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A REVIEW: MUCORMYCOSIS COVID-19

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ABSTRACT

Now days many cases of coronavirus disease has been reported worldwide due to which the frequency of bacterial and fungal co-infection has been rising continuously While mucormycosis cases are also recognized in association with COVID-19.The fungal co-infection developed in COVID-19 patients known as mucormycosis a black fungal infection which mainly leads to loss of sight and hearing capacity which eventually leads to death of that patient. The main reason of this arising disease is the steroid treatment given in COVID-19 cases. This report aims to address the importance of short term follow up in COVID-19 patients who have received corticosteroids which results in life threatening mucormycosis infection. The early detection, aggressive treatment is essential for management of invasive fungal infection. This report mainly focus on the mucormycosis , black fungal infection caused during post COVID complications. It usually affects those which have health problems or who are taking drugs that limits body ability to compete with germs and illness. The main cause of this infection is use of steroids in management of COVID infection as well as the fact that many COVID patients had diabetes as co-morbidity.

Keywords: *Mucormycosis; Covid-19;causes; Treatment; infection; prevention; control*

1. INTRODUCTION

COVID-19 caused by severe acute respiratory syndrome corona virus- 2(SARS -COV -2) has been associated with opportunistic bacterial and fungal infection. The Aspergillosis and Candida both are responsible for co-infection in people with COVID-19. Now days many cases of mucormycosis are reported worldwide in COVID-19 patients.

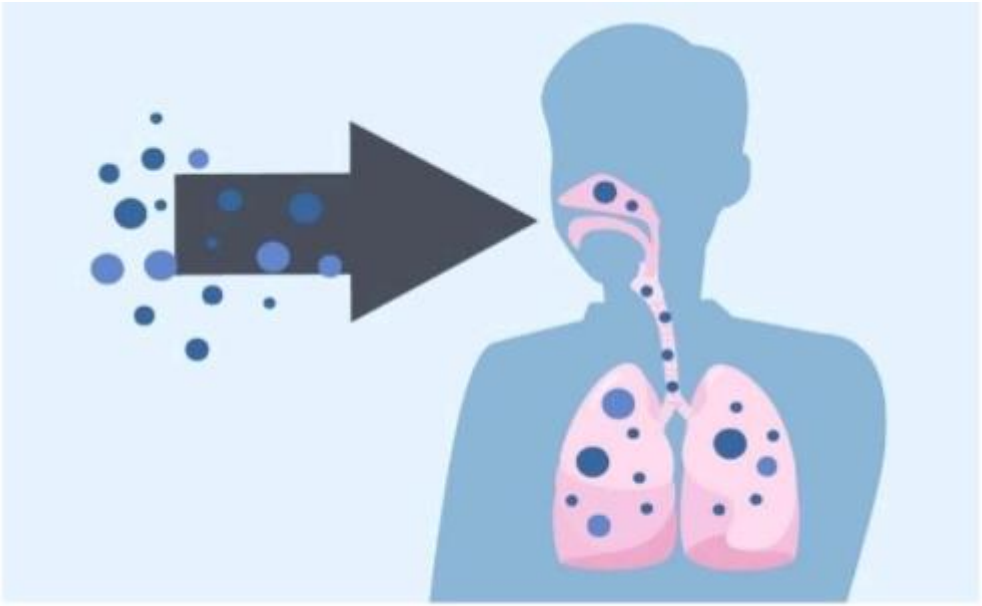
The main reason of germinating Mucorales spores in people with COVID-19 is the conditions such as low oxygen (hypoxia) ,high glucose (diabetes new onset hyperglycemia ,steroid induced hyperglycemia), acidic medium (metabolic acidosis ,diabetic ketoacidosis),high iron levels and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS COV- 2 mediated , steroid mediated or background comorbidies) such conditions or due to other risk factors such as prolonged hospitalization with or without mechanical ventilators are responsible for increasing cases of mucormycosis in COVID-19 patients

In 1885 Phycomycosis and Zygomycosis was described by Paltauf and later it coined as mucormycosis by Baker in 1957. Mucormycosis is fatal fungal infection which affects patients with altered immunity. Mucormycosis caused by mold fungi of genus Rhizopus mucor, rhizomucor, cunninghamella and absidia of order Mucorales class -zygomycetes. Nearly 60%of mucormycosis caused by Rhizopus Oryzae This infection occurs through inhalation of fungal spores

Mucormycosis:

Mucormycosis caused by group of molds called mucormycetes also known as black fungus which is rare but dangerous infection

How mucormycosis spread?



