



INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A MINI REVIEW ON COVID-19 ASSOCIATED MUCORMYCOSIS

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Abstract: This review of literature upgrades about the unanticipated surge of mucormycosis or black fungus during the outbreak of the second wave of Covid-19. The emergency of this uncommon disease was described as Covid Associated Mucormycosis (CAM) which was caused due to fungi mucormycetes or zygomycosis. This infection emerged as a threat to patients who were recovering from corona virus and additional risk factors that contributed to this disease were diabetes, extended stay in ICU, organ and stem transplant, kidney dysfunction, use of broad-spectrum antibiotics etc. Symptoms vary depending on the area of the body being affected and that includes headache, coughing, distress, deprivation of sensation, etc. This manuscript provides a fleeting overview on various forms of mucormycosis, its epidemiology, pathogenesis and treatment that is divided into three stages as first line therapy, salvage therapy and lastly surgical therapy. The treatment included amphotericin B as primary treatment followed by posaconazole, itraconazole, and isavuconazole and the surgical debridement in case of deep infected tissues. In conclusion, it necessitates comprehensive understanding and timely management of the mucormycosis to treat it effectively.

Index Terms: Black fungus, covid associated mucormycosis, risk factors, pathogenesis, clinical manifestation.

I. INTRODUCTION

The emergence of novel coronavirus (COVID-19), a global pandemic, started in Wuhan, China in December 2019. (Divya Pujari Jayakeerthy et.al.,2022). The coronavirus (COVID-19) was caused by (SARS-CoV-2) Severe acute respiratory syndrome Coronavirus-2. Kerala was the first state in India where the earliest case was reported on 30th January 2020. (Naveen Kumar Chaudhary et.al.,2021) Uptil April, 2022 it was reported that 6.2 million people died and more than half a billion people were infected by coronavirus. (Sheikh Mansoor, et.al., 2022)

The virus had a devastating effect on public health and eventually led to many complications and threats among people. Majorly the bacterial and fungal infections were reported as post coronavirus complications. (GogineniH, et.al.,2022) Among those one of the most rare and serious fatal infections reported was Black fungus/Mucormycosis. (Tahani Tabassum et.al., 2022) The World Health Organisation and Pan American Health Organisation described Mucormycosis as Covid Associated Mucormycosis CAM. (Datta S, et.al.,2022) It is an uncommon disease that occurs for 1.8 cases per 1 million per year worldwide but post covid more cases were reported. (Divya Pujari Jayakeerthy et.al.,2022)

India had recorded 28,252 cases of mucormycosis from 28 states until June 7, 2021. 8848 cases were reported of those patients who suffered from black fungus after being infected by coronavirus uptil May 22, 2021. (Naveen Kumar Chaudhary et.al.,2021) In India the states that majorly reported these cases were Maharashtra, Gujrat, Rajasthan, Madhya Pradesh, Haryana, Delhi, Punjab. (Ramandeep Singh Gambhir, et.al., 2021)

The first human case of mucormycosis was found in 1855. The pulmonary mucormycosis was initially observed in cancer patients who were suffering from hemorrhagic infarct in the right lung that had fungal hyphae and spores and this was identified by Furbringer in Germany. (Iyer Mahalaxmi, et.al.,2021)

II. MICROBIOLOGY OF BLACK FUNGUS: Mucormycosis is an angioinvasive fungal infection, caused by fungi Mucormycetes a type of mould of the genus Mucor, order Mucorales, division Zygomycota thus also known as Zygomycosis. (Nimoshini G, et.al.,2023) The other genera causative agents are Mucor, Cunninghamella, Apophysomyces, Lictheimia, Rhizomucor that belong to Entomophthorales. (Ravindra B., et.al.2021) Rhizopus is the most common pathogenic agent causing mucormycosis in humans. (Kevin T, et.al., 2023)

This fungus originates from soil, compost, animal wastes, rotten vegetables, agriculture debris and other organic matter from plants, animals, and fungi. (Ravindra B et.al., 2021)

III. MODE OF INFECTION: The spores of fungi are aerial and airborne thus can be found on human skin through contact with this infected air. (Md Rezaul Islam, et.al.,2022)

