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Review Article

A review of COVID-19-associated mucormycosis in India

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ABSTRACT

The resurgence of COVID-19 with the delta variant has accompanied a doubling in the prevalence of COVID-19-associated mucormycosis (CAM) in India. The prevalence grew to 80 times that of the global average. In this review, we describe the epidemiology, the clinical presentation, and treatment of CAM. We conducted a literature search on the PubMed, Google Scholar, Embase, and Harvard Library databases. The cytokine storm with high interleukin-6 (IL-6), hyperglycemia, ketoacidosis culminates into impaired endothelial and immune response, causing improved survival of the fungus. The most common presentation is rhinoorbital cerebral mucormycosis followed by pulmonary mucormycosis in patients with COVID-19. CAM patients have active or prior pulmonary tuberculosis, hyperglycemia, or a prolonged stay in the intensive care unit (ICU). A recent history of steroid medications and a high prevalence of tuberculosis (TB) may have contributed to an increased prevalence of CAM infections. Hypoxemic COVID-19 patients have a substantial improvement with steroid treatment but increases the risk of opportunistic infections. Although radiological signs have been described but the most common presentation is a subtle sign of eye, nasal, oral cavity, or pulmonary symptoms which requires high index of suspicion. Hence, one should not rely on radiological signs alone. Amphotericin B or isavuconazole along with surgical debridement is the treatment of choice for CAM. Early admission, diagnosis, and treatment lead to favorable outcomes.

Keywords: COVID-19 associated mucormycosis, Rhinoorbital cerebral mucormycosis, Angioinvasive fungus, Pulmonary mucormycosis, Mucormycosis

INTRODUCTION

Mucormycosis is a rare angio-invasive fungal infection with a worldwide prevalence of 0.005 to 1.7 per million population.[1] In India, the estimated baseline prevalence is 140 per million population, which is about 80 times greater than the global average.[1,2] Respiratory viral infections have been associated with invasive mucormycosis in the post-infectious phase in both immunocompetent and immunosuppressed patients. With the COVID-19 pandemic, there has been an unprecedented wave of COVID-19 associated mucormycosis (CAM) in the year

2020.[3] The total number of cases reported in India between May to August 2021 was 47,508 cases and had 4,425 deaths during the same period of study.[4] During the same period of study, Nepal reported twenty-two cases with four deaths, Bangladesh and Mexico reported three cases with one death.4 During our review, we wanted to explore the reasons behind the unusual rise in the cases and mortality figures.

We conducted a literature search on PubMed, Google Scholar, Embase, Harvard library databases and restricted our study to articles in the English literature on mucormycosis. Our search terms included "COVID-19 and mucormycosis", "COVID-19 associated mucormycosis", "mucormycosis" and "COVID-19". We excluded articles related to pregnancy and pediatrics. All relevant articles were included in the study due to the rare clinical presentation of the fungus. This article aims to review the epidemiology, clinical presentation, treatment strategies for CAM in India.

Epidemiology and risk factors

The cases of COVID-19 have exponentially increased in India during the second wave, which began in March 2021. The most recent surge is believed to be due to newer strains such as B.1.617 +, B.1.1.7, B.1.351, and P.1.[5] A few studies estimate a 71% CAM case contribution from India in the backdrop of COVID-19 second wave.[6] According to a multicenter study conducted in India, the prevalence of mucormycosis doubled in the year 2020.[3]

A retrospective study on 2826 CAM patients in India identified the mean age of the patients as 51.9 years with a male predominance of 71%.[7] Immunosuppressive individuals, uncontrolled diabetes, chemotherapy-induced immunosuppression, autoimmune conditions, chronic kidney disease, infectious causes of immunosuppression are at risk of CAM. In the above-cited study, a majority (87%) of the patients had a recent history of corticosteroid treatment and 78% of the patients had diabetes mellitus irrespective of the severity.[7] The second most common comorbidity associated with CAM was hypertension followed by acute kidney injury.[7] Additional risk factors for CAM include the use of tocilizumab and itolizumab along with the steroid therapy used in COVID-19 therapy, prolonged hospital stay or ICU, recent organ transplantation, and history of newly diagnosed malignancies, and the use of Voriconazole therapy to treat other fungal infections.[8]

Pathogenesis

Mucorales spores are inhaled, cutaneous inoculation, or ingestion to cause infection.[10] Spores then transform into hyphae leading to angioinvasion, hematogenous dissemination, and multiorgan involvement. Angioinvasion leads to vascular thrombosis and tissue necrosis that prevent the penetration of leukocytes in the foci of infection.[10]

