

# Mucormycosis in COVID-19

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## ABSTRACT

COVID-19 a global pandemic started in December 2019 and in these last year it has been linked to a range of bacterial, fungal, and viral infections. Mucormycosis sometimes known as black fungus is one of the rare but deadly angioinvasive fungal infection caused by group of fungi mucormycocetes which leads to upsurge of Mucormycosis in COVID-19 patients. Many states in India have declared mucormycosis as an epidemic due to its upsurge in numbers and higher fatality rate. Though mucorales can affect the any part of body but it has tissue tropism towards nasal sinuses, orbit, CNS, pulmonary, skin. Most common clinical presentation of fungi is infection of sinus with nasal blockage and discharge.

Mucormycosis is a non-contagious fungal infection, more common in immune compromised patient. Acute inflammatory reactions in COVID-19, corticosteroids treatment and diabetes enfeeble the immunity and it makes the perfect storm for Mucormycosis. Diabetes that isn't well managed results in the acidosis a satisfactory environment for fungi to grow. An early diagnosis and management can decrease the fatality rate.

**Aim:** The goal of this study is to provide a comprehensive overview of the literature concerning Mucormycosis aetiology, features, and management and how it can be prevented in COVID-19 (SARSCoV-2) patients.

**Conclusion:** COVID-19, overuse of corticosteroid along with uncontrolled diabetes leads to an upsurge of mucormycosis. So an effort should be made to stringently monitor and keep the blood glucose level under control and judicious use of corticosteroid and antibiotics should be practiced in COVID-19 patients.

**Key words:** COVID-19, Mucormycosis, Corticosteroid, Diabetes

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## INTRODUCTION

The first human case of corona virus illness, also known as COVID-19, was documented in Wuhan, China in December 2019. It was caused by a coronavirus that causes severe acute respiratory syndrome (SARSCoV-2); it is the 7<sup>th</sup> coronavirus [1]. On March 11, 2020, the WHO classified the outbreak as pandemic [2]. COVID-19 primarily causes respiratory symptoms from mild to severe pneumonia.

COVID-19 infection is related with a lot of bacterial and fungi co-infection. In the first wave of the COVID-19 epidemic in India, the first instance of black fungus was detected a few weeks after the patient was discharged from the hospital. Several incidences of mucormycosis have been documented during the second wave of COVID-19. The emergence of mucormycosis is another unwelcome consequence of the COVID-19 pandemic. Mucorales infects the facial bones and nasal sinuses penetrate the CNS, and if it affects the orbit, it can cause

blindness. If not treated, mucormycosis can kill almost 50% of patients; treatment consumes a lot of time and challenging. The accepted treatment for severe SARS-CoV-2 infection is an elevated dosage of steroids, antivirals and antibacterial, all of which impair the immune response which exposes the individual to contamination by fungi and bacteria present beforehand in body or in the habitat.

Mold fungi of class zygomycetes, order mucorales, and genus *Rhizopus*, *Mucor*, *Rhizomucor* cause mucormycosis, which is an angioinvasive fungal infection [3]. Spores of these ubiquitous fungi can be inhaled and then it infect the lungs, sinuses, and extend into the brain and eyes [4]. Diabetes (especially diabetic ketoacidosis), extended corticosteroid misuse, haematopoietic and lymphoid tumour, transplantation of organ, chronic liver and kidney illness, and immunological disorders are indeed factors which increase the risks for mucormycosis [5]. Mucormycosis has also been associated to underweight babies, chronic alcoholism, intravenous drug use, malnourishment, and acquired immunodeficiency syndrome.

Mucormycosis is eighty times more prevalent in India than in Western countries, with about 0.14 cases per 1000 people [5]. The diabetic population in India is already the

second largest in the world [6]. Diabetes Mellitus (DM) is the most prevalent cause of mucormycosis in India [7], while overuse of corticosteroids has also been linked to opportunistic fungal infections like Mucormycosis. If an immunocompromised patient has had a cumulative dosage of prednisolone higher than 600 mg or total methylprednisone dose of 2-7 g in the previous quarter, they are at risk for mucormycosis [8-15].

Although antifungal medicine can help with mucormycosis, surgery is ultimately required. Traditionally, mucormycosis was treated with an I.V. infusion of saline followed by amphotericin infusion. Because of the infection's high fatality rate, primordial recognition and recovery from predisposing circumstances are critical for effective treatment. Debridement procedures and medicinal delivery can also assist to ameliorate the situation [16-20].

