

Mucormycosis – The black menace in COVID-19

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Abstract

The current outbreak of second wave of COVID-19 in India has seen the rise of opportunistic infections, a deadly one being mucormycosis or “black fungus.” As of now, there are over 9000 cases of this deadly disease which have been reported from several states in India. Nine states in India including Punjab, Uttar Pradesh, Rajasthan, and Bihar have declared mucormycosis as an epidemic. There are five types of mucormycosis – rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated. Out of these, rhino-orbital-cerebral and pulmonary mucormycoses are most common in post-COVID patients. The clinical presentation of such patients include cough, fever, breathlessness, chest pain, sinusitis, pain on one side of the face with lack of sensation and proptosis of eye. Diagnosis could be done through analysis of clinical findings, direct microscopy, serum antigen tests, culture, histopathology, radio imaging, and polymerase chain reaction/matrix-assisted laser desorption ionization time-of-flight. Treatment will include preventive measures taken at home or at hospital for post-COVID patients. Medical treatment of mucormycosis mainly includes installing a central catheter (line), maintaining adequate systemic hydration, and infusion of normal intravenous saline before antifungal amphotericin B infusion. Since amphotericin is nephrotoxic, alternative drugs, such as posaconazole or isavuconazole, can be suggested. Adjuvant therapy with caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen may have to be considered as well. Extensive surgical debridement can also be suggested to remove all necrotic tissues. This review emphasizes the different aspects of mucormycosis such as epidemiology, etiopathogenesis, risk factors, diagnosis, preventive measures, and treatment strategies that can be adopted to tackle this fungal menace in COVID-19.

Keywords: Amphotericin B, COVID-19, diabetes, mucormycosis

INTRODUCTION

For the last couple of months, India is confronting the second wave of coronavirus and the medical fraternity in our country is encountering not only this deadly contagious virus but also other various post-COVID essential and actionable complications. One such lethal complication recently observed in recovering COVID-19 (as well as SARI) patients, is a fungal disease called mucormycosis, also known as COVID-associated mucormycosis. This has triggered another wave of panic among the general public and posed a major challenge for the medical fraternity. Mucormycosis has been misreported as black fungus. Melanin pigment-containing yeast is known as black fungus. Mucormycosis induces black eschar (dry and dark scab-tissue blackening) caused due to tissue necrosis, and devitalizing its blood supply makes it informally black fungus.

Mucormycosis (or zygomycosis) is a dangerous fungal infection, though it is rare in incidence. It is caused by a

group of molds called mucormycetes, belonging to the scientific order Mucorales. These fungi are found all around the environment, particularly in soil and in decaying organic matter, such as leaves, compost piles, or rotten wood.^[1] Mucormycosis is most commonly caused by *Rhizopus* and *Mucor* species^[2] in humans.

Rhizomucor, *Syncephalastrum*, *Cunninghamella bertholletiae*, *Apophysomyces*, *Lichtheimia*, and *Saksenaia* are other species which may cause human infections.^[3] *Apophysomyces*, usually found in tropical and subtropical climates, commonly causes infection in India.

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Types of mucormycosis

- **Rhino-orbital-cerebral mucormycosis (ROCM)** – This is the most common presentation of mucormycosis with high fatality. It begins after inhalation of spores and the formation of coenocytic hyphae at the paranasal sinus, which eventually spreads to the orbit by direct invasion or through nasolacrimal duct. It can potentially extend to brain through angioinvasion of blood vessels (most common), orbital apex, cavernous sinus, or cribriform plate. It is mostly seen in patients with diabetes that remains uncontrolled and in renal transplant recipients.^[4,5]
- **Pulmonary mucormycosis** – After ROCM, the second common clinical manifestation is pulmonary mucormycosis that is caused by inhalation of spores which is seen among patients with hematological malignancy with neutropenia and in organ/stem cell transplant recipients.
- **Cutaneous mucormycosis** – Cutaneous mucormycosis is the third most common clinical form of the disease. This type of invasive fungal infection occurs due to the entry of the fungi through a breach/injury in the skin (after surgery, burn, or trauma etc.), mainly affecting immunocompromised patients, but can be seen even in immunocompetent individuals.
- **Gastrointestinal mucormycosis** – It is commonly observed in children as compared to adults, particularly low birth infants (mostly <1 month of age) and premature babies, who have undergone surgery or who are on prolonged antibiotics or immunosuppressive medications.^[6,7]
- **Disseminated mucormycosis** – In this type, the infection spreads through angioinvasion to other organs of the body, where brain is commonly affected, but can also attack other organs such as spleen and heart.

