COVID-19 is a Global Threat, But Why Mucormycosis upsurged in India Alone?

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ABSTRACT

A fatal problem associated with SARS-CoV-2 called mucormycosis or black fungus was observed in COVID-19 patients worldwide, in particular from India. The rare infection rose more rapidly during the second wave of COVID in India. Upswing in mucormycosis is a public health concern as the fatality rate is pretty high, upto 90%. These realities demanded a search for the reason for upsurging cases of mucormycosis in India alone. The probable explanations for COVID patients developing mucormycosis include injudicious use of steroids, uncontrolled diabetes with or without diabetic ketoacidosis (DKA), absurd use of immuno-modulants with steroids, and extensive use of antimicrobials. Besides, overuse of zinc and iron supplements, features of B.1.617 variant of SARS-CoV-2 that suppress immunity, along with several other risk factors including long intensive care unit (ICU) stays with or without mechanical ventilators might have contributed to the increased prevalence of mucormycosis in patients with COVID-19. India is regarded as the "mucor capital of the world", having 70 times higher pre-COVID incidence than the global data. Therefore, it is vital to rectify the aggravating factors and curb the spread of mucormycosis. If this isn't brought under control, there are chances of other deadly infections to remain in the background. Rational glycemic control in COVID patients should be ensured. Use of steroids and immuno-modulants along with steroids should be reserved. Also, use of immunity boosters like zinc and iron should be limited. Furthermore, a holistic approach to improve the use of self-medication through public education should be introduced. Government should make sure that the oxygen cylinders are hygienic and rightly maintained. Sterile normal saline or distilled water should be used in humidifiers and oxygen flow meters has to be changed periodically. Negligence of all these imparts a huge mess not only on individuals but also on government. If the tribulations of overuse of drugs and insufficient hygiene persist, chances of outbreak of secondary infections alongside epidemics and pandemics should be expected in future.

Key words: Mucormycosis, Blackfungus, COVID-19, India, Infection.

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INTRODUCTION

Over the past weeks, India has encountered an epidemic within the pandemic. A lethal complication associated with SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) called mucormycosis or black fungus was observed in recovering and recovered COVID-19 patients worldwide, in particular from India.[1] It is a life-threatening and rare fungal infection caused by exposure to group of mould called mucormycetes, infecting people with compromised immune system.[2] Mucormycosis affects sinuses, lungs, brain, and eyes of individuals.[3] The rare infection continued to rage across India and rose more rapidly during the second wave of COVID with 14, 872 cases, as of May 28, 2021.[4] Hence, mucormycosisis declared as a notifiable disease under Epidemic Diseases Act 1897 by various states of India.[5] Treating the devastating mucormycosis is crucial with either antifungal therapy or surgery but the financial burden is immense. Amphotericin B remains the drug of choice, but long term treatment with nephrotoxic drug can impose

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a burden to the healthcare system with increasing demands of hospitalizations and hemodialysis due to renal failure. Therefore, liposomal amphotericin B is considered to be the safest option.[6-8] Rise in mucormycosis is a public health concern as the fatality rate is pretty high, upto 90%. Moreover, a delay of 12 hr in the diagnosis of the disease could be fatal. Conversely, 50% of cases are diagnosed in the autopsy series.[5]

These realities necessitated a search for the reason for rising cases of mucormycosis in India alone. It is now presumed that multiple factors may be determinant. The probable explanations for COVID patients developing mucormycosis include indiscriminate use of steroids, uncontrolled diabetes with or without diabetic ketoacidosis (DKA), absurd use of immuno-modulants with steroids, and extensive use of antimicrobials.[5,9] Moreover, overuse of zinc and iron supplements, features of B.1.617 variant of SARS-CoV-2 that suppress immunity, along with several other risk factors including long intensive care unit (ICU) stays with or without mechanical ventilators might have contributed to the rising incidence of mucormycosis in patients with COVID-19.[5,9]

Diabetes mellitus – key in the emergence of mucormycosis

Owing to the subtropical nature of India, chances of fungal infections are higher. Besides this, one of the leading predisposing factor implicated in mucormycosis is uncontrolled diabetes mellitus.[5] Precipitation of DKA associated with steroid use also paves the path for mucormycosis. Diabetic patients are liable to mucormycosis due to diverse aspects. Mostly, presence of high glucose and low pH render phagocytes dysfunctional, impair chemotaxis, and inhibit intracellular killing of pathogens by both oxidative and non-oxidative mechanisms.[10] Furthermore, diabetic ketoacidosis temporarily obstruct the ability of transferrin to bind iron and increases free iron. This modification destroys the host defense mechanism and provides an excellent environment for mucor spores to germinate.[11] additionally, elevated glucose and iron as observed in DKA, augment the expression of GRP-78. According to a recent research GRP-78 acts as a receptor to negotiate access and invasion of endothelial cells by mucorales, leading to angioinvasion.[12] All these are setting Indian COVID patients up for a disaster, as India accounts for the second-largest population with diabetes mellitus, earlier known as the 'diabetic capital of the world'.[5] Furthermore, apart from high proportion of diagnosed diabetic patients, there are many who do not receive health care and remains undiagnosed. The use of steroids out of panic without any medical advice among the undiagnosed diabetic patients also contributes to the source of mucormycosis outbreak.[13] A systematic review published in May 2021, reported hyperglycemia as the notable risk factor for evolution of mucormycosis cases (83.3%) in COVID-19 victims. Pre-existing diabetes mellitus was present in 80% of cases, while concomitant DKA was observed in 15% of COVID patients with mucormycosis.[5]