This fungus enters human body through

- inhalation of spores,
- ingestion contaminated food,
- skin
- wounds etc. (Iyer Mahalaxmi, et.al., 2021)
- through insects that sting or bite (Md Rezaul Islam, et.al.,2022)

On entering the body this infection produces a wound having black colouration thus the condition is stated as “Black Fungus”. (Disha kesharwani, et.al.,2023) It is reported to be a non-contagious infection. (Rais N, et.al.,2023)

Mostly this infection occurs in patients who are immunocompromised, suffering from ailments like diabetes, cancer, heart and kidney disorders and those who retrieved from coronavirus. (Karthikeyan S, et.al.,2022) The disease frequently affects sinuses, eyes, lungs, brain, nose, gastrointestinal tract, skin and kidneys. (Shreya Dogra, et.al.,2022)

IV. SYMPTOMS: It includes various symptoms like fever, headache, coughing, dyspnea, hematemesis, distress and redness near eyes and nose. It may also involve inflammation on either side of the face and deprivation of sensation. (Md Rezaul Islam, et.al.,2022) Additional indications comprise facial pain, inflammation of periorbital and nose region, proptosis, drooping eyes, edema, weakness or paralysis of eye muscles causing blurred or loss of vision, bulging eyes and nasal hemorrhage. (Sundaram N, et.al.,2021) When the disease grows towards the cranial region it may cause sluggishness, blindness, convulsions and eventually death of the patient. (Sundaram N, et.al.,2021) As the name of the disease indicates it causes blackish discoloration on affected tissues. (Ramandeep Singh Gambhir et.al.,2022) It is reported that the disease may cause dental problems like toothache and droopy teeth. (Rajasekar Panthamoorthy, Prathinisha Prabhakar, 2022)

V. RISK FACTORS: Mucormycosis in covid positive patients was developed in the second wave of coronavirus which was associated with various underlying factors, also certain normal individuals are prone to this infection due to these same factors. (Dr. Ak Dwivedi 2021) (Sundaram N, et.al.,2021) (Mohinsa FP, et.al.2021) (Rais N, et.al.,2023)

- Diabetes
- Extended stay in ICU
- Compromised immunity due to steroids
- Chronic sinusitis
- Haematological malignancies
- Organ and stem transplant
- Kidney dysfunction/disorders
- Dermal lesions
- Malnourishment
- Ketoacidosis
- Neutropenia
- HIV
- Broad spectrum Antibiotics
- Drug abuse
- Insufficient ventilation in hospitals
- Infected/dirty wound dressing
- Patients having oxygen support requirement
- Tuberculosis, lymphoma

- Pre covid treatment
- Patients undergoing anticancer treatment Use of steam inhalation

Diabetes Mellitus and ketoacidosis: This condition is associated with impairment of insulin production due to destruction of pancreatic beta cells which cause high blood sugar levels leading to poor immunity. (Disha et al. 2023) The enzyme ketone reductase in rhizopus species enhances glucose production and produces acidic conditions i.e ketoacidosis thus providing suitable conditions for fungus to grow. (P. Monika and M.N. Chandraprabha 2022) The high sugar levels also cause dysfunction of neutrophils while acidic conditions impairs motility and activity of neutrophils. (Sheikh et al., 2022) The patients with neutropenia are more prone to this infection. (Rais et al., 2023)

Steroids: To fight against coronavirus patients administered steroids, anti-cytokines, mTOR (mammalian target of rapamycin) inhibitors and anti-metabolites, these agents behaved as immunosuppressive thus weakening immunity of patients. (Tahani et al., 2022) The prolonged use of steroids brought the immunocompromised state of patients due to lymphopenia and immoderate T lymphocytes. (Disha et al., 2023)

Transplantation: Based on type of transplantation it occurs 0.4-16%. (Sheikh et al., 2022) The recipients having hematopoietic melanoma, acute myelogenous leukemia are at higher risk than those who had organ transplant. (Sheikh et al., 2022) As these patients are under treatment of steroids and immunosuppressants it contributes as a risk factor to this infection. (Iyer et al., 2021)