COVID-associated mucormycosis (CAM) is mainly by ROCM and pulmonary disease.

Epidemiology of mucormycosis and India's present scenario

Majority cases of mucormycosis are sporadic. Though rarely but serious outbreaks or clusters of mucormycosis have occurred in the past. It is difficult to determine especially for sporadic case whether mucormycosis is health care associated or whether the infections are acquired somewhere else, but mucormycosis outbreaks mostly happen in hospital/care settings (for instance, surgical transplant/grafting ward). The sources implicated in health-care-associated mucormycosis outbreaks include contaminated adhesive bandages, wooden tongue depressors, hospital linens, negative pressure rooms, water leaks, poor air filtration, and nonsterile medical devices, and in the vicinity of hospital building construction.^[8] Mucormycosis is a life-threatening infection, associated with a mortality rate of 54%.^[9] This mortality rate varies, depending on underlying patient condition, type of fungus, and affected body site (as per the latest data, the mortality rate among people with sinus

infections was 46%, with pulmonary infections was 76%, and for disseminated mucormycosis was 96%).^[10]

In the pre-COVID pandemic era, mucormycosis was designated as the diabetes-defining illness and India had the maximum prevalence of mucormycosis than any other country. Official data are scarce, but it is said to have affected an estimated 14 per 100,000 people in India, which is around 70 times higher than the rest of the world.^[10] Till March 2021, around 41 cases of CAM had been reported around the world, with most cases, i.e., about 70%, from India.^[11] Given the current wave of COVID infections in India, the number of cases has gone up much higher. In April, Maharashtra has recorded around 200 cases of mucormycosis following recovery from COVID-19, out of which 8 of them have died.^[12] Mumbai is considered as one of the worst-hit cities in the second wave with maximum number of CAM cases. Most of the diabetics who suffered and recovered from COVID-19 are commonly affected by this. Among them, around 11–12 patients had to have an eye surgically removed. The mucormycosis cases reported in Mumbai, Bangalore, Hyderabad, Delhi, and Pune showed that most of the patients contracted the infection between 12 and 15 days after recovery from COVID-19. As of now, there are over 9000 cases of this deadly disease which have been reported from several states in India. Nine states in India including Punjab, Uttar Pradesh, Rajasthan, and Bihar have declared mucormycosis as an epidemic.

Pathogenesis of mucormycosis

Infection can occur because of several species of fungi. The ubiquitous fungi, named Mucorales, are generally found in decaying matter and soil. One more species, known as *Rhizopus*, are found in moldy bread. These fungi are globally abundant in nature, therefore, the exposure of humans to these organisms is on a regular (daily or weekly) basis. However, disease-causing capacity is rare in such organisms because of the lower virulence. They primarily affect immunocompromised individuals including people with uncontrolled diabetes mellitus receiving glucocorticosteroids, patients having neutropenia due to hematological or solid malignancy, who had a transplantation surgery, who have iron overload, and burns patients.^[13] Such hosts are at risk for the disease.

Inhalation of conidia is the primary route of infection, while other routes include trauma and ingestion. On inhalation, the spores get deposited in the nasal turbinates, developing rhinocerebral disease. Pulmonary disease develops via inhalation when the spores reach lungs, and on oral ingestion, GI disease progresses. Cutaneous disease develops, if the agents enter through interrupted skin.^[14] Mucorales derive their nutrition from the host's body by manipulating its environment and disseminate by escaping recognition and immune attack by the host.