## LITERATURE REVIEW

### Methodology

Databases of PubMed and Google Scholar were screened for studies on Mucormycosis in COVID-19. After going through abstracts of the studies the articles for review were selected. The selected articles focused on etiology, features, diagnosis and treatment of mucormycosis. Articles that had been recently published were given priority.

### Diagnosis

A significant amount of anticipation, recognition of host issues, and early examination of clinical symptoms are all necessary for mucormycosis diagnosis. Double vision in a diabetic individual and pleuritic discomfort in a neutropenia host could be indicators of infection, necessitating the imaging modalities use and subsequent sample collection for histological, microbiological, and complex molecular testing. Mucorales infection usually shows up as rhino cerebral, pulmonary, soft tissues, and disseminated disease, but it can affect any organ [21].

Corzo Leon, et al. postulated a method for detecting rhino cerebral mucormycosis in diabetic patients. Clinical manifestations that should be regarded as "red flags" includes cranial nerve palsy, double vision, pain in sinuses, proptosis, periorbital edoema, along palate ulcers [22]. Radiologically Mucormycosis is said to be associated with numerous (>10) nodules and pleural effusion [23]. The reverse halo sign, which appears to indicate the presence of mucormycosis on a Computerized Tomography (CT) scan, is another finding that suggests the existence of mucormycosis [24]. In neutropenic leukaemic patient along with lung infection, the appearance of reverse halo sign on CT is a robust predictor of pulmonary mucormycosis. MRI brain can be done for the better demarcation of CNS involvement. PET/CT with (18 Fdg) is another new imaging technology that may aid in the diagnosis and treatment of mucormycosis [25]. Endo bronchial ultrasound-guided

fine needle aspiration is also an efficacious diagnostic technique whenever it is available [26].

Direct microscopy is convenient in detection of hyphae in clinical specimens since it is quick and implies pathology. After staining with potassium hydroxide, optical brightener (calcofluor white), or with Gomorimethamine-silver specimens can be analysed [27]. With a diameter 5-25 um that are non-or pauciseptate hyphae are hyaline, ribbon like structures. With branching angles of 90°, the width is uneven. When hyphae are shattered, direct examination is difficult, hence culture is required for the confirmation of diagnosis. Tissue staining could be done with Gomorimethamine silver and PAS. Hyphae could be visualised in necrosed tissue with indications of angioinvasion or infarction; in non granulocytopenic or those who have more latent infection, neutrophil infiltrates or granuloma development can be seen. Immunohistochemistry done with commercially accessible antizygomycete antibodies can occasionally aid in the diagnosis [28]. With varying degrees of effectiveness, ELISA [29], immunoblots [30], and immune diffusion tests [31] were also assessed. An Enzyme Linked Imuno Spot (ELISPOT) assay was used to detect Mucorales specific T lymphocytes in haematological patients who developed invasive mucormycosis [32]. Mucorales-specific T lymphocytes were not seen in any of the controls.

In order to make a diagnosis, biological specimens from clinically affected locations must be analysed. When possible, tissue samples for histopathology and culture should be collected. Unfortunately, in those with hematologic malignancies, this is usually an issue due to severe thrombocytopenia. If a biopsy isn't an option, all obtainable specimen, such as sputum, ought to be analysed and cultured immediately. In the case of sinusitis, biopsies are required. To measure therapeutic response, endoscopy of ear, nose, and throat to be performed and done on a frequent basis.

### Treatment

Mucormycosis is best treated with a multimodal approach that includes correcting or eliminating core predisposing factors, as well as the use of potent antifungal drugs early on at the appropriate dose, total eradication of all infected tissues, and adjuvant treatment. Patients with uncontrolled diabetes who have been diagnosed with mucormycosis should have their metabolic abnormalities rectified as soon as possible. Corticosteroids and immune suppressants to be lowered to the smallest dose practicable as soon as possible. Early detection is essential in order to begin therapeutic measures as soon as possible in order to avoid continuous tissue invasion and its deadly consequences, mitigate the probability of Corrective surgery can be disfiguring, but it can also improve the outcome and survival rate [33].

