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MUCORMYCOSIS: THE 'BLACK FUNGUS'

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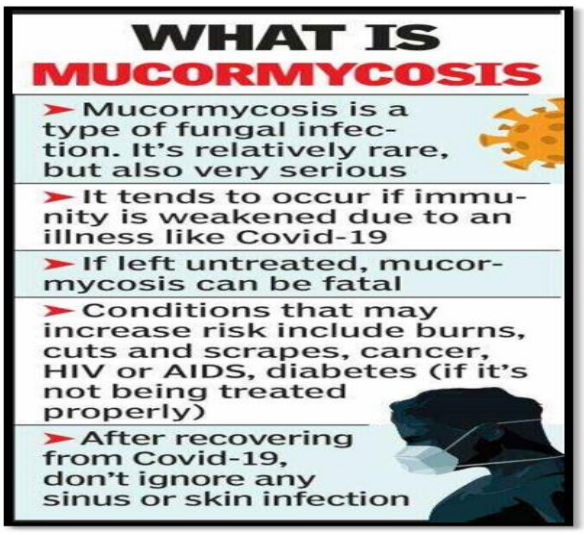
ABSTRACT
Mucormycosis is an angio-invasive fungal infection, associated with high morbidity and mortality. A change in the epidemiology of mucormycosis has been observed in recent years with the rise in incidence, new causative agents and susceptible population. The rise has been perceived globally, but it is very high in the Asian continent. Though diabetes mellitus overshadow all other risk factors in Asia, post-tuberculosis and chronic renal failure have emerged as new risk groups. The rhino-cerebral form of mucormycosis is most commonly seen in patients with diabetes mellitus, whereas, pulmonary mucormycosis in patients with haematological malignancy and transplant recipients. In immunocompetent hosts, cutaneous mucormycosis is commonly seen following trauma. The intriguing clinical entity, isolated renal mucormycosis in immunocompetent patients is only reported from China and India. A new clinical entity, indolent mucormycosis in nasal sinuses, is recently recognized. The causative agents of mucormycosis vary across different geographic locations. Though Rhizopus arrhizus is the most common agent isolated worldwide, Apophysomyces variabilis is predominant in Asia and Lichtheimia species in Europe. The new causative agents, Rhizopus homothallicus, Mucor irregularis, and Thamnostylum lucknowense are reported from Asia. In conclusion, with the change in epidemiology of mucormycosis country-wise studies are warranted to estimate disease burden in different risk groups, analyse the clinical disease pattern and identify the new etiological agents.

KEYWORDS: Mucormycosis; incidence; diabetes mellitus; haematological malignancy; Rhizopus arrhizus.

INTRODUCTION
Mucormycosis is a very rare infection. It is caused by exposure to mucor mould which is commonly found in soil, plants, manure, and decaying fruits and vegetables.[1]