There are mostly two types of manifestations of mucormycosis in patients with post-COVID-19 complications, which are rhino-orbital-cerebral and pulmonary. Cutaneous or

rhinocerebral mucormycosis lesions differ in size, and are raised red nodules or plaques, occasionally producing purulent material. They could also manifest as ulcerated lesions with cavitation, red exuding centers, and raised epidermal margins. Older lesions may be covered either partly or fully by thickened and irregular epidermis.^[15] A black eschar formation takes place indicating necrosis and ischemia. Histology of the skin showed discrete, badly encapsulated granulomas or diffuse granulomatous or pyogranulomatous inflammation. Inflammatory infiltrate consists of neutrophils or eosinophils, few plasma cells and lymphocytes, numerous macrophages, and occasional multinucleated giant cells. Fibrovascular tissue is diffusely and irregularly scattered in the granulomatous area.^[16]

Post-COVID immune suppression and opportunistic infection

Although considerable amount of preliminary evidence has been generated recently, it is yet to be proven whether similar synergies exist between COVID and mucormycosis, as exists for postviral (or secondary) and bacterial infections (specifically for respiratory tract infection). Respiratory viral infections, during/ after the course may alter (reduce) innate as well as cellular immune response (and function) – that produces a temporary immune paralysis, which promotes opportunistic infections by: (1) overburdening macrophages with virus-infected apoptotic cells, so their capacity to phagocytose opportunistic pathogens becomes limited;^[17] (2) inhibiting antigen-presenting ability of both dendritic cells and macrophages following any bacterial and viral infections; (3) T (Treg) cell^[18]-mediated transient immune impairment by production of immunosuppressive cytokines such as interleukin-10 (IL-10),^[18] IL-35, and transforming growth factor β , utilization of IL-2, granzyme- and perforin-mediated apoptosis of effector cells, inhibition of antigens presenting capacity of antigens presenting cells (APC) due to downregulation of costimulatory molecules on the surface of APCs, and metabolic alteration like generation of adenosine; (4) alteration of respiratory tract microbiome by initial immune response to a viral infection reduces local defenses against opportunistic pathogens; and (5) providing nidus/nutritive environment^[19] – postviral infection alteration of epithelial cells, fluid/pus-filled physiologically altered alveoli, disrupted mucociliary clearance, and mucus thickening (these also hinder the immune cell movements). All these ultimately make the immediate post-COVID patients more prone to get opportunistic infections including mucormycosis (CAM).

Risk factors for COVID-associated mucormycosis

Not all patients suffering or already cured from COVID-19 get infected with mucormycosis. The risk factors that endangered the patients to suffer from this deadly fungus are:

- Uncontrolled diabetes mellitus (including diabetic ketoacidosis)
- Persistent post-COVID syndrome^[20] – resulting in persistent immunosuppression
- COVID-19 patients who received immunomodulator for longer time such as steroids, tofacitinib, and baricitinib
- Injudicious use of steroids (wrong dose, timing, and duration)
- Any preexisting illness, being treated by prolonged steroids or immunosuppressant therapy
- Prolonged treatment in intensive care units
- Transplant (solid organ/stem cell) recipients.
- Solid or hematological malignancy on therapy
- Neutropenia of various etiology
- Iron (and possibly zinc) overload
- Prolonged antifungal therapy (i.e., voriconazole as part of comorbid care or prophylaxis).

Symptoms of rhinocerebral mucormycosis in COVID-19

Along with COVID-19 manifestations, the following symptoms of rhinocerebral mucormycosis should be carefully monitored:^[21]

- Sinusitis, along with clogging of the nasal tract and bloody or blackish mucus emission from the nose
- Pain on only one side of the face, cheekbones, with inflammation and redness
- Well defined blackish discoloration on the bridge of the nose
- Pain in teeth, jawbone as well as degrading of tooth structures
- Decreased visual acuity progressing to blindness and loss of corneal reflex
- Ptosis of the eyelid
- Fixed dilated pupil
- Loss of extraocular movements
- Abnormal blood clotting or thrombosis of tissues
- Pleural effusion and hemoptysis
- Progressive lethargy.