COVID-19 infection in diabetics leads to an imbalance in angiotensin-converting enzyme-2 (ACE-2) activation pathways creating an inflammatory response in the pancreas causing beta-cell dysfunction and hyperglycemic state.[11] This leads to rapid increase in glucose levels that are linked to insulin resistance and cytokine storm.[14,15] Potential similarities with severe acute respiratory syndrome coronavirus-1 (SAR-CoV-1) infection, which had long-term damage to pancreatic beta cells, and in a small subset of the population, SAR-CoV-2 can trigger diabetic ketoacidosis that persists for weeks to months after recovery from COVID infection. This could be a possible link to the late onset of mucormycosis.[1,16]

Growth and dissemination of fungus

Mucorales survive by deriving host nutrition and spread by eluding recognition and response from the host immune system.[15] Iron is essential for Mucorales to grow as they undergo apoptosis in iron-deprived conditions.[16] Iron is acquired from the host through high-affinity iron permeases (rFTR1) secreted by fungi.[17] Mucorales also use iron chelators such as ferrioxamine (an iron-rich form of deferoxamine) as xenosiderophores to capture iron.[18] Iron chelator therapy with deferoxamine (DFO) enhances angioinvasion because DFO acts as a xenosiderophore after free iron is bound.[19] Hyperglycemia leads to glycosylation of ferritin, transferrin, and lactoferrin, thus decreasing their iron affinity and increasing free iron. Ketone bodies and acidosis decrease the chelation ability of transferrin.[20] Ketoacidosis also affects neutrophil chemotaxis and phagocytosis, thus favoring the dissemination of fungus.[22,24]

COVID-19 infection is associated with a cytokine storm, particularly IL-6, which stimulates the synthesis of ferritin and hepcidin synthesis.[26] Hepcidin seizes iron in enterocytes and macrophages by preventing its efflux.[25] Increased free iron reacts with oxygen, nitrogen, and sulfur to generate reactive species which leads to oxidative damage.[24] A hallmark of iron overload is interaction with proteins of coagulation cascade resulting in coagulopathy.[24]

Epithelial and endothelial interactions

Spores of mucorales attach to extracellular matrix proteins, laminins, and collagen IV of damaged epithelium. Mucorales invade the host by secreting proteases, lipolytic enzymes, and subtilases.[22,30] Spore coat homolog (CotH) proteins are exclusive to mucorales and facilitate endothelial adherence.[27] CotH proteins help in invasion by attaching to the glucose-regulated protein 78 (GRP78) present in endothelial cells.[28] A study has shown ineffective endothelial invasion by *Rhizopus oryzae* (*R. oryzae*) with the use of anti-GRP78 antibodies or anti-CotH antibodies.[29] Hyperglycemia and acidic pH-induced availability of iron also enhance cellular expression of CotH and GRP78 proteins.[27] Figure 1 shows a summary of the above-mentioned pathologic mechanisms.