Steroids – the double edged sword

While several treatment options have been evaluated, glucocorticoids are the only drugs shown to improve survival in COVID-19 patients. Due to its cheap price, easy availability, and ability to cut down mortality in hypoxemic patients, glucocorticoids are widely in use in India.[14] The systematic review cited ahead reported 76.3% of cases with history of corticosteroid intake for COVID-19 treatment.[3] It is noteworthy that Indian Council of Medical Research (ICMR) guidelines suggested the use of only inhaled budesonide for mild disease and injection methyl prednisolone in moderate to severe COVID-19 patients.[15] However, World Health Organization (WHO) warned against the use of corticosteroids in non-severe COVID-19 patients unless it is consumed by the patient for some other ailments.[16] In fact, glucocorticoids are double-edged sword, as it reduces the inflammation in lungs, and also pushes down the immunity. Thus, glucocorticoids intensify the chance for secondary bacterial and fungal infections along with the significant increase in sugar levels of both diabetic and non-diabetic COVID-19 patients.[5,17] In addition; steroids are capable of increasing the replication of virus in the body. Initially, the response to virus starts with the assignment of innate immunity. If viral self-propagation is not controlled, the number of infected epithelial cells and cell debris increase. This triggers a cytokine storm with hyper inflammation and immune suppression. Therefore use of steroids in the initial days may favor viral propagation as steroids are capable of restricting the front-line of defense, the innate immunity. So, the right time to consume steroids is after the replication of virus in the body.[18] Taking into account all these realities, the centre has advised doctors and healthcare professionals, only for the evidence-based use of corticosteroids in patients with COVID-19 and to refrain from excessive use of steroids to treat COVID-19 patients.[5]

Whether polyprescriptions stirred up outbreak?

Just like steroid overuse and misuse, antibiotics are also misused while no guideline recommends antibiotic use in patients without secondary bacterial infections.

Antibiotics, if used unnecessarily, can destroy good gut bacteria and disturb the body's microbiological balance. Antibiotic resistance due to overuse is also a concern.[19] Besides steroids, immuno-modulating drugs like tocilizumab, itolizumab used to treat inflammatory airways and cytokine storm, also suppress the immune system. Inappropriate use of these drugs increases the risk for mucormycosis, as our immune system fails to fight the fungal infection.[20] In India, patients with mild COVID-19 symptoms are prescribed with five to seven drugs including paracetamol along with vitamin supplements, antibiotics and anti-parasitic medicines.[9] On the other hand, in western countries, the prescribed drug for 80% of COVID-19 patients is paracetamol alone. Perhaps, poly-prescriptions ordered by Indian doctors may be contributing to the mucormycosis epidemic.[21]

Overconsumption of immunity boosters may be contributory

As the second wave broke out in India, due to dearth of COVID emergency treatment across the country, many people took self-medications by either swapping prescriptions over WhatsApp or looking up medical advices on the internet. Drugs like steroids, antimicrobials and supplements were used as home-remedies.[22] Use of zinc supplements is considered a trigger point for contractingmucormycosis.[23] Researchers claim that the use of zinc and iron supplements could be a possible culprit, as metallic zinc and iron in the body create a breeding ground for fungal infections, especially mucormycetes.[22] A report by All India Organization of Chemists and Druggists (AIOCD) claims that 185 crore pills of supplements were consumed last year as a result of panic buying to build up immunity.[24] There is no proof that these supplements helps to prevent or treat COVID-19, but can improve the immunity of those deficient in micronutrients. Thus, the expert panel of American National Institute of Health warned against consumption of zinc more than the daily dietary requirement for preventing or treating COVID-19.[25] In addition, based on a study that came up in JAMA Network Open in January, SARS-CoV-2 symptoms are not affected by the treatment with zinc, ascorbic acid, or both.[26]

Are hospitals a breeding ground for mucormycosis?