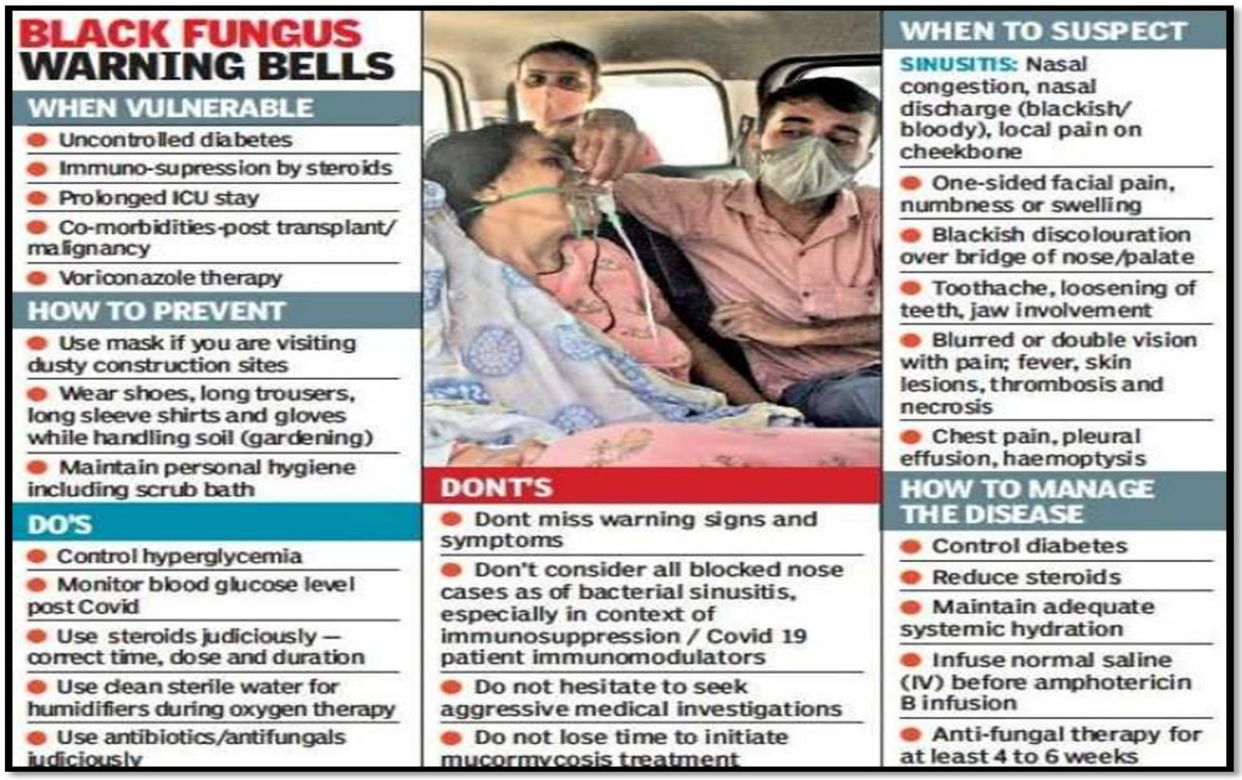
It affects the sinuses, the brain and the lungs and can be life-threatening in diabetic or severely immunocompromised individuals, such as cancer patients or people with HIV/AIDS.[2]

Patients suffering from the fungal infection typically have symptoms of stuffy and bleeding nose; swelling of and pain in the eye; drooping of eyelids; and blurred and finally, loss of vision. There could be black patches of skin around the nose.[3]



What is a fungus?

These are organisms separate from the plants and animal kingdoms. They are ubiquitous in nature and are found in the soil, plants, decaying organic matter, water, air, damp places, and also in humans and animals.[4] They play a very important role in our ecosystem along with bacteria, by degrading organic matter into simpler forms for the consumption of plants.[5]



There are about 1,44,000 species of fungi (plural for fungus), out of which some of them are pathogenic to humans. The most common being Candida, Aspergillus, Cryptococcus, Histoplasma, Pneumocystis, and Mucormycetes.[6]

Who is susceptible to fungal infections?

As previously mentioned, people with reduced immune response are more susceptible to infection. Conditions that reduce our immunity include[7]

- Diabetes: High blood sugars with an acidic environment as seen in diabetic ketoacidosis are the right recipe for the rapid growth of these organisms. Diabetes is also associated with reduced immune response.
- Steroid's medication increases blood sugar levels and decreases the immune response of the body.
- Blood malignancies, which again results in the defective immune system
- Patients on immunosuppressants as seen with organ recipients and haematologic stem cell recipients.
- Patients with excess iron or taking deferoxamine (specifically used in iron overdose).
- Trauma, burns, and malnourished people.