Chronic kidney disease: Indian and Turkish studies have reported that 9-32% and 18% patients respectively with CKD were infected with black fungus. (Rais et al., 2023) The treatment of deferoxamine in patients with kidney failure, diabetes ketoacidosis and transfusion related disorders with aim of reducing iron level contributed as a major factor for causing mucormycosis. As this reduced iron was uptaken by fungi for its growth. (Prakash H and Chakrabarti A, 2019)

Zinc supplements and steam inhalers: The study by Dr. VP Pandey observed that the use of antibiotics like azithromycin, doxycycline and carbapenem increases the risk of infection as the zinc rich supplements provide a favourable environment for fungi. The use of steam inhalers causes mucosal damage that helped fungi to pass first natural defense of humans. (Acharya et al., 2022) as it is easier for fungi to infect the wounds.

Increased in demand of oxygen cylinders: Industrial oxygen cylinders were redirected to hospital use which were associated with development of risk of growth of fungi inside those cylinders due to polluted air and water. (Acharya et al., 2022) The risk was also caused due to usage of a poor-quality piping system of oxygen. (Disha et al., 2023)

Prolong stay in ICU: Increased spread of virus caused the emergence to expand the capacity of ICU which led to poor maintenance of control measures that ultimately caused hospital acquired infections to patients. (Rehab et al., 2023)

VI. CLINICAL MANIFESTATION OF MUCORMYCOSIS: This is based on site of infection

- **Rhino-Orbital-Cerebral Mucormycosis:** This is the most common form of mucormycosis which defines the infection in paranasal sinuses to orbits and cerebral parenchyma (Selva et al., 2022) which indicates the infection observed in the neck and head region. (Shreya et al., 2022) The species that cause the infection are Cunninghamella, mucor, rhizopus, absidia and apophysomyces elegans. (Mohsina et al., 2021) This type is generally observed in immunocompromised, diabetic patients and its variable form occurs as a result of thrombosis of cavernous sinuses. (Selva et al., 2022) The symptoms involved are headache, nasal congestion, black lesions, fever, lethargy, orbital pain, edema, sensory loss, seizures, trigeminal nerve disruption and other neurological disturbances. (Pranave et al., 2023) (Rais et al., 2023)

- **Pulmonary Mucormycosis:** is usually observed in hematological malignancies accompanied by chest pain and hemoptysis and the common species involved are rhizopus, mucor, lichthemia, rhizomucor, cunnighamella, apophysomyces and skasenaia. (Vidya et al., 2022) The clinical manifestation is of an angio-invasive and thrombotic nature that leads to necrosis, this is the reason it usually occurs in lungs parenchyma. (Kumar et al., 2022) The symptoms comprise fever, cough, dyspnea, chest pain and lesions. (Alexandra et al., 2019)

- **Cutaneous Mucormycosis:** occurs due to injury or any harm in skin tissues (Shreya et al., 2022) which may be due to needlestick, animal sting, bite, burns. The infection may start from skin and extend to fascia, bone or throughout the body. (Md Rezaul et al., 2022) The symptoms are blisters, black lesions, pain, redness, swelling. (Rais et al., 2023) Here the causative agents are apophysomyces elegance, lichthemia and mucor species. (Alexandra et al., 2019) This infection may be localised, deep or disseminated or is also classified as

primary cutaneous mucormycosis (PCM) and secondary cutaneous mucormycosis (SCM). PCM occurs as a result of direct inoculation of infection while SCM caused by dissemination of infection and commonly is secondary to rhino orbital cerebral mucormycosis. (Shrikant et al., 2021)

- **Gastrointestinal mucormycosis:** This form of mucormycosis affects the organs like stomach and colon and is reported to be an uncommon form of mucormycosis. The symptoms associated with this are imprecise, including fever, nausea, vomiting, abdominal pain, GI bleeding and perforation. (Mayank et al., 2022) This type is observed in premature neonates and other immunocompromised patients including AIDS, organ transplants, systemic lupus erythematosus. It involves rupture of intestine and is reported to be caused as a result of intake of bakery pathogenic products like bread and fermented milk. (Pranave et al., 2023)