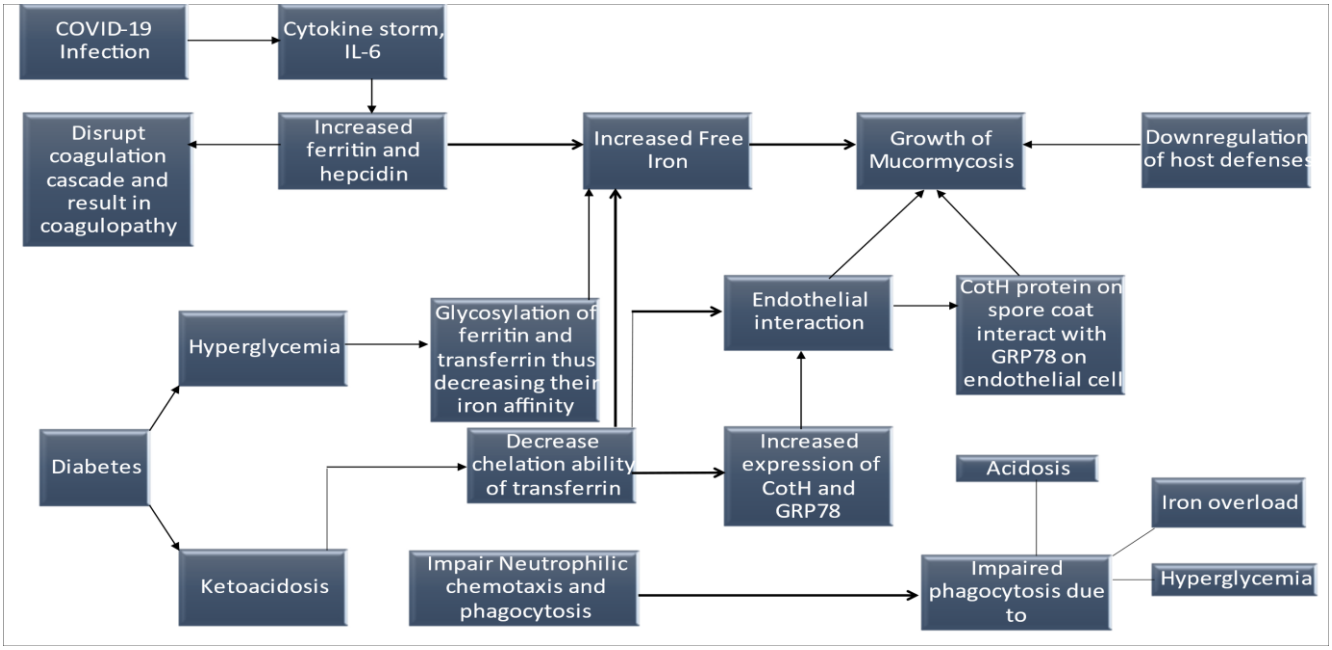


Figure 1: Pathogenic mechanisms responsible for CAM.

Downregulation of host defenses

The innate immune system like the neutrophils, macrophages, and dendritic cells forms the first layer of defense.[25,30] Toll-like receptors (TLR) recognize *R. oryzae* and upregulates the secretion of chemokines and cytokines from phagocytes including TNF-alpha and IL-6.[33,34] Adaptive immunity is vital in host defense, Th-1 cells by increasing the activity of phagocytes and natural killer cells by secretion of immunoregulatory molecules like INF-gamma and RANTES (CCL5).[30] Platelets secrete granules containing TGF-beta and thrombocidins which contain fungicidal properties, and expression of CD-154 and platelets TLR which bind to and activate macrophages and lymphocytes.[36-38] Additionally, platelet adherence and aggregation suppress hyphal growth and prevent fungal dissemination.[31]

Mucorales down-regulate the genes responsible for pathogen identification, innate immune defenses, and tissue repair mechanisms.[39] Neutropenia, hyperglycemia, acidosis, and iron overload are some host factors that impair phagocytic functions.[22] Patients with endogenous Cushing syndrome or exogenous glucocorticoids therapy, are at increased risk of fungal infections. Decreased lymphocyte proliferation and migration of lymphocytes, impaired NK cell cytotoxicity, and impaired phagocytosis are among the mechanisms responsible for decreased immune response in these groups.[36]

Clinical manifestations

Rhino-orbital cerebral mucormycosis

Rhino-orbital cerebral mucormycosis (ROCM) is the most common presentation in CAM patients.7 According to a study carried out in CAM patients in India, the mean interval for developing ROCM was 14.5±10 days post-COVID infection.[7] Delayed manifestation after 14 days was observed in 44%.[7] The most common symptoms of ROCM are orbital/facial pain (23%), orbital/facial edema (21%), loss of vision (19%), ptosis (11%), and nasal block (9%) as shown in Table 1.[7]

Table 1: Signs and symptoms of ROCM.[5]

System	Signs and symptoms of mucormycosis
General	Fever, fatigue, nausea, and vomiting
ENT	Symptoms: nasal congestion, black, brown, or blood-tinged nasal discharge, toothache, and loosening, and persistent refractory headache; and signs: acute sinusitis, epistaxis, characteristic black necrotic eschar on nasal mucosa/ palate, nasal crusting, and discharge
Eye	Symptoms: visual disturbances such as double vision or blurred vision, redness and swelling of the eye, facial pain, pain in the back of the eye, and drooping of eyelids; and signs: chemosis, eschar, ophthalmoplegia, and orbital cellulitis
Cerebral	Symptoms: loss of vision, facial weakness, and numbness, altered mental status, unstable gait, seizures, slurred speech, and headache; and signs: cranial nerve palsies, hemiplegia, and coma

The diagnosis of ROCM is graded as possible, probable, and proven. Symptomatic patients with a history of less than 6-weeks post COVID-19 treatment, diabetes, steroid therapy, tocilizumab, supplemental oxygen, and mechanical ventilation can be considered as a possible case of ROCM.[38] Once symptoms are verified by nasal endoscopy or contrast-enhanced magnetic resonance imaging or computed tomography (CT), the patient can be classified as probable ROCM.[40] Further microbiological tests like direct microscopy, culture, biopsy with histopathology with special stains along radiological tests should be considered to term a proven case of ROCM.[38] The first sign seen in magnetic resonance imaging (MRI) in earlier stages of ROCM is the 'black turbinate sign', as shown in an axial scan in Figures 2a and 2b.[7]