The upswing in mucormycosis cases can also be linked to the utilization of industrial oxygen and its possible contamination. Owing to the acute shortage of medical grade oxygen across the country, the government insisted oxygen manufacturers to convert industrial grade oxygen cylinders for medical use.[27] The industrial oxygen production and storage is not carried out under strict aseptic condition as required for medical grade oxygen, thus, carries a significant risk of contamination with microbes including bacteria and fungi. Inside the hospitals, use of tap water instead of distilled water to humidify the oxygen is also another possible source of contamination. Moreover acute respiratory distress syndrome (ARDS) is a common complication in COVID patients that oblige intensive care unit (ICU) admission and mechanical ventilation (MV).[28] Therefore, if ventilator circuits and oxygen pipes are not properly sterilized, the fungi will thrive in hospitals.[29] Besides this, contaminated hospital settings as a result of massive influx of patients in the wake of second wave, along with already short-staffed healthcare system can also be considered a major reason for the spike in mucromycosis cases. The huge disproportion in doctor-to-patient ratio (8 physicians per 10,000 population) often lead to negligence and ultimately to the advent of new fungal epidemics.[8,13]

Role of evolving COVID variants – a concern

Experts claim that the viral new-comer,"double-mutant" variants such as delta and delta plus variants are also responsible for the mucormycosis epidemic. The link between COVID-19 variants and mucormycosis is that they damage the beta cells of the pancreas, resulting in hyperglycemia.[30] Also, in patients with COVID-19, viral pneumonia injures alveolar epithelium and endothelium, collapses immune system and causes cellular immune dysfunction. Mucormycosis spore seed into airways and exploit host settings such as high blood sugar, ketoacidosis, hemochromatosis and neutropenia, causing endothelial damage. This results into bleeding, blood clot and necrosis; and spread to multiple organs.[28] Thus, collective contribution of lung damage, immune system failure, corticosteroid therapy, hyperglycaemia, ketoacidosis, and iron overload grounds to mucormycosis.[6,31]

Did precautions turn to havoc?

Ever since the coronavirus outbreak, one advisory that has been circulating among people was the importance of steam inhalation in treating and preventing COVID-19. Infact, steam inhalation can work to ease respiratory symptoms but not a cure for coronvirus. Benefits of steam inhalation storming social media and other platforms persuade the public to opt for steaming in order to safeguard themselves from COVID-19. Over use of steam inhalation can damage the respiratory mucosa, permitting easy entry of the mucorales.[29] Also, steaminhalation, if not done in isolation can result in further spread of infection, rather than containing it. Therefore, it should be controlled in post-COVID individuals. In order to prevent infection with SARS-

CoV-2 and lessen the risk of inhalation of fungal spores, use of mask is necessary. However, reusing the same masks for many days may increase the risk of contracting mucormycosis.[29]

CONCLUSION

India is deemed as the "mucor capital of the world", having 70 times higher pre-COVID incidence than the global data. Thus, mucormycosis is not a new disease and has upsurged in COVID patients due to multiple factors including uncontrolled diabetes mellitus particularly with ketoacidosis, injudicious use of steroids, overuse of medicines, prolonged Intensive Care Unit (ICU) stay, and unhygienic practices from hospitals. Amalgamation of these factors in a single patient predisposes to acquire mucormycosis. Consequently, it is imperative to rectify the aggravating factors and suppress the spread of mucormycosis. If this isn't brought under control, there are chances of other fatal infections to linger in the background. Reasonable glycemic control in COVID patients should be ensured. Use of steroids and immuno-modulants along with steroids should be reserved and narrowed. Also, use of immunity boosters like zinc and iron should be restricted. In addition, a holistic approach to improve the use of self-medication through public education should be instituted. Government should make sure that the oxygen cylinders are hygienic and properly maintained. Sterile normal saline or distilled water should be used in humidifiers and oxygen flow meter and have to be replaced periodically. The mismanagement of all these imparts a huge burden not only on individuals but also on government since the treatment for COVID-19 patients in government hospitals is met by the government itself. Mucormycosis aren't exactly a rare or new disease in itself, nevertheless the proportion of cases identified in association with COVID-19 and high mortality rate brought this into notice. If the problems of overuse of drugs and inadequate hygiene persist, chance of outbreak of secondary infections alongside epidemics and pandemics should be anticipated in future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DKA: diabetic ketoacidosis; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus-2; **ICMR:** Indian Council of Medical Research; **WHO:** World Health Organization; **AIOCD:** All India Organization of Chemists and Druggists; **ARDS:** acute respiratory distress syndrome; **ICU:** intensive care unit; **MV:** mechanical ventilation.