Clinical Diagnosis and Red flags in mucormycosis[8]

1. Mobile Teeth
2. Halitosis
3. Dental Pain
4. Palatal Ulceration
5. Intraoral Draining Sinuses
6. Para-sinusal pain
7. Nasal stuffiness
8. Nasal Discharge with epistaxis, black purulent discharge
9. Erythema of nasal mucosa
10. Facial Erythema
11. Black Discoloration of Skin
12. Periorbital erythema and edema
13. Orbital Pain, Ptosis, Diplopia
14. Fever

What is rocm or black fungus infection?

Mucormycosis (previously known as Zygomycosis) is a serious but rare fungal infection caused by a group of molds known as micromycetes.[9] 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.[10] These molds live throughout the environment and their spores are present in the air. They get lodged in the nasal cavity and adjoining sinuses.

On reaching a favourable milieu they ensconce themselves within the tissue. The spores germinate, hyphae (filamentous processes) outgrow and release destructive juices which digest the host tissue and provide nutrition to the rapidly growing fungi.[11] As they grow in the nasal cavity they relentlessly destroy the surrounding host tissue. The bones in the nasal cavity and sinuses are destroyed. These include the hard palate, the orbital bones, and the skull base bones. Black masses may be seen in the nasal cavity and oral cavity. If it destroys the orbit and enters the eye socket it may cause bulging of the eyes, pain, frozen eye movements, and blindness. Once it enters the cranial cavity by breaching the skull base it blocks major arteries and venous lakes resulting in major life-threatening brain strokes and bleeds.

The spores can sometimes travel into the depths of the respiratory system and get comfortably lodged in the lung parenchyma (alveoli and bronchioles). Here the fungi grow rapidly, destroying the lung tissue and compromising blood oxygenation. From there it can spread into the circulatory system resulting in an existential crisis.[12]

Is it contagious?

The disease is not contagious and doesn't spread from one person to another.

Lab investigation for diagnosis of mucormycosis[13]

1. Deep Nasal Swab for KOH smear & Fungal Culture
2. CRP level
3. Negative Galatomannan and Beta-Glucan Test(to exclude aspergilosis)
4. Biopsy

- 50% tissue in saline for fungal culture
- 50% tissue in 10% formalin for histopathology

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.[14]

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.[15] 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.[16] 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 factors leads to mucormycosis infection.

What are the clinical features of mucormycosis infection? How do we diagnose them?

Nasal blockage, bleeding, discharge from the nose are initial features of mucormycosis. On endoscopic visualization of the nasal cavity an unmistakable black eschar (slough or dead tissue) coated masses will be present which gives away the diagnosis. As the disease progresses the palate may be destroyed as a large black necrotic mass may be seen on opening the mouth.[17] When the orbit is involved there will be proptosis (protrusion of eyeball), loss of movements of the eyeball with consequent double vision. Eye pain, redness with blindness can follow. If the brain is invaded due to blood vessel blockage there will be strokes, hemorrhages, and even death. Patients can also have headaches, drowsiness, limb weakness, seizures and even death.[18]

Based on clinical suspicion MRI and CT scan of the nasal cavity, sinuses, and brain is performed. These give a clear picture of the presence of the lesion along with its extent.

In lung mucormycosis clinical features are similar to COVID-19 with fever, cough, shortness of breath, making clinical diagnosis difficult. Suspicion of fungal infection must be considered when a patient despite getting appropriate medications is not improving or was improving and has unexplained deterioration. CT chest helps in diagnosis by revealing additional lung lesions. Diagnosis is by microscopic evaluation of the bronchopulmonary lavage aspirate.[19]

Can there be other fungal infections in Covid 19 patients?

In western countries, Mucor has not caused as much havoc as it has in India. However, there has been an increased incidence of other fungal infections like aspergillosis and candidiasis in COVID-19 patients.