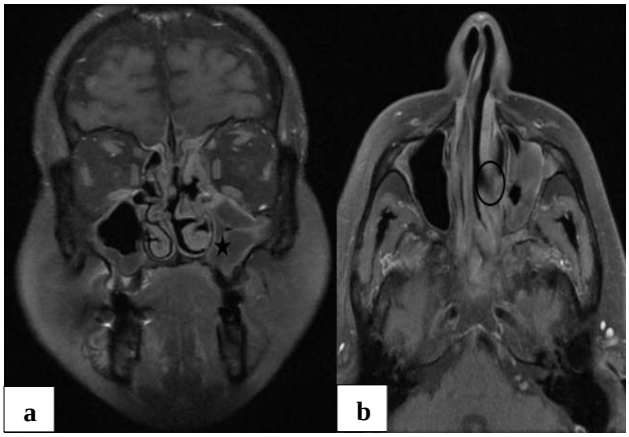


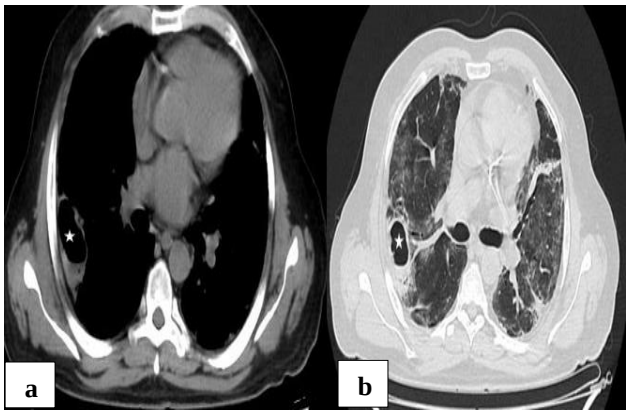
Figure 2: (a) A coronal magnetic resonance imaging scan showing irregular hyperdense growth of mucor (star); and (b) the axial MRI scan showing a decrease in the intensity of the left nasal turbinate (circle).

Cerebral invasion and infarction are best diagnosed by magnetic resonance imaging. Imaging findings include rim enhancement on T1 post-contrast imaging, central hyperintensity on T2 sequences, and diffusion restriction, usually seen in the basal ganglia. Mucormycosis has an established affinity for this area.[39] ROCM is best managed by a combination of medical and surgical therapy. Medical therapy include a combination of liposomal amphotericin B and posaconazole or isavuconazole.[37]

Surgical therapy includes functional endoscopic sinus surgery (FESS) or paranasal septal debridement.[7] Orbital involvement may require eye exenteration and is sometimes the initial option to curb rapid fungal spread to the brain.[7]

Pulmonary mucormycosis

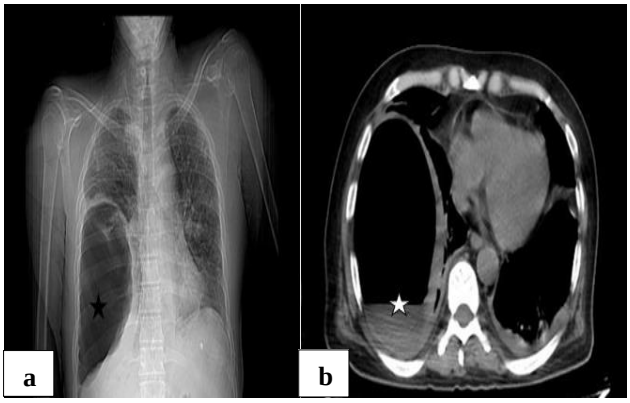
Pulmonary mucormycosis (PM) is the second most common form of mucormycosis after ROCM in COVID-19 patients.[40] Risk factors for PM include heme malignancies, particularly leukemia, bone marrow transplant, solid organ transplant, neutropenia, deferoxamine, and corticosteroid therapy.[41] Taking into account the angioinvasive properties of the disease, patients present with fever, cough, shortness of breath, chest pain, and hemoptysis.[3] PM can also present with peripheral lung cavities as shown in Figures 3a and 3b.



Figures 3: (a) and (b) The peripheral right lung cavity (star) after severe COVID-19. This is a clinical case of a long-term stay in the ICU of a COVID patient who presented mucormycosis symptoms a day before discharge.