People get mucormycosis when they comes in contact with fungal spores in environment

For example – mainly lung and sinus form of infection caused when someone breaths in spores

These form of mucormycosis mainly usually occurs in people who have health problems or who take medicines which lowers body's ability to fight germs and sickness mainly who suppress immune system These infection also develops on skin after fungus enters the skin through cut , scrape, burn or other type of skin trauma

Mucormycosis does not spread from people to people

Fungi which causes mucormycosis :

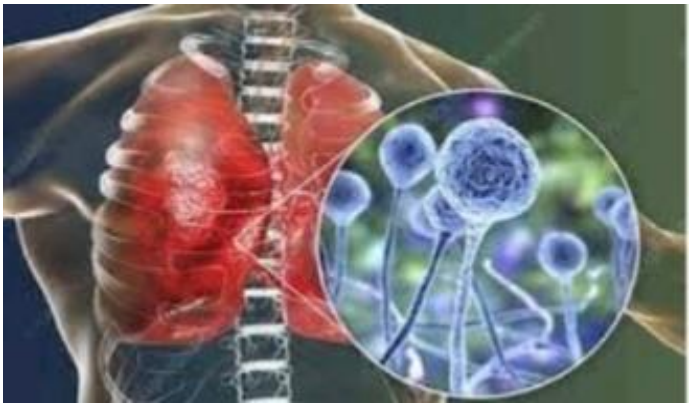
- Rhizopus species
- Mucor species
- Rhizomucor species
- Syncephalastrum species
- Cunninghamella bertholletiaea apophysomyces species
- Lichtheimia(formerly absidia)species

Types Of Mucormycosis-

1) Rhinocerebral (sinus and brain) mucormycosis
2) Pulmonary (lung) mucormycosis
3) Gastrointestinal mucormycosis
4) Cutaneous (skin) mucormycosis
5) Disseminated mucormycosis

1) Rhinocerebral (sinus and brain) mucormycosis

Rhinocerebral mycormycosis is the infection in the sinus that can spread to the brain. This type of mucormycosis is commonly seen in people who already suffers from uncontrolled diabetes and who had kidney transplant. This type of infection rapidly results in death



2) Pulmonary (lung) mucormycosis

- This infection is recognized as secondary complications of COVID-19.
- This type of mucormycosis mainly occurs in lungs
- This type of infection commonly seen in people with cancer and in people who have had an organ transplant or a stem cell transplant

3) Gastrointestinal mucormycosis

This is most common type of infection occurs mainly in young children's than adults mainly premature and low birth weight infants less than 1 moth of age also seen in peoples who have had antibiotic, surgery on medication that lowers body ability to fight germs and sickness

4) Cutaneous (skin) mucormycosis

This type of infection mainly causes when fungi enters into the skin through break in skin for e.g. After surgery ,burn, or other type of skin trauma. These is most common form of mucormycosis found also in peoples who do not have weakened immune system

5) Disseminated Mucormycosis:

These type of mucormycosis occurs when infection spread through bloodstream to affect another body parts it mainly affects brain but also can affects other organs such as spleen ,heart and skin

Causes of mucormycosis

- Various conditions are responsible for mucormycosis infection which are as follows:
- Low oxygen level (hypoxia)
- High glucose level (diabetes, new onset hyperglycemia, steroid induced hyperglycemia)
- Acidic medium (metabolic acidosis, diabetic ketoacidosis)
- High iron level
- Decreased phagocytic activity of white blood cells (WBC) which is due to immunosuppression
- (SARS-COV-2 mediated, steroid mediated, or background comorbidies)
- Prolonged hospitalization with or without mechanical ventilators

Pathogenesis of mucormycosis

Mucormycosis is the lifethreatening infections which generally occurs in patients who are immunocompromised because of various reasons such as diabetic ketoacidosis, increased serum level of iron, organ transplantation. Number of peoples are at risk because of this deadly infection which is caused due to increased prevalence of diabetes mellitus, cancer, organ transplantation. To treat this infection new strategies are urgently needed proper understanding of the pathogenesis of mucormycosis and the host response will provide better novel therapeutic interventions

Host defense against mucormycosis at higher risk according to the clinical and experimental data. For example – individuals who have severe neutropenia are at higher risk for developing mucormycosis. In contrast of this persons suffering with AIDS are not at risk of developing mucormycois so the neutrophils, not necessarily T lymphocytes are plays important role in inhibiting fugal spore proliferation. By generating oxidative metabolites and cationic peptides the both mononuclear and polymorphonuclear phagocytes kills Mucorales. In the presence of low PH and hyperglycemia phagocytes are dysfunctional and causes defective intracellular killing by both oxidative and nonoxidative mechanism

STEROIDS IN TRATMENT OF COVID-19

Steroids are artificial or man-made version of chemicals which works similar to natural hormone which are present in our body. When they are produced naturally they are called as natural steroids Or when they are produced medically it is called as synthetic steroids.

Steroids are generally reduce the inflammation which are caused when body's own natural immune system tries to fight any virus, infection or any bacteria. Steroids only give relief to patients by reducing inflammation in body but it cannot cure the condition.