Symptoms of pulmonary mucormycosis in COVID-19

- Fever
- Cough
- Shortness of breath
- Chest pain.

Diagnosis of mucormycosis

Patients with suspected CAM should be investigated thoroughly for diagnostic confirmation, though it depends on availability of mycological, histological, and radiological facilities. However, treatment should be initiated without any delay. The diagnosis is made by:

- Clinical findings – A suspected case of mucormycosis should be analyzed as per symptoms, sign (mentioned above), and clinical examination
- Staining/direct microscopy – Microscopy of clinical specimens (deep or endoscopic guided tissue or nasal swab) using a KOH mount should be done and fluorescent brighteners (like calcofluor white) are used as a rapid detection tool. Parameters such as septation, branching angle, and hyphal width are mainly identified by these methods

- Serum antigen test – A repeat negative 1,3-beta-D-glucan and galactomannan assay eliminates the chance of invasive aspergillosis and other fungal infections
- Culture – Sample of endoscopically collected tissue, bronchoalveolar lavage, mimi-BAL, and nonbronchoscopic lavage is used for culture. Often, culture does not show any growth as *Mucor* is difficult to culture routinely. As high as 50% of the samples from probable ROCM do not show any growth. Due to ubiquitous nature, the chance of contamination is very high, so the isolation of these fungi in a culture does not necessarily prove infection.^[22] Separate incubation of cultures at 30°C and 37°C is the current recommendation. Culture is usually done to identify genus and species as well as for susceptibility testing to antifungal agents. Comparing the culture findings with patient's signs and symptoms and underlying disease is necessary to decide whether antifungal therapy should be given
- Histopathology – Histopathologic detection of the fungus with a characteristic structure of Mucorales (nonpigmented hyphae showing tissue invasion), stained by hematoxylin-eosin, periodic acid-Schiff stain, or Grocott-Gomori's methenamine silver, may provide the only confirmative evidence of infection. A physician should perform/request for invasive procedure without delay to confirm the diagnosis, as benefits of biopsy always outweigh the risk even from a 'difficult to access' site or in the presence of coagulopathy.^[23] Endoscopic collection of tissue sample, transbronchial biopsy, or CT-guided biopsy from lung is used for histopathology
- Polymerase chain reaction/matrix-assisted laser desorption ionization time-of-flight (PCR/MALDI-TOF) – PCR sequencing, MALDI-TOF mass spectrometry can be used to identify the causative species from culture specimens
- Radio imaging – X-ray and/or high-resolution computed tomography (CT) chest shows reversed halo sign (as opposed to halo sign of pulmonary aspergillosis) – an area of ground-glass opacity surrounded by a ring of consolidation. CT pulmonary angiography shows vessel occlusion sign. CT or magnetic resonance imaging of paranasal sinus orbit and brain is used for suspected ROCM.^[24]

Treatment of COVID-associated mucormycosis – real need of the hour

The phrase “prevention is better than cure” is extremely applicable for CAM as literally it can be prevented to a large extent. These measures not only avert significant discomfort, morbidity (functional as well as psychological), and mortality but also reduce undue utilization of already overburdened health-care resources (cost, manpower, time, hospital bed occupancy, etc.), especially at present pandemic situation. The successful and optimum management of CAM is only possible by multidisciplinary involvement, including microbiologists, internal medicine specialists, ENT

specialists, ophthalmologists, intensivist, neurologist, clinical pharmacologists, pathologist, dentists, surgeons (maxillofacial/plastic), trained nurses, and other health workers. Nevertheless, early suspicion, investigation, and treatment initiation reduce the mortality as well as morbidity in a great extent.