VII. EPIDEMIOLOGY: After the second wave of coronavirus mortality rate increased to 54%, before it was reported that CAM was associated with diabetic patients but official data stated 14 per 1000,000 people in India were affected which contributed upto 70 times greater than the rest of the world. In march 2021, around 41 cases of CAM were reported around the world, in that 70% cases from India. (Chaitali et al., 2022) In the current second wave of covid infections in India, the number of cases has gone up much higher. In 2021, cases of mucormycosis progressively increased in different states of India including Maharashtra (6389 cases), Madhya Pradesh (764 cases), Gujarat (5486 cases) and in Uttar Pradesh (800 cases). (Shrikant et al., 2021) The disease is said to be fatal as mortality rate associated with it is high, the gastrointestinal mucormycosis is associated with 66.7% mortality rate while pulmonary 61.3%, cutaneous 57.1%, renal 50% and rhino orbital cerebral 48.6%. It is reported that it can outstretch to 100% if not diagnosed and treated at time. (P Monika and M.N. Chandrababha 2022)

VIII. PATHOGENESIS: (IN ABSENCE OF COVID 19) The fungi mucorales causing mucormycosis occurs as spores in hot spells and is non communicable. (Yasmin et al., 2022) Although non communicable these spores can be inhaled through the nasal cavity, pulmonary alveolar region. (Neelam et al., 2023) As they enter through these routes the first site of infection is nasal turbinates which then expands to sinuses, palates, orbit and brain. This fungus has affinity towards blood vessels thus possessing an angio invasive nature which causes ischemia and necrosis. (Sundaram et al., 2021) The infection to nasal tissues causes the nasal congestion and spread of the infection to the jawbone accompanied by neutropenia. (Yasmin et al., 2022) This fungal spore on interaction with CoH7 protein in lung epithelial binds to β -1 integrin receptor causing the destruction of these epithelial cells. (Chandley et al., 2022)

IX. PATHOGENESIS: (PRESENCE OF COVID 19) In case of immune-compromised patients SARS-CoV-2 interacts with angiotensin converting enzyme 2 (ACE2) receptor causing pneumonia, vascular, endothelial damage and reduce CD4+ and CD8+ T cells count thus making easier for bacteria and fungi to invade the host. (Yasmin et al., 2022) In such patients the spores are converted to hyphae and since the count of white cells is low, they exhibit lower efficacy on hyphae and therefore get proliferated easily. (Sundaram et al., 2021) Mucorales spores have the ability to interact with glucose regulated 78kDa protein (GRP78) to enhance its production and deregulation of iron homeostasis to increase plasma concentration of free iron. (Chandley et al., 2022) The availability of free iron in plasma is associated with ketoacidosis which ultimately is taken up by mucorales for their growth and this results in thrombosis of vascular compartment and tissue necrosis. (Neelam et al., 2023)