Body's reactions when steroids are taken

Inflammation is the body's natural response to towards any infection, bacteria or virus. To fight with this bacteria or virus immune system will show some signs such as swelling b, redness, hear or acute pain in particular part of our body. Some of patients have balanced immune response but some patients have immune response which is dis regulated and which cause inappropriate inflammation. Basically Steroids does not cure illness but gives temporary relief and it work only when it given in right amount or dosage

Steroids and covid-19

IIf steroids are not given in right time or in right amount they can do more harm to your body .in case of covid-19 86 percent people heal on their own because their natural immunity will take care of disease

Adverse effects of steroids

Steroids can actually cause more harm to our body because it disturbing the natural immune response of the body and also lowered body's defense mechanism which may leads to develop secondary infection For example- mucormycosis which is caused in immunocompromised condition because Steroids lowers the body's natural immune response. The people who are fighting with corona virus leads to compromised and weakened immune system which may have higher chances of developing mucormycosis.

Use of steroids drugs to treat covid-19 set stage for mucormycosis

Steroids drugs are useful in reducing mortality (death rate) in covid-19 patients which has low oxygen saturation level. Steroids generally reduce inflammation but they can negatively affects on the body's natural ability to fight with infection So it is important to to get right dose of steroids if it is not taken in appropriate amount then there are higher chances of contracting another infection. If covid patients have uncontrolled blood sugar and also they are using steroids on top of that then their blood sugar is going to be very high level and high blood sugar leads to acidic blood. Anyone who have Suppressed immune system is at risk for mucormycosis

Mechanisms of action of corticosteroid in COVID- 19

Corticosteroid have pleiotropic effect. Glucocorticoid have anti-inflammatory action which exert by stimulating synthesis and release of anti- inflammatory proteins and also by inhibiting pro inflammatory proteins. Glucocorticoid binds to glucocorticoid receptors (GR). Glucocorticoid receptors present in cytoplasm of almost all cells. When glucocorticoid binds to glucocorticoid receptors, the glucocorticoid receptors dissociates from chaperone proteins heat shock protein 70 (Hsp70) Hsp90, and immunophilin. After that it enters into nucleus to interact with specific DNA sequence (glucocorticoid responsive elements) of regulatory region of target genes with subsequent chromatic remodeling. Activated glucocorticoid receptors inhibits histone acetyltransferase and activate histone deacetylase which represses expression of pro inflammation. The expression of interferon regulatory factor 3(IRF3) transcription factor is regulated by glucocorticoid . The GR- glucocorticoid complex inhibit production of pro- inflammatory proteins. Glucocorticoid prevents leucocyte recruitment by suppressing production of acute phase reactants and chemokines. As India fights covid-19 the deadly second wave so names of many steroids have now commonly known Some of the steroids are effective in curing severe or moderate cases of covid-19 patients who requires oxygen or ventilators support. According to expert these steroids are only effective if and only if they are given in right dosage and at the time. Recently addressing the media on the rise of black fungus cases in the Which the misuse of steroids is main reason behind the rise of cases of mucormycosis during post COVID recovery.

Symptoms Of Mucormycosis-

I. Rhinocerebral mucormycosis –

- one sided facial swelling
- Fever
- Nasal congestion
- Headache
- Black lesions on nasal bridge or upper inside of mouth that quickly become more severe

II. Pulmonary mucormycosis

- Fever
- Cough
- Shortness of breath
- Chest pain

III. Gastrointestinal mucormycosis

- Abdominal pain
- Nausea
- Vomiting

- Gastrointestinal bleeding

IV. Cutaneous (skin) mucormycosis

- Infected area may turns black
- Pain
- Warmth
- Excessive redness
- Swelling around the wound

V. Disseminated mucormycosis

- Develop mental status changes
- Coma

Treatment of Mucormycosis-

- Antifungal agents - Amphotericin B, isavuconazole posaconazole

I. Polyenes - Amphotericine B

Amphotericine B belongs to the polyene class of antifungal drugs. It shows excellent activity against the mucorales in several in vitro studies. Amphotericine B deoxycholate is the only antifungal drug which is approved by US Food and Drug Administration for the treatment of mucormycosis however the d-AmB is nephrotoxic so another liposomal AmB is formulated which is less toxic In the largest review the people treated with d-AmB shows response rate 61% white people treated with liposomal amphotericine B shows 69% response rate . The other lipid formulation of AmB used for treatment of mucormycosis is ABLC.

Mechanism of action

Ergosterol is the component of fungal cell membrane Amphotericine B binds with this ergosterol and forms the spores which causes the leakage of monovalent intracellular ions (k+, Na+ H+ and cl-) which causes the death of fungal cell. The ergosterol present in fungal cell membrane is the principle site of action for Amphotericine B.