Mucormycosis treatment guidelines were published by European Conference on Infection in Leukemia (ECIL) in

2017 [34], and the European Confederation of Medical Mycology (ECMM) updated them in 2019 [35]. Liposomal Amphotericin-B (L72 AMB) is strongly recommended for first line treatment in adults by both societies. According to the ECIL, alternative lipid formulations, Amphotericin-B Lipid Complex (ABLC), might be utilised in mucormycosis without involving the CNS. L-AMB and ABLC are invincibly suggested as first-line treatments for neonates and children.

Mucormycosis is treated with liposomal Am-B, which has been shown to be efficacious. Amphotericin-B attaches to ergosterol in the fungi cell membrane, causing holes and subsequent ion leakage, which causes the fungus to die. In hospitalised adults and children, liposomal Am-B injections at a beginning dosage of 5-7.5 mg/kg/day, diluted in 500 mL of 5% dextrose over 4-5 hours for 14-21 days, are widely utilised. Alternative therapies, such as an oral suspension of posaconazole, 400 mg twice day or 200 mg four times day, may be administered to patients who are intolerant or nonresponsive to Am-B.

Posaconazole along with isavuconazole are examples of triazoles. Posaconazole is recommended as a salvaged or maintenance treatment by ECIL-6, while it is recommended as a first-line treatment by ESCMID/ECMM at a dose of 200 mg q6 h of the oral solution by ESCMID/ECMM. The introduction of intravenous and tablet forms of posaconazole have resulted in increased availability and drug exposure [36]. This could boost the triazole's position in the antifungal arsenal, particularly against the difficulty to treat mucormycosis.

Coth-3, a Mucorales peptide that binds the endothelial cell receptor GRP78, has recently been related to mucormycosis endothelial invasion. Antibodies in opposition Coth-3 were created for the inhibition of endothelial invasion. Anti Coth-3 antibodies prevented mucormycosis in neutropenia and diabetic mice and worked in conjunction with antifungal therapies [37].

VT-1161 new inhibitor of the fungus CYP-51 enzymes along Mucorales action *in vitro*. In *R. arrhizus* models, VT-1161 given as a curative or preventative medication increased the lifespan of neutropenic mice [38].

The angio-invasive nature of mucormycosis agent's causes widespread thrombosis, tissue infarction, and necrosis, all of which might make it difficult for antifungal drugs to reach the infection site. Debridement of all devitalized tissue as soon as feasible, appears to be reasonable in order to attenuate the mass of infectious moulds and avoid the spread of mucormycosis to surrounding structures. Surgery is useful in rhino orbital cerebral mucormycosis. Preoperative MRI or CT scans should be utilised to evaluate the extent of the tissues and its margins before undergoing extensive surgery. Surgical excision of necrotic lesions on a regular basis has demonstrated to improve outcomes. After a successful operative procedure; the patient may undergo plastic surgery. Surgical recommendations vary depending on the location and severity of the problem.

### Preventive measure

For the prevention of mucormycosis in COVID-19 patients The Indian Council of Medical Research (ICMR) has released basic guidelines which are as follow [39].

- With or without the use of steroids, good sugar control to be achieved during COVID-19.
- Use of steroids in a rational way, at right dose, at right time, and for right length of time
- Antibiotic/antifungal use that is prudent.
- During oxygen therapy, use sterile or clean water as a humidifier.

### DISCUSSION

Commonly seen mucormycosis in clinical practice is Rhino orbital cerebral mucormycosis, but it can affect any region of the body, including the nose, orbit, sinuses, CNS, lungs, liver, skin, jaw bone, and cardiovascular system.

Smith and Krichner's clinical diagnosis criteria for mucormycosis, published in 1950, are still regarded the gold standard they include [9].

- Facial discomfort and Blood from nasal discharge on same side
- Black, necrosed turbinates
- Peri-nasal and soft periorbital edoema with discolouration and induration
- Proptosis and ptosis of the eye ball and eyelids respectively, and total paralysis of eye muscles, as well
- Cranial nerve palsy that are not related to lesions that have been recorded.