Preventive measures – better to adopt

For home care/postdischarge COVID patients – (1) wear face masks and face shields, fully covered clothing, shoes, and gloves, especially when there is possibility of coming in contact with soil and polluted environment such as construction sites or gardening activities; (2) maintain appropriate personal hygiene by bathing and scrubbing after outside visit; (3) maintain prescription adherence and regular follow-up to physician to monitor and control blood sugar, for those who have had diabetes or developed it during steroid therapy; and (4) alert (but do not apprehend) the patients about early warning symptoms and signs of mucormycosis such as nasal blockage, excessive discharge, facial pain, blurred vision and pain, and chest pain or shortness of breath.

At hospital care setting – (1) judicious use of steroids and other immunosuppressants – in terms of initiation timing, appropriate dose, and duration as per national/state guideline conformance; (2) pertinent use of antibiotics (on the basis of clinical judgment first and then considering laboratory reports) and antifungals (keeping in mind – no role of prophylaxis antibiotics); (3) intensive monitoring and control of blood glucose levels in diabetic patients; and (4) use of clean and sterile water for humidifiers during oxygen therapy (though controversies exist to consider it as a potential source)

Early suspicion by health-care providers – If a patient, who has or is recovering from COVID-19, being treated with immunosuppressive agents (including steroids) and has one or other risk factors mentioned above, presents with nasal blockage then, it is always wise to make a differential diagnosis of suspected mucormycosis in such patient. Further, the physician should become more attentive in clinical examination and attempt early and aggressive investigations, if any doubt is encountered to confirm diagnosis. Early initiation of treatment for mucormycosis (even on suspicion for immunocompromised patients) should not be delayed under any circumstances and must be taken as medical emergency.

Treatment of COVID-associated mucormycosis

General treatment – The risk factor(s) that might have predisposed for mucormycosis infection should be identified and treated first, for instance, hyperglycemia, metabolic acidosis (ketoacidosis), iron overload should be managed promptly. If a patient is on immunosuppressive drugs (other than steroid), it should be discontinued at instant. If on steroids, then the dosage should be gradually tapered down and ultimately stopped.^[25] A peripherally inserted central catheter (line) is introduced and fixed. Adequate hydration should be maintained by infusing normal saline. Apprehension, depression, or disfigurement of patients should be tackled sympathetically and their pain and discomfort should be managed accordingly.

Medical (specific antifungal treatment) treatment

Initial therapy

Amphotericin B stands as the drug of choice for mucormycosis and should be regarded as the initial standard of care if not otherwise contraindicated or unavailable. Less nephrotoxic lipid formulation of amphotericin B (like liposomal amphotericin B or amphotericin B lipid complex) is always preferred than amphotericin B deoxycholate. Appropriate systemic hydration by infusion of normal saline should be achieved before amphotericin B infusion to reduce nephrotoxicity. The usual starting dose is 5 mg/kg daily of liposomal amphotericin B or amphotericin B lipid complex, and it could be increased up to 10 mg/kg daily. Slow escalation of dose is not recommended, rather full and appropriate daily dose should be given from the 1st day of treatment initiation. It should be continued until obvious signs of improvement are seen which may take up to 4–6 weeks, after that step-down therapy is initiated.^[21]

If the COVID-19 has already developed acute or acute in preexisting chronic renal failure (which are not uncommon), then relatively less nephrotoxic (i.v. posaconazole) or nonnephrotoxic (posaconazole ER tablets or isavuconazole i.v. or capsule) options should be used after risk–benefit assessment and clinical justification.

Adjuvant therapy with caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen may have to be considered as well.

Step-down therapy

Two broad-spectrum azoles – posaconazole and isavuconazole – are also used in invasive mucormycosis usually as oral step-down therapy for amphotericin B responders, or patients who have kidney diseases (as mentioned above). Both of these drugs are available as parenteral and oral formulations.

For posaconazole (both oral and intravenous preparations) – a loading dose of 300 mg every 12 h should be given on the 1st day, then maintenance dose of 300 mg every 24 h thereafter. Intravenous formulation contains a vehicle – betadex sulfobutyl ether sodium, which can lead to accumulation of toxicity in patients with renal impairment and should be avoided, especially on those having creatinine clearance <50 mL/minute.^[25] It can be used in patients with renal impairment after assessing and justifying possible benefits over risks, close monitoring of serum creatinine should be done, and timely decision to change formulation of posaconazole or to switch over to isavuconazole should be taken.