Imaging signs suggesting PM as described in the literature are: the "halo sign" on CT viz. is defined as a ground-glass opacity encompassing a pulmonary mass or a nodule, which pathologically represents an area of necrosis; and a focal round area of ground-glass opacity but surrounded by a crescent or a complete consolidation ring refers to the 'reverse halo sign' or 'atoll sign'.[42]

It should be emphasized that no radiological features are diagnostic of PM.[37] A decrease in the intensity of ground-glass opacities serves as a radiological sign of improvement in clinical status.[37]



Figures 4: A case of mucormycosis which presented as right-sided tuberculous hydropneumothorax with right lung cavity, (a) is a chest radiograph showing a large cavity in the right lung (black star), and (b) hydropneumothorax on the right side (white star). This presentation prompts us to consider the simultaneous presentation of tuberculosis and mucormycosis in TB endemic countries like India.[5]

PM is also known to present as hydropneumothorax as shown in Figures 4a and 4b. In the only clinical trial ever conducted on mucormycosis, no radiological signs were present indicating a recovery in the first 30 days did not show negative outcomes at the end of 90 days.[37] This indicates that physicians should not change their decisions based on mere radiological recovery signs.[37] A CT-guided needle biopsy was found to be superior to BAL in diagnosing PM. CT-guided needle biopsy is contraindicated in patients with thrombocytopenia and coagulopathies, and therefore BAL is used in hematological malignancies.[37] Less than 50% of patients are diagnosed before death.[40] PM is usually treated with liposomal amphotericin B, in combination with isavuconazole or posaconazole. The lipid formulations have a favorable side effect profile compared to other formulations.

However, even liposomal amphotericin B causes nephrotoxicity and hypokalemia when dosed 10 mg/kg in up to 30% of cases.[37]

Several complications have been observed, such as extensive bronchial necrosis, broncho-mediastinal fistula, and life-threatening hemorrhage.[42]

Treatment of CAM in India

The National Center for Disease Control under the Directorate General of Health Services India emphasizes the treatment recommendations of the fungal infection study forum (FISF) to treat CAM when the availability of antifungal drugs is limited.[45] The recommendations are summarized in Table 2.[46]

Table 2: The treatment recommendations made by the fungal infection study forum (FISF). AmB – amphotericin B.[46]

S. no.	Fungal infection study forum recommendations
1.	Treatment of diabetes and diabetic ketoacidosis is essential.
2.	Taper the dosage of ongoing steroid treatment to discontinue, depending on the severity of the disease and the clinical acumen of the physician.
3.	Continue immunomodulatory drugs like baricitinib and tofacitinib.
4.	Extensive surgical debridement may involve exenteration of the eye, pulmonary lobectomy, and debridement of the necrotic foci of disease.
5.	5a - Insert peripheral inserted central catheter (PICC) line or central venous catheter.
	5b - Maintain adequate systemic hydration and perhydrate with normal saline to avoid the nephrotoxic complication of the infusion of amphotericin B.
	5c - Antifungal therapy of choice for CAM: liposomal amphotericin B(L-AmB) 5 mg/kg/day to be diluted in 200 cc in 5% dextrose over 2-3 hours infusion. Avoid slow escalation. A dose of 10 mg/kg/day may be given in brain involvement. Amphotericin B deoxycholate (D-AmB) should be used when L-AmB is unavailable or unaffordable due to cost constraints. D-AmB 1 mg/kg/day in 5% dextrose, slow infusion for 6-8 hours. Pre-medication is essential to avoid infusion reactions.
	5d - Monitor patients for renal toxicity and potassium level white treating with amphotericin B. If patients are intolerant to amphotericin B, Posaconazole or Isavuconazole should be used as injections or oral medications according to severity.
	5e - Isavuconazole 200 mg should be given three times a day for two days, followed by 200 mg once a day
6.	Apart from clinical monitoring, a radio-imaging treatment response with microbiological confirmation should be instituted to document recovery.
7.	Post 3-6 weeks of AmB treatment, a consolidation therapy of posaconazole or isavuconazole for 3-6 months.

