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COVID-19 Associated Mucormycosis (CAM): A Brief Review



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ABSTRACT

Mucormycosis is also known as “**Black Fungus**”. It has come into light as mucormycosis as a formidable infection in patients with severe and fatal immunosuppression. Heavy intake of steroids with no vitamin supplements and immune supplementation has led to further deterioration of health of covid-19 recovered patients. Patients are reporting back to the hospital with complaints of the black fungus, UTI, recurrent diarrhoea and compromised lungs functioning. According to the doctors, cases of mucormycosis are being seen among Covid patients who were administered steroids to treat the symptoms, particularly among who are suffering from diabetes, cancer and other co-morbidities. The most prominent predisposing factors are immunosuppression followed by neutropenia and haematopoietin, stem cell transplantation, uncontrolled DM, burns, morbidity leads to increased demand of antifungal drugs. Black fungus is manifest in the air pockets located behind the forehead, nose, cheekbones and in between the eyes and teeth. Black fungus is spread to the eyes, lungs and spread even to the brain. Treatment of this fungal infection requires a multi-disciplinary approach consisting of eyes surgeons, ENT specialist, general surgeons, neurosurgeons and dental maxillofacial surgeons, among other, and the institution of the Amphotericin-B as an antifungal medicine. From COVID-19 pandemic, many reports came of the very high incidence of COVID-19 induced mucormycosis in patients with diabetes and who are on steroids during their stay in hospitals.

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INTRODUCTION

Mucormycosis is a fungal infection that affects subjects who are adhered on other morbid drug regime, which reduces body's ability against other environmental antigens. It has come into light as mucormycosis as a formidable infection in patients with severe immunosuppression [1,2]. Due to inhalation of fungal spores, the lungs and airway gets infected to mucormycosis and related symptoms. In view of increasing cases of black fungus in covid-19 treated patients, this disease has been announced as epidemic in about 14 states including Haryana, Madhya Pradesh, Himachal Pradesh, Karnataka, Chandigarh, Uttarakhand, Telangana, UP, Punjab, Gujarat, Tamil Nadu, Rajasthan, Odisha, Bihar.

Mucormycosis is a serious juncturous infection caused by a vast number of moulds, “mucoraceous molds” commonly, *Lichtheimia* species, *Phizomucor* species, *mucor* species, and *rhizopus* species etc. it mainly affects craniofacial, rhino cerebral, cutaneous, pulmonary and systemic diseases followed by almost fatal rapid organ/ tissue

necrosis which remains untreated. It is caused by the fungus belonging to order Mucorales, *Rhizopus oryzae*, the most common organism isolated from patients with black fungus which is responsible to cause 70% of all cases of mucormycosis [3,4,5]. Risk factors include uncontrolled DM, in ketoacidosis, metabolic acidosis, corticosteroid treatment, neutropenia, trauma and burns, deferoxamine therapy [6]. This infection is caused by the groups of moulds called mucormycetes which are naturally present in the environment (especially in soil and other decaying organic matter like leaves, compost piles and animal dung). In the present scenario, the infection is especially affecting COVID-19 recovered patients with weakened immunity or treated with steroids and recovered individuals with added comorbidities like DM, cancer and kidney or heart failure that reduce their ability to fight environmental pathogens [7,8].

The epidemiology of MCM over past 2 decades has been complex, and at the same time controversial [9]. Exact prevalence and incidence are unclear because previously it wasn't reportable, having low atopsy rates [10], inaccuracy in hospital discharge codes [11], according to the studies conducted in France and United States, Mucormycosis is developing rapidly especially in hematology and hematopoietic stem cell transplant unit depending upon patients characteristics, and site of infection, mortality increases, near 70-90% for the cases of disseminated mucormycosis [12-14]. Mucormycosis is not contagious;

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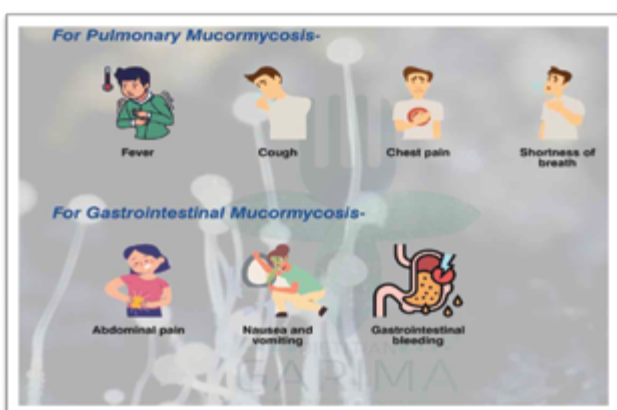
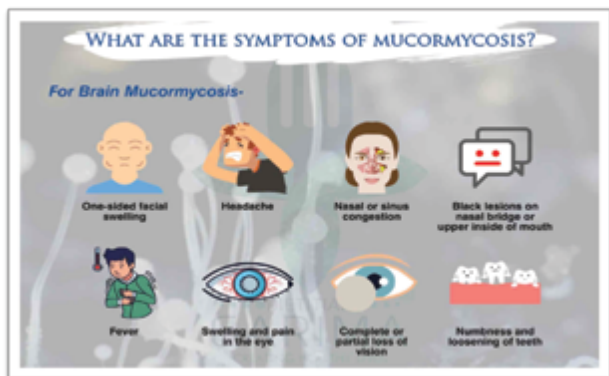
it can not transmit between people and animals; individuals contract this infection by coming in contact with the fungal spores in the environment. The fungi can also enter the body through open wounds/ cuts. The infection can subsequently spread to the blood stream, and reach organs like brain, heart and spleen as well [15,16].



