damages the airway mucosa and blood vessels. It also causes an increase in the serum iron which is very important for the fungus to grow. Medications like steroids increase blood sugar. Broad-spectrum antibiotics not only wipe out the potentially pathogenic bacteria but also the protective commensals. Antifungals like Voriconazole inhibit Aspergillosis but Mucor remains unscathed and thrives due to lack of competition. Long-term ventilation reduces immunity and there are speculations of the fungus being transmitted by the humidifier water being given along with oxygen. All the above make for a perfect recipe for mucormycosis infection,"

PREVENTION AND CONTROL OF MUCORMYCOSIS

- Ensuring personal hygiene by bathing and scrubbing the body thoroughly, particularly after returning home from work, working out or visiting neighbours, relatives, friends
- Wearing face masks and face shields when going to dirty polluted environments such as construction sites
- Making sure to don fully covered clothing of concealed shoes, long pants, long-sleeved shirts and gloves while coming in contact with soil, moss, manure, like in gardening activities
- It is important that the patients are aware of the infections and their presentations so that they can make an early visit to the hospital.
- Prevention and control of these infections are based on the early diagnosis of the disease and the maintenance of a proper immune system.
- Individuals at risk with different underlying conditions should be careful about any possible symptoms and other conditions.
- It is imperative to maintain a healthy diet and appropriate lifestyle in order to prevent severe cases of infection.

DIAGNOSIS OF MUCORMYCOSIS

A systematic, step-by-step approach is adopted for the diagnosis of mucormycosis, involving the following strategies-

- Medical History: A detailed medical history will be taken in order to establish where and how the infection was acquired.
- Clinical Examination: A suspected case will undergo a full clinical examination of the nose and other facial structures for evidence of infection. Since the respiratory tract is the most common route of entry of the pathogen, the nose and sinuses are thoroughly examined for any black crusts and other lesions.
- Tissue Biopsy: Skin tissue biopsies canbe taken if cutaneous mucormycosis is suspected. These biopsy samples are analyzed for histopathological evidence of Mucormycetes by microscopic examination.

Fig. No. 11:- Microscopy.

- Imaging: Imaging techniques, such as computed tomography (CT) scans may be used to pinpoint the exact location and extent of the infection in a particular location in the body. A CT scan can be taken of the lungs, sinuses, facial structures, or any other parts of the body, where the infection is suspected to be present.

Fig.No. 12:- Fungal Culture.

- Fungal Culture: Fluids from the respiratory tract (bronchoalveolar lavage), including sputum can be sent for culture, if pulmonary mucormycosis is suspected. Evidence of the

presence of Mucormycetes in the culture fluid indicates a positive and definitive diagnosis.

- Molecular Diagnostics: DNA-based molecular techniques, such as the polymerase chain reaction (PCR) are very promising, but are still in experimental stage. These tests are not fully standardized, and have not been clinically evaluated and are currently unavailable for commercial use.

TREATMENTS FOR MUCORMYCOSIS

There are essentially two main treatment modalities – antifungal therapy and surgery. Besides these, adjunctive treatment approaches and controlling the underlying immunocompromising condition, have also been suggested. These are briefly discussed below-

- Antifungal Therapy: Prompt administration of antifungals is vital for killing the infectious fungus and preventing it from causing further harm. This treatment needs to be timely and is of the utmost importance for improving the outcomes of patients with mycormycosis. The most effective antifungal drugs for treating mucormycosis include amphotericin B, posaconazole, and isavuconazole. While amphotericin B can only be administered intravenously (IV), posaconazole and isavuconazole can be administered both by the IV route, as well as the oral route.
- Surgery: Surgical debridement and resection of infected or dead tissue is often necessary and should be performed as soon as the diagnosis is confirmed. In case of cutaneous mucormycosis, damaged skin and associated subcutaneous tissues may also need to be surgically removed. Patients with rhinocerebral mucormycosis can exhibit significant alteration in facial appearance. Specific surgical procedures usually vary with the location, extent and severity of the infection.
- Adjunctive Treatment: Adjunctive treatment is defined as an additional treatment strategy, besides the primary treatment. Treatment with hyperbaric oxygen is one such adjunctive treatment approach. This treatment involves exposure of the patient to pressurized pure oxygen, either in a pressure chamber or through a tube. Although hyperbaric oxygen has been found to be effective for treating some types of infections, its efficacy in treating mucormycosis is still not well established. More research and large-scale clinical trials are necessary to determine the effectiveness of this adjunctive treatment strategy.
- Salvage therapy: If desease refractory or intolerance toward previous antifungal therapy.

1 Posaconazol (A)

2 Posaconazole (B)+polymers

3. Lipid complex, liposomal colloidal dispersion (B)

4. Polyenes +caspofungin (C)

COMPLICATIONS OF MUCORMYCOSIS

- The complications of mucormycosis are serious and are related to the body area initially infected but also can occur in other body regions because the fungi often spread to the organs or tissues that physically contact or are near the originally infected area.
- In addition, because surgical debridement is almost uniformly needed, some normal tissue may be destroyed because the surgeon must remove all tissue that is dead or dying.
- Unfortunately, that means the surgeon may have to remove some normal tissue to insure all of the fungi are removed.
- An example is infection of the eye orbit; often the whole eye must be removed.
- Consequently, serious complications may occur, such as
  - **blindness**,
  - **meningitis**,
  - brain abscesses,
  - **osteomyelitis**,
  - pulmonary hemorrhages,
  - gastrointestinal hemorrhages,
  - cavitary lesions in organs and eventually secondary **bacterial infections**, **sepsis**, and death.

CONCLUSION

Mucormycosis is a rare but emerging fungal infection with a high mortality rate The literature contains few prospective, population-wide studies of it. The incidence of mucormycosis seems to be increasing in leukemic patients and stem cell transplant recipients chronically exposed to Aspergillus-active agents, although the generalizability of this observation is controversial. Despite the diabetes epidemic in developed countries, the incidence of mucormycosis in diabetics may be decreasing. In contrast, in developing countries, uncontrolled diabetes mellitus and trauma are the most common risk factors for mucormycosis.

More representative data on specific groups of patients (eg, leukemic patients, transplant recipients, diabetics) are needed for better evaluation of the infection. Well-organized global registries are needed to estimate the burden of mucormycosis. The pleiotropic clinical manifestations and elusive presentation of mucormycosis often delay diagnosis, with resultant poor outcomes. A high index of suspicion for mucormycosis based on appropriate risk stratification and improved laboratory diagnosis are important for improving the natural history of this devastating infection.

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