Steps taken to check the spread of CAM in India

FISF recommended aggressive glycemic control, steroids use to be limited to hypoxemic patients, oral steroid medications are contraindicated in patients with normal oxygen saturation in room air, glucose monitoring if a steroid is prescribed, dose and duration of steroid therapy to be limited to dexamethasone 0.1 mg/kg/day for 5-10 days.[46]

Proper patient education with early signs of CAM such as facial pain, nasal blockage, excessive discharge, loosening of teeth, and respiratory difficulty should be given while leaving the COVID care facility.[46]

UNIQUE CHALLENGES IN DIAGNOSIS AND TREATMENT OF CAM IN INDIA

Increasing incidence of with tuberculosis associated CAM in India

India accounts for 1.4 million global deaths due to TB annually.[47] Continuous lockdown imposed nationwide has severely affected health care services in India. The country had a severe 24% reduction in GDP from April to June 2020.[47] While the COVID-19 cases grew, the public health sector collapsed with the TB notification rate falling by 60%, and the private health sector became costlier day by day.[47] Many hospitals turned into COVID treatment

facilities where only COVID patients were admitted. This led to the abrupt withdrawal of TB patients seeking healthcare. Due to the increase in the prevalence of active cases of TB, some patients with mucormycosis were co-diagnosed with TB upon presentation as depicted in the above image.[47] Poor quality of TB healthcare and high case fatality of TB can be a major driving force in the spread of mucormycosis.[5]

Co-management challenges of tuberculosis and diabetes

The coexistence of TB or DM with CAM can pose peculiar problems such as nonspecific physical signs of extensive pulmonary TB and can present as hemoptysis.[48] Treatment challenges such as the lower likelihood of sputum conversion in patients with DM, an increased risk of multidrug resistance, treatment failure or relapse is possible, polypharmacy in the elderly can cause serious unwanted side effects and decrease patient compliance.[48] Rifampicin used for TB treatment interferes with oral antifungal drug (azoles) metabolism, reducing the efficacy of treatment unless the dose is adjusted using therapeutic drug monitoring.[48]

About 75 million people in India have diabetes.[48] COVID-19 can worsen diabetic control and can increase the risk of opportunistic infections. Several cases of new-onset diabetes have been reported with admissions to COVID-19, which could indicate diabetic ignorance of the Indian diaspora.[48] The unchecked use of steroids could have exacerbated hyperglycemia.[48] Inability to access pharmacy or healthcare services for routine diabetic care, inability to exercise with the closure of gyms, inability to buy medications, long pause in patient-physician interaction along with economic challenges forced many people to face diabetes or COVID-19.[48]

Isavuconazole: an alternative to amphotericin

A new drug called isavuconazole showed comparable efficacy to amphotericin B and is newly approved for mucormycosis in India in February 2020 by CDSCO for adults >18 years.[49] Isavuconazonium is available in injection and oral formulation. As a loading dose, 372 mg of isavuconazonium is bioequivalent to 200 mg of isavuconazole and can be given every 8 hours to the maximum of 6 doses requiring 48 hours.[50] Maintenance dosage is similar to loading dose, given once daily via the oral route (2 capsules) or intravenous route (1 reconstituted vial) starting 12-24 hours after last loading dose.[50] Hypersensitivity to the drug is possible like Steven-Johnson syndrome which mandates discontinuation.[50] It is a substrate of CYP 3A4 and coadministration with CYP 3A4 inhibitors like ketoconazole and high-dose ritonavir is not indicated.[50] Serious hepatic adverse reactions like elevated liver function tests (LFT) have been reported.[50] Common adverse reactions are nausea, vomiting, diarrhea, headache, and elevated LFT, hypokalemia, constipation, peripheral edema, cough, and back pain.[50]

CONCLUSION

Optimal treatment of CAM requires coordinated teamwork of doctors from various specialties of medicine. A high index of suspicion along with rapid screening tests should be employed to avoid devastating consequences. The long-term effects of corticosteroids on mortality and functional outcome in survivors of CAM are unknown and will be the subject of future research. As new immunomodulatory treatment strategies have evolved, it is important to investigate their interaction with steroid therapy in patients with COVID-19. Future clinical trials should focus on the adequate representation of low and middle-income areas of India to ensure the generalizability of study results adjusted to prevalent comorbidities.

It is hypothesized that cloth-based masking or double masking has a role in chronic exposure to mucormycosis infection, (as most patients with ROCM have necrotic signs on the hard palate with sinus invasion) leading to soft tissue invasion which is a subject of research. Although we have made a sincere effort to summarize the causes, there could be several confounding factors which need to be evaluated and should be considered for further research. We should form a rapid task force and employ scientific personnel to check any such surge in India in the near future.