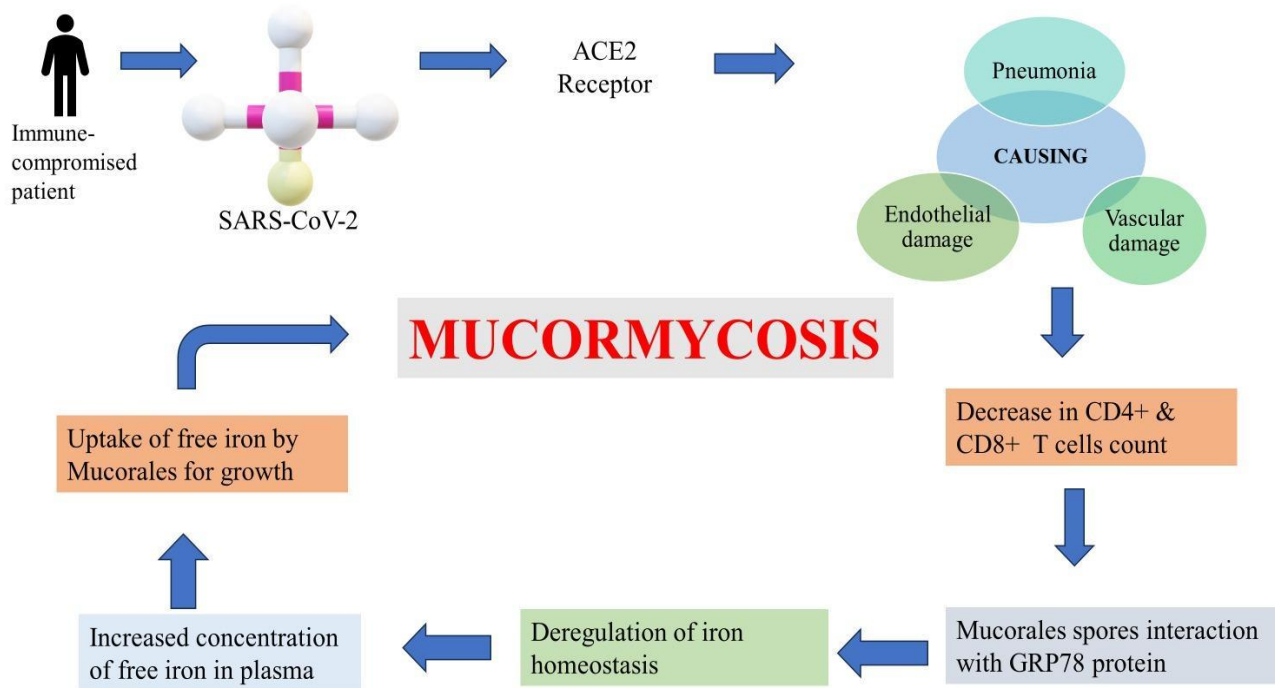


Figure 1: Pathogenesis of mucormycosis in presence of Covid 19

X. TREATMENT: Treatment of mucormycosis can be divided into first line therapy, step down or salvage therapy, surgical therapy.

First-line therapy: The primary treatment and the drug of choice for mucormycosis is Amphotericin B, its lipid formulation was prescribed to patients suffering from CAM. (Chaitali et al., 2022) According to European Confederation of Medical Mycology (ECMM) the dose of 5mg/kg/day was given to patients. (Vidya et al., 2022) Its higher dose can be administered for a longer period of time as it is less nephrotoxic (Selva et al., 2022). The research study demonstrated that the patients who were not provided with AMB therapy suffered doubled mortality rate after 12 weeks of diagnosis. (Neelam et al., 2023)

Step down or salvage therapy: Amphotericin B is the most potent drug against mucormycosis accompanied by posaconazole, itraconazole, and isavuconazole. Posaconazole suspension was used in treatment of this infection, the drug was administered orally or through an intravenous route having beta cyclodextrin to improve pharmacokinetic properties. Posaconazole 200 mg four times a day was prescribed to patients. (Chandley et al., 2022)

Isavuconazole having wide range pharmacokinetic and safety properties was administered orally as well as intravenously to treat mucormycosis. It is a recently developed triazole derivative which has a wide range of action against zygomycetes. Additional antifungal compounds included voriconazole, caspofungin, echinocandins. (Selva et al., 2022) In vitro studies of isavuconazole against mucorales species reported that the drug shows minimum inhibitory concentration MIC at 1-4 mg/L. (Chandley et al., 2022)

It is stated that step down therapy should be continual for 3-6 months or at least 6 weeks for clinical improvement. The administration of these antifungal drugs through intravenous routes lead to infusion related reactions including nausea, vomiting, chills and to inhibit this promethazine and prochlorperazine can be used. (Chaitali et al., 2022)

Surgical therapy: Mucormycosis is defined as an angioinvasive process that causes infarction and necrosis to involved tissues. In order to have an effective treatment it needs surgical removal of infected tissues. (Kevin et al., 2023) The only way to bring down death rate and problems of low drug bioavailability to infected tissue due to thrombosis is surgical debridement of infected tissue. This infected tissue is removed using MRI/CT guided endoscopic sinus technique. (Neelam et al., 2023) The surgical debridement is in the form of resection, lobectomy or pneumonectomy. (Vidya et al., 2022)

XI. SUGGESTED ANTI-FUNGAL HERBS FOR TREATMENT/ PREVENTION OF MUCORMYCOSIS (Rajasekar Panchamoorthy, Prathinisha Prabhakar, 2022). (Ravindra et al., 2021)