Figure 1: Postulated interaction of diabetes, corticosteroid and COVID-19 with mucormycosis. Sign & Symptoms of Mucormycosis/ Black Fungus.

This can lead to serious disease with warning sign and symptoms as follows:

1. Fever
2. Headache
3. Coughing
4. Shortness of breath
5. Bloody vomit
6. Altered mental status
7. Pain and redness around eyes and / or nose [17].



Predisposing Factors

1. Uncontrolled diabetes mellitus (DM) with or without ketoacidosis.
2. Immunosuppression by steroids.
3. Prolonged ICU stays.
4. Voriconazole therapy.
5. Comorbidities- post-transplant
6. Haematological malignancies
7. Prolonged neutropenia
8. Corticosteroids therapy
9. Trauma
10. Illicit IV drug use
11. Neonatal prematurity and malnourishment

Non sterile products use is the most common suspected cause of infection [18]. Adhesives, bandages, linen, nitro-glycerine patches, wooden tongue depressor, ostomy bags and probiotics have been implicated. Also reported the outbreak due to allopurinol and pre-packaged foods. Various medical devices like, catheters, insulin pumps, finger sticks, insertion tubes, tooth extraction and surgery [19]. Environmental factors may also be manifested as the source of infection. Moulds that are found in air, dust, water, or on any surface of water, defective ventilation systems and water leakage etc [20].

Mucormycosis Do's

1. Control hyperglycemia.
2. Monitoring the blood glucose levels after Covid-19 recovery and also in Diabetics.
3. Use steroids judiciously- corrects timing, correct dose & correct durations.
4. Use clean, sterile water for humidifiers during oxygen therapy.
5. Use antibiotics / antifungals judiciously.

Mucormycosis Don'ts

1. Do not miss warning signs and symptoms.
2. Do not consider all the cases with a blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and Covid-19 patients on immunomodulators.
3. Don't hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDITOF), for the detecting fungal aetiology.
4. Do not lose crucial time to initiate treatment for mucormycosis.

When to Suspect the Fatal Infection

1. Sinusitis- nasal blockage or congestion, nasal discharge (blackish / bloody), localized pain on the cheekbone or one-sided facial pain, numbness or swelling.
2. Loosening of teeth, Tooth ache, jaw involvement.
3. Blackish discoloration over the bridge of nose / palate.
4. Blurred or double vision with pain; skin lesion; thrombosis and necrosis (eschar).
5. Chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms.

Diagnose Mucormycosis / Black Fungus

Upon suspicion, mucormycosis is a serious disease, the suspected person needs to perform radiographic studies, MRIs, and CT thorax for pulmonary mucormycosis.

Rhino Orbito Cerebral

At first consult the ENT clinician for the collection of debris through biopsy/ endoscopy- by taking one portion in saline for the culture and other portion in other saline solution for histopathology.

- Pulmonary mucormycosis
- BAL, mini BAL, non-bronchoscopy lavage, transbronchial biopsy, biopsy from lung culture and biopsy.
- Chest X-ray, and high-resolution computed tomography, and beta glucan tests.

Detecting Mcm Infection

Those caring for covid-19 recovered patients should look out for the danger signs. Watch out for: Abnormal black discharge or crust or blood from the nose. Nasal blockage, headache or eye pain, swelling around the eyes, double vision, redness of eyes, loss of vision, difficulty in closing eyes, inability to open the eyes and prominence of the eyes. Facial numbness or tingling sensation, odynophagia, loosening of teeth. Black areas and swelling inside the mouth, palate, teeth or nose (oral and nasal examination). Regular self-examination: full face examination in daylight, for facial swelling (especially nose, cheek, around the eyes) or black discolouration, hardening, pain on touch. Corzo- Leon et al, proposed an algorithm for diagnosis and treatment of rhino orbital cerebral mucormycosis in DM patients. The “red flags/ warning signs” are cranial nerve palsy, diplopia, sinusoidal pain, proptosis, swelling, apex syndrome or palatine ulcer.

Treatment of CAM

Medical approach is required along with the infectious disease specialist, microbiologist, histopathologist, neurologist, ENT specialist, ophthalmologist, dentist, surgeons and radiologist etc.