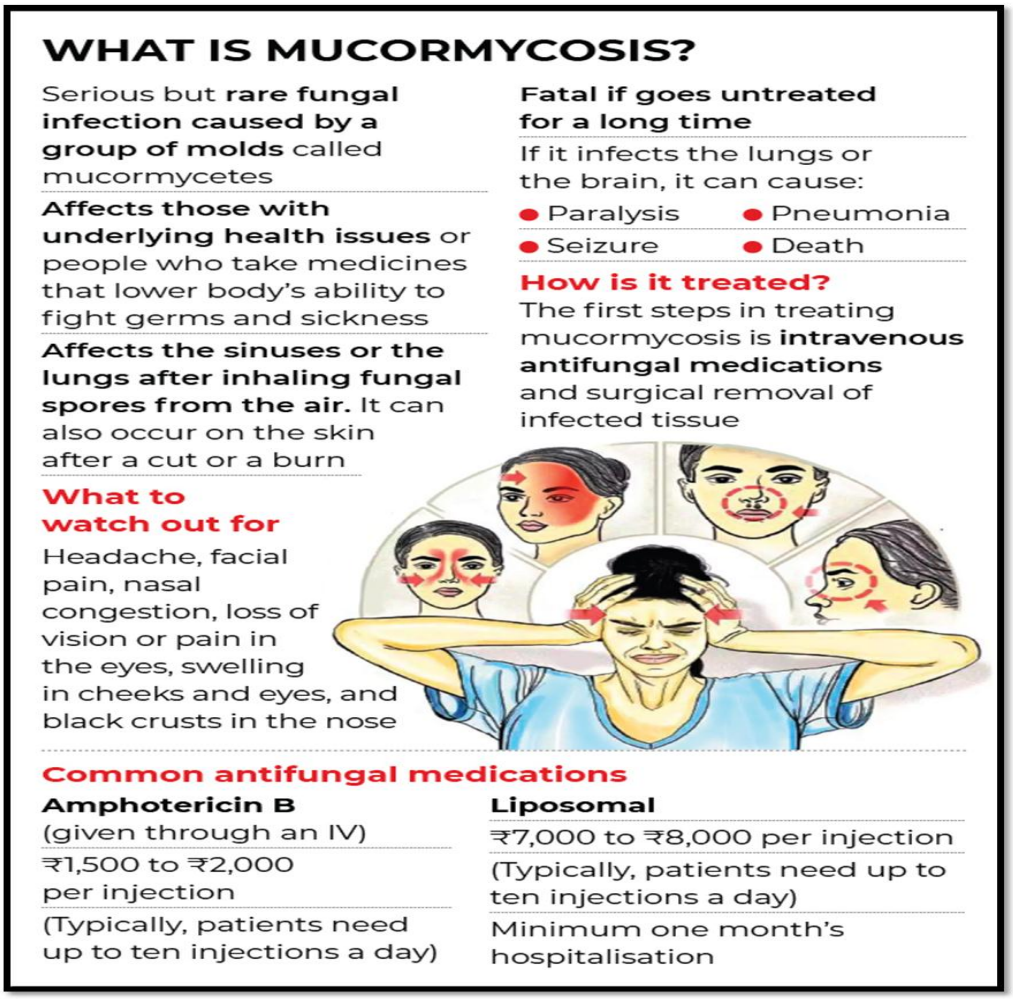
How is rocm treated?

It is a multi-pronged approach. Once a clinical and radiological diagnosis is made, endoscopic evaluation of the nasal cavity can confirm a fungal lesion.[20] Immediate surgical debulking is a must. The surgery can be radical and disfiguring but is acceptable considering the existential crisis of leaving behind any residual tissue. The entire nasal cavity needs to be scoured and all fungal, necrotic tissue needs to be removed. If the orbit is involved surgeries as drastic as exenteration of the eye socket contents may be required. Intracranial decompression may be required if the infection has spread to the brain. Surgical intervention should be undertaken a couple of hours after diagnosis.