For isavuconazole – a loading dose of 200 mg (i.e., 2 capsules of 100 mg or 1 vial of 200 mg) is given every 8 h for 6 doses, followed by 200 mg once daily starting 12–24 h after the last loading dose.^[26]

Step-down therapy should be continued for 3–6 months or for at least 6 weeks following clinical and radiological

improvement. Combination of antifungal therapy is not recommended. No antifungal prophylaxis is recommended to prevent CAM.

Since these antifungals are administered through intravenous route in CAM, patients often encounter some infusion-related reactions, particularly nausea, vomiting, and chills at administration, usually occurring either during infusion (within 15 min to 3 h following initiation) or immediately following administration of the dose. This could be treated or prevented by the use of phenothiazine analogs (promethazine and prochlorperazine) or ondansetron. Nephrotoxicity and electrolyte disturbances such as hypokalemia, hypomagnesemia, and hyperchloremic acidosis are other common complications of amphotericin B administration, hence it should not be given concurrently with digoxin, skeletal muscle relaxants, or other nephrotoxic agents. Conventional amphotericin B (deoxycholate) in the dose of 1–1.5 mg/kg may be used if liposomal form is not available and renal functions and serum electrolytes are within normal limits.

Surgical treatment

Extensive surgical debridement of affected tissues should be considered promptly, once the diagnosis of mucormycosis is confirmed. The appropriate timing of surgery not only reduces the operative risk (extensive surgery) to the already morbid COVID-19 patient but also reduces the risk of transmission to neighbor COVID patients. Surgical removal of necrotic tissues in ROCM often produces disfigurement due to destruction/removal of the palate, nasal cartilage, and the orbit.^[27] Reconstruction surgery is often needed for these purposes. Reports suggest that lobectomies in patients with early pulmonary mucormycosis had a good prognosis.^[28] Studies have shown that timely surgical intervention improves the survival of patients with rhino-orbito-cerebral and pulmonary mucormycosis.

Monitoring of patients

Patients are monitored clinically, biochemically, and radiologically (if possible) at weekly interval for therapeutic response, disease progression, or toxicity and then decision is taken for therapeutic optimization.

CONCLUSION

Mucormycosis is a rare but dangerous fungal infection which has emerged in the second wave of COVID-19. Most of the existing studies on this fungal infection are retrospective and limited. In developing countries like India, uncontrolled diabetes mellitus and immunocompromised states like in coronavirus are the most common risk factors for mucormycosis. There is a need for more data which is representative of specific groups for better evaluation of the infection and estimation of disease burden.

It is important to have a high index of suspicion for fungal coinfection in patients with COVID-19 presenting with comorbidities. They should undergo immediate diagnostic

procedures with an emphasis on the requirement of medical and surgical intervention. Immunosuppressants, though the need of the hour in this pandemic, should be used judiciously to avoid flaring up of the fungal infection.