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REFERENCES

1. Jose A, Singh S, Roychoudhury A, Kholakiya Y, Arya S, Roychoudhury S. Current Understanding in the Pathophysiology of SARS-CoV-2-Associated Rhino-Orbito-Cerebral Mucormycosis: A Comprehensive Review. J Maxillofac Oral Surg. 2021;20(3):373-80.
2. World Health Organization. Mucormycosis Key Facts. 2021. Available at: https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/mucormycosis. Accessed on 24 October 2021.
3. Rudramurthy SM, Hoenigl M, Meis JF, Cornely OA, Muthu V, Gangneux JP, et al. ECMM and ISHAM. ECMM/ISHAM recommendations for clinical management of COVID-19 associated mucormycosis in low- and middle-income countries. Mycoses. 2021;64(9):1028-37.
4. Governmentstats.com. Mucormycosis (Black Fungus). 2021. Available at: https://governmentstats.com/mucormycosis/index.html. Accessed on 25 October 2021.
5. Rocha ICN, Hasan MM, Goyal S, Patel T, Jain S, Ghosh A, et al. COVID-19 and mucormycosis syndemic: double health threat to a collapsing healthcare system in India. Trop Med Int Health. 2021;26(9):1016-8.

6. John TM, Jacob CN, Kontoyiannis DP. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. J Fungi (Basel). 2021;7(4):298.
7. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol. 2021;69(7):1670-92.
8. Press Information Bureau- Government of India. Stay Safe from Mucormycosis - a Fungal Complication being Detected in COVID-19 Patients Control Diabetes, Use Steroids Judiciously, Keep Good Hygiene, Don't Self-Medicate. 2021. Available at: https://pib.gov.in/PressReleseDetailm.aspx?PRID=1718501. Accessed on 24 October 2021.
9. Lamaris GA, Ben-Ami R, Lewis RE, Chamilos G, Samonis G, Kontoyiannis DP. Increased virulence of Zygomycetes organisms following exposure to voriconazole: a study involving fly and murine models of zygomycosis. J Infect Dis. 2009;199(9):1399-406.
10. Steinbrink JM, Miceli MH. Mucormycosis. Infect Dis Clin North Am. 2021;35(2):435-52.
11. Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. J Diabetes Complications. 2020;34(9):107637.
12. Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. Clin Endocrinol (Oxf). 2020;93(4):390-3.
13. Gianchandani R, Esfandiari NH, Ang L, Iyengar J, Knotts S, Choksi P, et al. Managing Hyperglycemia in the COVID-19 Inflammatory Storm. Diabetes. 2020;69(10):2048-53.
14. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47(3):193-9.
15. Hood MI, Skaar EP. Nutritional immunity: transition metals at the pathogen-host interface. Nat Rev Microbiol. 2012;10(8):525-37.
16. Stanford FA, Matthies N, Cseresnyés Z, Figge MT, Hassan MIA, Voigt K. Expression Patterns in Reductive Iron Assimilation and Functional Consequences during Phagocytosis of Lichtheimia corymbifera, an Emerging Cause of Mucormycosis. J Fungi (Basel). 2021;7(4):272.
17. Fu Y, Lee H, Collins M, Tsai HF, Spellberg B, Edwards JE, et al. Cloning and functional characterization of the Rhizopus oryzae high affinity iron permease (rFTR1) gene. FEMS Microbiol Lett. 2004;235(1):169-76.
18. Liu M, Lin L, Gebremariam T, Luo G, Skory CD, French SW, et al. Fob1 and Fob2 Proteins Are Virulence Determinants of Rhizopus oryzae via Facilitating Iron Uptake from Ferrioxamine. PLoS Pathog. 2015;11(5):e1004842.
19. Ibrahim AS, Spellberg B, Edwards J. Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment. Curr Opin Infect Dis. 2008;21(6):620-5.
20. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes. 1982;31(12):1109-14.
21. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev. 2000;13(2):236-301.
22. Binder U, Maurer E, Lass-Flörl C. Mucormycosis--from the pathogens to the disease. Clin Microbiol Infect. 2014;20:60-6.
23. Khadke S, Ahmed N, Ahmed N, Ratts R, Raju S, Gallogly M, et al. Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: a review of the phases of illness and therapeutic agents. Virol J. 2020;17(1):154.
24. Cortese-Krott MM, Koning A, Kuhnle GGC, Nagy P, Bianco CL, Pasch A, et al. The Reactive Species Interactome: Evolutionary Emergence, Biological Significance, and Opportunities for Redox Metabolomics and Personalized Medicine. Antioxid Redox Signal. 2017;27(10):684-712.
25. Daher R, Manceau H, Karim Z. Iron metabolism and the role of the iron-regulating hormone hepcidin in health and disease. Presse Med. 2017;46(12):272-8.
26. Spreer A, Rüchel R, Reichard U. Characterization of an extracellular subtilisin protease of Rhizopus microsporus and evidence for its expression during invasive rhinoorbital mycosis. Med Mycol. 2006;44(8):723-31.
27. Challa S. Mucormycosis: Pathogenesis and Pathology. Curr Fungal Infect Rep. 2019;13:11-20.
28. Roilides E, Antachopoulos C, Simitsopoulou M. Pathogenesis and host defence against Mucorales: the role of cytokines and interaction with antifungal drugs. Mycoses. 2014;57:40-7.
29. Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest. 2010;120(6):1914-24.
30. Schmidt S, Tramsen L, Perkhofer S, Lass-Flörl C, Hanisch M, Röger F, et al. Rhizopus oryzae hyphae are damaged by human natural killer (NK) cells, but suppress NK cell mediated immunity. Immunobiology. 2013;218(7):939-44.
31. Bruserud O. Bidirectional crosstalk between platelets and monocytes initiated by Toll-like receptor: An important step in the early defense against fungal infections? Platelets. 2013;24(2):85-97.
32. Semple JW, Italiano JE, Freedman J. Platelets and the immune continuum. Nature Rev Immunol. 2011;11(4):264-74.
33. Speth C, Rambach G, Lass-Flörl C. Platelet immunology in fungal infections. Thromb Haemost. 2014;112(4):632-9.
34. Alastruey-Izquierdo A, Hoffmann K, de Hoog GS, Rodriguez-Tudela JL, Voigt K, Bibashi E, et al.