In tandem, medical management with antifungal drugs, namely injection Liposomal amphotericin-B needs to be instituted. Older form amphotericin deoxycholate is significantly nephrotoxic. However, the liposomal cousin is safe and effective. Posaconazole tablets/ suspension and intravenous forms are available and are used in lieu

of amphotericin if the latter is not tolerated by the patient. Following several weeks of intravenous medication depending on the response the patient is put on oral posaconazole sustained release tablets for several months. Isavuconazole is also an alternative drug that can be used. Drugs are stopped after clinical and radiological clearance of the disease.[21]

During treatment, judicious use of steroids (keeping blood sugar levels under control), antibiotics, and other antifungal drugs need to be done.



Are these infections Life-threatening?

These infections are very lethal, and if not treated most will not make it. The mortality ranges between 25 to 90%. Once the infection spreads into the brain mortality is very high. Hence a lot of importance is given to early diagnosis and prompt institution of treatment.

Protocol for prevention of mucormycosis in admit Covid -19 patient

7 step approach

Step 1-Diagnosis of glycemic control on admission using glycated hemoglobin

Step 2-Judicious use of Steroid and Toclizumab

Step 3-Blood Sugar level monitoring and maintainace (110-180 mg/dl)

Step 4-Hygiene maintenance of O2 delivery system and use of distill water in Humidifiers

Step 5-ENT/OMFS evaluation of patient on day 3, day 7 and before discharge. (Nasalendoscopy,Biopsy,Deep nasal swab for fungal culture can be taken in suspected cases)

Step 6-Nasal Saline Spray twice daily

Step 7-Application of Amphotericin B gel intranasal for high risk patients

Protocol for prevention of mucormycosis in Post-Covid patient

7 step approach

Step 1-Maintenance of Oral hygiene and Use of 2% povidone Iodine Gargles.

Step 2-Steam inhalation to improve ciliary function and sinus health.

Step 3-Use of 0.5% Betadine Nasal Irrigation

Step 4-Patient education regarding early symptoms and signs of mucormycosis leading to early reporting.

Step 5-Strict Glycemic control

Step 6-Defer non-emergency invasive oral or dental procedure for 3 months after covid 19 infection.

Step 7-Use of Tablet Vitamin E 1000IU6,Tablet Vitamin A 6000IU7 and B-complex tablets and high protein low sugar diet,

Treatment of Rhino-orbito-maxillary mucormycosis
Combined team approach of ENT Surgeon, Maxillofacial Surgeon, Ophthalmologist, Neuro surgeon and Infectious Disease Specialist is required.

Surgical treatment
Aim of surgery- Aggressive clearance of pathologic tissue to make healthy tissue bed for perfusion of anti-fungal therapy.
ENT surgeon- Endoscopic sinus surgery for Sphenoid, Ethmoid and Maxillary Sinus. FESS or Denkers Operation can be done.
Maxillofacial surgeon- Dual role of maxillofacial surgeon in clearance surgery as well as post-mucormycosis reconstruction and dental rehabilitation. Resection of involved jaw bone by maxillectomy/Mandibulectomy, Cadwell-Luc operation for maxillary sinus debridement,resection of zygomatic bone. Use of free vascular grafts/regional soft tissue flaps for reconstruction and use of zygomatic implants for dental rehabilitation in indicated cases.
Ophthalmologist- Orbital exentration in indicated cases.
Neurosurgeon- Debridement of anterior table, posterior table of frontal
bone and osteomyelitic skull bone and involved cerebral parenchyma.