Controlled of DM & DKA

1. Reduction of steroids (if patient is getting steroids therapy) followed by rapid discontinuation.
2. Discontinuation of other immunosuppressants drugs if patient is taking baicitnib, tofacitinib

1. Surgical process: extensive- removal of necrotic material, if eye seems affected, exenteration of eyes etc.

Medical Treatment:

- a. insertion of central or peripheral catheter.
- b. maintenance of hydration, infusion of normal saline IV before amphotericin B therapy

antifungal therapy:

1. **Liposomal Amphotericin B:** (L-Amp B) 5mg/kg/day, diluted in 200 cc 5% dextrose for 2-3 hours infusion (higher dosage of 10mg/kg/day can be given in case of brain involvement)
2. **Amphotericin B Deoxycholate:** A Pharmacoeconomic option, 1 mg/kg/day in 5% dextrose, slow infusion for 6-8 hours. Pre medication might be required to avoid any infusion reaction.
3. Regular monitoring of renal function and potassium levels should be done while amphotericin-B therapy
4. Patient intolerant to amphotericin B can be given the alternative agents i.e: posaconazole or isavuconazole available in injection and tablet form are posaconazole or isavuconazole (injection/tablets).
 1. Tablet isavuconazole 200 mg TDS prescribed for two days followed by 200 mg therapy once in a day.
 2. Tab. Posaconazole 300 mg BD for the first day followed by 300 mg OD, along with regular monitoring of drug levels on each 4 days of therapy to avoid drug interaction.
 3. Regular monitoring of patient through radio imaging, microbiology for disease progression
 4. Consolidation therapy of posaconazole/ isavuconazole after 3-6 weeks of amphotericin B therapy for 3-6 month.

Prevent Mucormycosis / Black Fungus

Early diagnosis and timely treatment can help in successful treatment. Usually MRI scans determine the extent of the damage the fungus may have caused. The infection can be treated with antifungal medicines. Reduce steroids use and discontinue immunomodulating drugs.

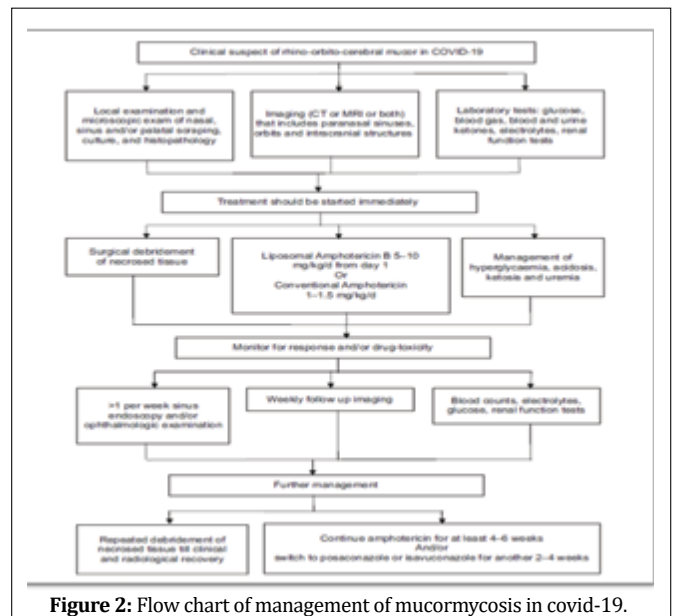


Figure 2: Flow chart of management of mucormycosis in covid-19.

In some cases, surgery may be required to Cut away infected part. If left undiagnosed or untreated, it may result in blindness, removal of nose, jaw-bone or even deaths.

1. If you are visiting dusty construction sites, they have proper use masks.
2. Long trousers, long sleeve shirts and gloves, wear shoes while handling soil (gardening), moss or manure.
3. Maintain personal hygiene, including through scrub bath.



Conclusion & Future Prospective

We observed, the focus has been to save the life of patients. There has been indiscriminate use of steroids. If one did not work, another was tried. No set protocol was being followed in the second wave of covid-19. Due to this, range of side effects are evident. Antibiotics and steroids are the schedule H drugs but were prescribed freely in the second wave of covid-19. Covid-19 associated mucormycosis (CAM) can be a very serious and dangerous complication of severe covid-19 in second wave of corona, especially in uncontrolled diabetes mellitus patients. The complexity between covid-19 and mucormycosis is still mostly unknown. The main predisposing and risk factor were CAM is uncontrolled DM, which was exacerbated by the irrational use of glucocorticoids during the treatment of second wave of COVID-19. As a Clinical Pharmacologist, this article concluded, the highest use of steroids namely dexamethasone and methylprednisolone were observed in the second wave of covid-19. After the schedule of the treatment went viral on the social media, these medicines were dispensed without prescription at pharmacies. Antibiotics and steroids have been overused by many patients for their self-treatment. The irrational use of steroids has led to a wide range of side effects. As a Clinical Pharmacologist & Pharmacotherapist it has been noted that patients who self-prescribed took the medicines for three days, if cough, cold and fatigue persisted during the 3 days, they took it again for 10-15 days. This kind of use is now backfiring.

Ethics Approval and Consent to Participate

Not applicable.

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Authors Contributions

The manuscript is prepared, and edited by the main and single author.

Consent for Publication

I am hereby giving my consent for publication.

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Conflicts of Interest

There are no conflicts of interest.

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