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REFERENCES

- Richardson M. The ecology of the zygomycetes and its impact on environmental exposure. *Clin Microbiol Infect* 2009;15 Suppl 5:2-9.
- Spellberg B, Edwards J Jr., Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005;18:556-69.
- Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, *et al.* Epidemiology and outcome of zygomycosis: A review of 929 reported cases. *Clin Infect Dis* 2005;41:634-53.
- Song Y, Qiao J, Giovanni G, Liu G, Yang H, Wu J, *et al.* Mucormycosis in renal transplant recipients: Review of 174 reported cases. *BMC Infect Dis* 2017;17:283.
- Ahmed A, Adelmann D, Fahal A, Verbrugh H, van Belkum A, de Hoog S. Environmental occurrence of *Madurella mycetomatis*, the major agent of human eumycetoma in Sudan. *J Clin Microbiol* 2002;40:1031-6.
- Vallabhaneni S, Mody RK. Gastrointestinal mucormycosis in neonates: A review. *Curr Fungal Infect Rep* 2015;9:269-74.
- Francis JR, Villanueva P, Bryant P, Blyth CC. Mucormycosis in children: Review and recommendations for management. *J Pediatric Infect Dis Soc* 2018;7:159-64.
- Novosad SA, Vasquez AM, Nambiar A, Arduino MJ, Christensen E, Moulton-Meissner H, *et al.* Notes from the field: Probable mucormycosis among adult solid organ transplant recipients at an acute care hospital – Pennsylvania, 2014-2015. *MMWR Morb Mortal Wkly Rep* 2016;65:481-2.
- Garner D, Machin K. Investigation and management of an outbreak of mucormycosis in a paediatric oncology unit. *J Hosp Infect* 2008;70:53-9.
- Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. *J Fungi (Basel)* 2019;5:E26.
- Available from: <https://thewire.in/health/what-is-mucormycosis-the-fungal-infection-affecting-covid-patients-in-india>. [Last accessed on 2021 May 21].
- Available from: <https://www.nationalgeographic.com/science/article/rare-black-fungus-is-infecting-many-of-indias-covid-19-patients>. [Last accessed on 2021 May 21].
- Revannavar SM, P S S, Samaga L, V K V. COVID-19 triggering mucormycosis in a susceptible patient: A new phenomenon in the developing world? *BMJ Case Rep* 2021;14:e241663. [Doi: 10.1136/bcr-2021-241663].
- Kanwar A, Jordan A, Olewiler S, Wehberg K, Cortes M, Jackson BR. A fatal case of *Rhizopus azygosporus* pneumonia following COVID-19. *J Fungi (Basel)* 2021;7:174.
- Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. *Cureus* 2020;12:e10726.
- Veisi A, Bagheri A, Eshaghi M, Rikhtehgar MH, Rezaei Kanavi M, Farjad R. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: A case report. *Eur J Ophthalmol* 2021;11206721211009450. [doi: 10.1177/11206721211009450]. Epub ahead of print.
- Heung LJ. Monocytes and the host response to fungal pathogens. *Front Cell Infect Microbiol* 2020;10:34.
- Schmidt A, Oberle N, Krammer PH. Molecular mechanisms of treg-mediated T cell suppression. *Front Immunol* 2012;3:51.
- Veldhoen M, Moncrieffe H, Hocking RJ, Atkins CJ, Stockinger B. Modulation of dendritic cell function by naive and regulatory CD4+ T cells. *J Immunol* 2006;176:6202-10.
- Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, *et al.* A Review of Persistent Post-COVID Syndrome (PPCS). *Clin Rev Allergy Immunol* 2021. [doi: 10.1007/s12016-021-08848-3]. Epub ahead of print.
- Honavar SG. Code Mucor. *Indian J Ophthalmol* 2021;69:1361-5. [doi: 10.4103/ijo.IJO_1165_21].
- Kung VL, Chernock RD, Burnham CD. Diagnostic accuracy of fungal identification in histopathology and cytopathology specimens. *Eur J Clin Microbiol Infect Dis* 2018;37:157-65.
- Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev* 2011;24:247-80.
- Lass-Flörl C, Resch G, Nachbaur D, Mayr A, Gastl G, Auberger J, *et al.* The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. *Clin Infect Dis* 2007;45:e101-4.
- Gupta S, Goyal R, Kaore NM. Rhino-orbital-cerebral mucormycosis: Battle with the deadly enemy. *Indian J Otolaryngol Head Neck Surg* 2020;72:104-11.
- Safi M, Ang MJ, Patel P, Silkiss RZ. Rhino-orbital-cerebral mucormycosis (ROCM) and associated cerebritis treated with adjuvant retrobulbar amphotericin B. *Am J Ophthalmol Case Rep* 2020;19:100771.
- Available from: https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis_ADVISORY_FROM_ICMR_In_COVID19_time.pdf. [Last accessed on 2021 May 24].
- Available from: <https://dghs.gov.in/WriteReadData/News/202105171119301555988MucormycosismanagementinCovid-19.pdf>. [Last accessed on 2021 May 24].