Medical management
First line antifungal therapy- Amphotericin B Therapy (Inj.Liposomal Amphotericin B,Inj. Amphotericin B lipid complex,Inj Amphotericin B Deoxycholate)

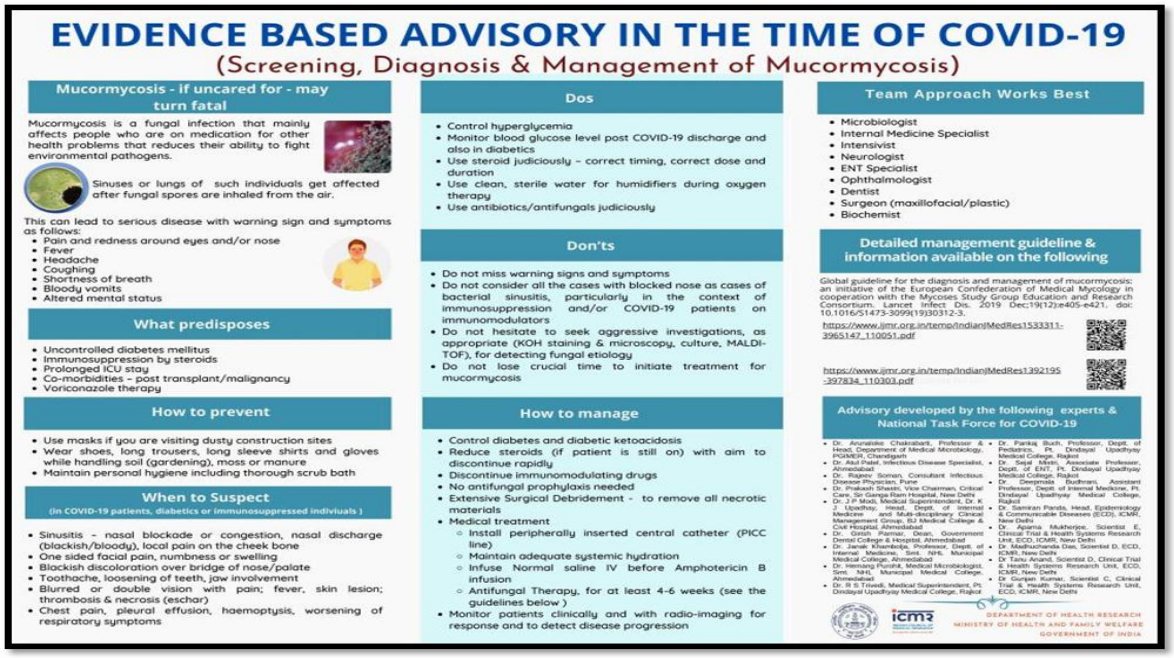
Second line antifungal therapy
1. Isavuconazole (Injection/Tablet)
2. Posaconazole (Tablet)

How to prevent the occurrence of rocm?[22]
Prevention is always better than cure.

In hospital
*Maintenance of good hygiene and cleanliness is a must. Regular oral hygiene care with mouthwash, povidone-iodine gargles must be done.
*While administering oxygen, water for humidification must be sterile and there should be no leakage from the humidifier.
*Steroid usage must be limited to no more than necessary with strict blood glucose control.
*Unnecessary use of broad-spectrum antibiotics, antifungals should not do as this removes the normal commensal flora resulting in the growth of unwanted organisms due to lack of competition.

Once discharged
*Stay indoors as much as possible
*Regular exercises
*Control of blood sugars
*At home, the surroundings must be clean and free from dust and dampness
*Maintain oral and nasal hygiene
*While going out always wear an N-95 mask
*Avoid construction areas, fields, grounds.
*Soil and plants are the areas that abound with fungi. Hence better to avoid working with soil, gardening. If unavoidable, masks, rubber gloves, and boots are a must.

Post-Covid, during recovery, if a patient develops sinus headache, facial pain, stuffy nose, bloody nasal discharge, blackish discoloration over nose or palate, eye pain, swelling, diminished of vision or double vision, tooth pain, headache, seizures, drowsiness, limb weakness then immediate medical help must be attained.



CONCLUSION

The key take-home messages are opportunistic fungal infections are occurring in COVID-19 patients, awareness among health care providers and the public is important, early diagnosis and aggressive treatment are paramount for improving outcomes in an otherwise dismal disease, together we can definitely win this battle against COVID 19 and mucormycosis.

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