In COVID-19 infected patients mucormycosis can be triggered by number of factors like: The SARS-CoV-2 virus may infiltrate and flourish in islet cells [10], impairing pancreatic beta cell function and leading to acute DKA. Mucormycosis is more likely to occur in Diabetic Ketoacidosis [DKA] than in people who do not have DKA [11]. Hyperglycaemia causes transferrin and ferritin to be glycosylated, reducing iron binding and resulting in free iron. Fungal growth is aided by acidosis and increased availability of free iron. Ferrioxamine (iron-rich form of deferoxamine) ferrioxamine utilised by mucorales as a xenosiderophore to gather iron. Iron chelation therapy with deferiprone or deferasirox in diabetic ketoacidotic mice has been proven in several investigations to prevent mucormycosis and increase longevity. While adjunctive deferasirox was efficacious and well tolerated. Iron's inhibitory effect on neutrophil chemotaxis was likewise reduced by deferasirox.

At normal value of ketone bodies there is an elevated expression of fungal protein Coth-3 and GRP78 (Glucose Regulator Protein 78) in endothelium [12].

The uncontrolled utilisation of glucocorticoid in COVID-19 patient has resulted in increase in COVID associated mucormycosis [13]. Corticosteroid and immunosuppressive drug at high doses for a long time (>3 weeks) use can lead to infection of angioinvasive

fungi [14]. Glucocorticoid leads to immunosuppression, hyperglycaemia, and lymphopenia which lead to impaired immunity.

Platelets serve a critical function in enhancing host immunity after being exposed to an invading pathogen, and they also have antifungal and antibacterial properties: membrane bound molecules CD154 and platelet TLR that let the platelet attachment and activation of many cell; association with spores and hyphae induces platelet triggering, platelet accumulation and clotting, and fungi elimination by preventing hyphae development. The existence of necrotic areas in tissues that did not show any signs of fungal development suggests that thrombotic ischemia was induced by systematic platelet activation. Severely affected COVID-19 patients more likely develop the clot in vital organs, which further complicates the condition. As a result of this, mucormycosis spreads swiftly.

Natural killer cells (NK cells) can directly and indirectly kill fungi. They also synthesize chemokines and cytokines that modulate other immune cells activity. Natural killer cells can harm Mucorales hyphae. In COVID-19 Natural killer cell counts above a certain threshold can seriously compromise IgG immunity. CD16 present on NK cells interacts with the infected cell coated with antibody, results in antibody dependent cellular toxicity. As a first line of defence, the innate immune system modifies immunological responses and defends against COVID-19.

Mucormycosis is distinguished by its ability to enter the vasculature and induce tissue necrosis and thrombosis [15]. Mucor interacts with the GRP78 which helps in fungal endocytosis. Fungal ligand which binds to GRP78 comes under the spore coating family protein (CotH-3) [16].

Stress causes GRP78 to be released from endoplasmic reticulum of endothelial cells [17]. SARS-CoV-2 infection leads to endoplasmic reticulum stress which leads to the release of GRP78, it has been seen that SARS-CoV-2 virus use GRP78 for internalization in host tissue [18]. GRP78 also leads to the internalization and increases virulence and pathogenicity of mucorales [16].

An indirect association between COVID-19 infection and mucormycosis is dissemination of fungal spores through water use in oxygen humidifier [19].

COVID-19 infection leads to impairment of immunity due to decrease in CD4+ and CD8+ count, lymphopenia which leads to secondary fungal infection [20].

Mucormycosis affects the sinuses, brain, and lungs; however, it can also have an impact on the GIT, mouth cavity, cutaneous tissue, and other organs. It can induce a variety of symptoms in various organs:

- When sinusitis gets worse, it clogs the nostrils and causes a black release
- Cheekbone pain, as well as inconsistency in facial pain
- Fever, headache
- Decrease in sensation over one half of face
- Poor vision or double vision (diplopia)

- Jaw and teeth loosening
- Breathlessness, chest discomfort, bloody sputum
- Abdominal pain, bleeding from GIT

### CONCLUSION

In conclusion, COVID-19 has been linked to variety of fungal and bacterial infections due to impairment of immunity. Also the rampant use of corticosteroid and diabetes mellitus has increased the risk of opportunistic fungal infection. An effort should be made at the health care level to judiciously use the corticosteroid in COVID-19 infection and optimal management of hyperglycaemia in patients. Avoidance of unnecessary anti-bacterial and immunosuppressant Rhino cerebral mucormycosis causes inflammation on one side of the face, a bluish lesion within and outside the stoma, headaches, and sinus blockage. These symptoms increases the suspicion in post COVID patient for mucormycosis and one should seek of medical advice one should strictly monitor the blood glucose level. Early detection and treatment of mucormycosis can improve survival rates and minimizes fatality.

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