II. Azoles - Posaconazole, isavuconazole

Posaconazole is found to be useful against the mucormycosis. As compared to itraconazole and Isavuconazole Posaconazole has enhanced in vitro activity . Fungicidal activity of Posaconazole has been demonstrated against Rhizopus and Mucor spp. Posaconazole prolonged the survival and reduce tissue burden in mucor infection and it is effective as standard AmB at highest dose level.

Mechanism of action

Azoles

Squalene 2,3 epoxide 14 α demethylase

Squalene ⟶ Lanosterol ⟶ Ergosterol

Lanosterol is formed from squalene with the help of enzyme squalene 2,3 epoxide . Then ergosterol is formed from lanosterol with the help of enzyme 14 α demethylase .Ergosterol is the main component of fungal cell wall . Azoles inhibit the enzyme 14 α demethylase which is needed for ergosterol synthesis and due to inhibition of this enzyme ergosterol is not formed which eventually leading to death of fungal cell.

Intravenous - Amphotericin B , posaconazole, isavuconazole

Orally - posaconazole, isavuconazole

Other antifungal drugs such as fluconazole, voriconazole, echinocandin do not work against fungi that cause mucormycosis.

Role of surgery

The mucormycosis results in formation of thrombosis, tissue infection and necrosis which may affect the penetration of antifungal agents at the site of infection. In severe cases doctor may recommend surgery to remove infected or dead tissue to stop the fungus from spreading this may include removing various parts such as nose, eyes but it is crucial to treat this lifethreatening disease. The role of surgery and its timely performance supported in treatment of mucormycosis. In case of rhino-orbito-cerebral disease the surgery before disease progression to cerebral structure improves the chances of successful treatment. In this case survival rate was higher in patients who start treatment within two weeks following the strat of symptoms compared with those who delayed iin diagnosis.

Other treatments

- Adjunctive treatment with deferasirox or deferiprone
- Adjunctive treatment with hyperbaric oxygen
- Adjunctive cytokines

- **Diagnosis Of Mucormycosis-**

The diagnosis of mucormycosis is the challenging task and treatment should be start as early as possible there is no any circulating antigen detection test is available for diagnosis of mucormycosis. And there ais no any standardized blood polymerase chain reaction (PCR)test is available therefore analysis of biological specimen from clinically involved sites is mandatory for diagnosis.

While diagnosing mucormycosis the symptoms, medical history, physical examination and laboratory test are considered. For diagnosis of mucormycosis in case of sinus and lung mucormycosis healthcare professionals collect sample of fluid from respiratory system and then send it in the laboratory for diagnosis

Tissue biopsy is another option in which small sample of affected tissue is collected and analyzed in laboratory for evidence of mucormycosis under a microscope.but unfortunately this is often difficult in patients who have hematological malignancies because of severe thrombocytopenia. In case if biopsy is not possible then other available specimens such as sputum should be used for examination For sinusitis sinus biopsies are required In case of ear, nose and throat endoscopy should be performed. In pulmonary case if sputum smear analysis is negative then broncho- alveolarlavage or pulmonary biopsies should be performed depending upon CT scan the material taken from biopsies should be carefully handled or managed because it may crushed because zygomycetes are fragile and because of this culture may remain negative

Depending on the infection the imaging tests are also performed such as CT scan for lung , sinus and other body parts .

Rhino-orbito-cerebral diagnosis

MRI-PNS with brain contrast study for ROCM

Endoscopic collection of debrided tissue /biopsy

KOH, LPCB, PAS staining

Pulmonary mucormycosis diagnosis

Chest X-ray or HRCT

Repeated negative galactomannan and beta-D-glucan test

Transbronchial biopsy

CT guided biopsy from lung

Prevention and control of Mucormycosis-

Diabetes and diabetic ketoacidosis should be controlled

Reduce steroids uptake (if patient is still on) with aim to discontinue rapidly

Discontinue immunomodulating drugs

Antifungal prophylaxis not needed

Extensive Surgical Debridement – to remove all necrotic materials

Medical treatment

Install peripherally inserted central catheter (PICC Line)

- **Management of mucormycosis in covid-19 patients**

Keep the doctor informed about all your co-morbidities such as heart disease, diabetes, hypertension, or any malignancy.

Tell the doctor about all the medicines which are taken especially any immunosuppressant drug which are taken for any immune disorder

Always use mask and keep personal hygiene

Immediately inform to doctor if you observe any of symptoms such as blocked nose with nasal discharge, eye swelling or any difficulty in vision facial pain/numbness, discoloration around mouth nose or eye.

Don't self -medicate or do not take steroids on your own ✓ Don't ignore the warning signs of this disease.

2. CONCLUSION

Mucormycosis is a highly invasive and rapidly progressing form of fungal infection that can be fatal. Although rare, indolent disease course of this infection has been reported.

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