Species recognition and clinical relevance of the zygomycetous genus Lichtheimia (syn. Absidia pro parte, Mycocladus). J Clin Microbiol. 2010;48(6):2154-70.
35. Morace G, Borghi E. Invasive mold infections: virulence and pathogenesis of mucorales. Int J Microbiol. 2012;349278.
36. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet. 2003;362(9398):1828-38.
37. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):405-21.
38. Honavar SG. Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-Orbito-Cerebral Mucormycosis in the Setting of COVID-19. Indian J Ophthalmol. 2021;69(6):1361-5.
39. Kashyap S, Bernstein, Ghanchi JH, Bowen I, Cortez V. Diagnosis of Rhinocerebral Mucormycosis by Treatment of Cavernous Right Internal Carotid Artery Occlusion With Mechanical Thrombectomy: Special Case Presentation and Literature Review. Front Neurol. 2019;10.
40. Mempin R, Kamangar N. Pulmonary Artery Pseudoaneurysm due to Mucormycosis: Case Report and Literature Review. J Clin Imaging Sci. 2020;10:55.
41. Agrawal R, Yeldandi A, Savas H, Parekh ND, Lombardi PJ, Hart EM. Pulmonary Mucormycosis: Risk Factors, Radiologic Findings, and Pathologic Correlation. Radiographics. 2020;40(3):656-66.
42. Seifert S, Wiley J, Kirkham J, Lena S, Schiers K. Pulmonary mucormycosis with extensive bronchial necrosis and bronchomediastinal fistula: A case report and review. Respir Med Case Rep. 2020;30:101082.
43. Peng M, Meng H, Sun Y, Xiao Y, Zhang H, Lv K, et al. Clinical features of pulmonary mucormycosis in patients with different immune status. J Thorac Dis. 2019;11(12):5042-52.
44. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis. 2011;52(9):1144-55.
45. National Centre for Disease Control. 2021. Available at: https://www.ncdc.gov.in/WriteReadData/l892s/2291183923162574385 3.pdf. Accessed on 24 October 2021.
46. Fungal Infection Study Forum Recommentation, "COVID-19-associated mucormycosis (CAM). 2021. Available at: http://www.fisftrust.org/covid-19/Asscoiated-Mucormycosis/. Accessed on 24 October 2021.
47. Shrinivasan R, Rane S, Pai M. India's syndemic of tuberculosis and COVID-19. BMJ Glob Health. 2020;5(11):e003979.
48. Unnikrishnan R, Misra A. Infections and diabetes: Risks and mitigation with reference to India. Diabetes Metab Syndr. 2020;14(6):1889-94.
49. Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. Microorganisms. 2021;9(3):523.
50. Drug Information Bulletin, Regulatory Affairs Division (RAD), IPA. 2020. Available at: https://ipapharma.org/wp-content/uploads/2020/03/Drug-Information-Bulletin-13_25_.pdf. Accessed on 24 October 2021.

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