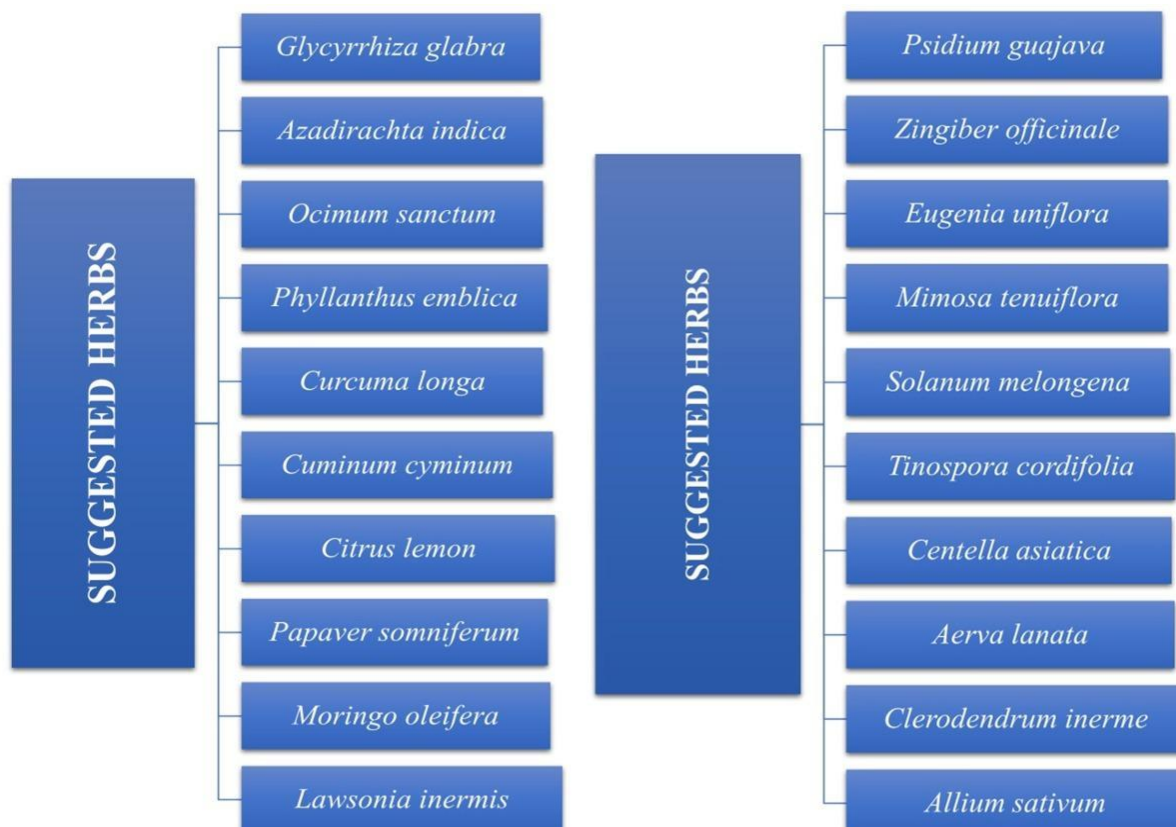


Figure 2: Suggested herbs

Discussion

Mucormycosis or black fungus that emerged from Wuhan, China was found to be a deadly disease during the second wave of coronavirus. This secondary fungal infection arised due to covid-19 infection and its immunosuppressive treatment. The various risk factors that contributed were diabetes, organ or stem transplant, extended stay in ICU, usage of broad-spectrum antibiotics etc. The major causative agents reported were Mucor, Cunninghamella, Apophysomyces, Lichtheimia, Rhizomucor. Rhizopus is the most common pathogenic agent causing mucormycosis in humans. This disease is characterised by formation of black lesions on entering the body and additional indications includes distress, inflammation on face or facial pain, drooping eyes, blurred vision and dental problems. Although it is a fatal and rare disorder it is treatable with coordinated teamwork from healthcare specialists and in order to increase the survival rate there should be early diagnosis and treatment along with preventive measures like proper sterilization of medical devices, maintenance of sterile areas to prevent infection, this multidisciplinary approach will help in management and treatment of the mucormycosis. Additionally, we have also suggested a possible herbal remedy for mucormycosis.

Acknowledgment

Authors would like to acknowledgment Principal and Management of KJ Trinity College of Pharmacy for the support and availability of resources in written this review.

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