REFERENCES

1. Revannavar SM, PSS, Samaga L, VKV. COVID-19 triggering mucormycosis in a susceptible patient: A new phenomenon in the Developing World? BMJ Case Rep. 2021;14(4):e241663. doi: 10.1136/bcr-2021-241663, PMID 33906877.
2. Centers for Disease Control and Prevention. Fungal Diseases | Types of Fungal Disease [cited Jun 22 2021]. Available from: https://www.cdc.gov/fungal/diseases/mucormycosis/index.html.
3. Binder U, Maurer E, Lass-Flörl C. Mucormycosis--from the pathogens to the disease. Clin Microbiol Infect. 2014 June;20;Suppl 6:60-6. doi: 10.1111/1469-0691.12566, PMID 24476149.
4. Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: Another challenge for India amidst the second wave? Lancet Respir Med. 2021 June 3;9(8):e77. doi: 10.1016/S2213-2600(21)00265-4, PMID 34090607.
5. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021 May 21;15(4):102146. doi: 10.1016/j.dsx.2021.05.019, PMID 34192610.
6. Verma DK, Bali RK. COVID-19 and Mucormycosis of the Craniofacial skeleton: Causal, Contributory or Coincidental?. J Maxillofac Oral Surg. March 27 2021:1-2. doi: 10.1007/s12663-021-01547-8, PMID 33814812.
7. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, *et al.* Coronavirus disease (Covid-19) associated mucormycosis (CAM): Case report and systematic review of literature. Mycopathologia. 2021 February 5; 186(2):289-98. doi: 10.1007/s11046-021-00528-2, PMID 33544266.
8. 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 June 11;26(9):1016-8. doi: 10.1111/tmi.13641, PMID 34117677.
9. Zinc overuse driving black fungus epidemic within pandemic? Doctors want study. The Times of India [cited Jun 22, 2021]. Available from: http://indiatimes.com/city/mumbai/mumbai-zinc-overuse-driving-mucor-epidemic-within-pandemic-docs-want-study/articleshow/82922957.cmsDate, May 25:2021https://timesofindia.
10. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis. 2012 February 1;54;Suppl 1(suppl_1):S16-22. doi: 10.1093/cid/cir865, PMID 22247441.
11. Afroze SN, Korlepara R, Rao GV, Madala J. Mucormycosis in a diabetic patient: A case report with an insight into its pathophysiology. Contemp Clin Dent. 2017 October;8(4):662-6. doi: 10.4103/ccd.ccd_558_17, PMID 29326525.
12. Chakrabarti A, Singh R. Mucormycosis in India: Unique features. Mycoses. 2014 December;57;Suppl 3:85-90. doi: 10.1111/myc.12243, PMID 25187095.
13. Szarpak L, Chirico F, Pruc M, Szarpak L, Dzieciatkowski T, Rafique Z. Mucormycosis-A serious threat in the COVID-19 pandemic? J Infect. 2021 May 21;83(2):237-79. doi: 10.1016/j.jinf.2021.05.015, PMID 34029629.
14. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective. Diabetes Metab Syndr. 2020 September 1;14(5):971-8. doi: 10.1016/j.dsx.2020.06.054, PMID 32610262.
15. AIIMS/ICMR. COVID-19 national task force. Joint Monitoring Group (Dte. GHS) Ministry of Health and Family Welfare, Government of IndiaClinical Guidance for ManagementofAdultCOVID-19Patients. Available from: https://www.icmr.gov.in/pdf/covid/techdoc/COVID_Management_Algorithm_17052021.pdfDate [cited 4/2/2022] published : May 17,2021Date accessed : June 22,2021.
16. World Health Organization. WHO updates clinical care guidance with corticosteroid recommendationshttps://www: September 2. p. 2020Date

accessed: June 22,2021. Available from: http://who.int/news-room/feature-stories/detail/who-updates-clinical-care-guidance-with-corticosteroid-recommendationsDate [cited 4/2/2022].
17. Shinde RV, KaRande GS, Mohite ST, Patil SR. Rhino-orbital mucormycosis in diabetes mellitus. J Clin Diagn Res. 2013 June;7(6):1145-7. doi: 10.7860/JCDR/2013/5528.3083, PMID 23905123.
18. Isidori AM, Arnaldi G, Boscaro M, Falorni A, Giordano C, *et al*. COVID-19 infection and glucocorticoids: Update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency. J Endocrinol Invest. 2020 August;43(8):1141-7. doi: 10.1007/s40618-020-01266-w, PMID 32335855.
19. Experts flag use of antibiotics in mild Covid cases. The Times of India [cited Jun 22, 2021]. Available from: http://indiatimes.com/city/pune/experts-flag-use-of-antibiotics-in-mild-covid-cases/articleshow/82961759.cmsDate, May 26:2021https://timesofindia.
20. Ministry of Health and Family Welfare. 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; May 14, 2021. Posted on. Available from: https://pib.gov.in/PressReleasePage.aspx?PRID=1718501 [cited Jun 22, 2021].
21. Bhaumik S, John O, Jha V. Low-value medical care in the pandemic-is this what the doctor ordered? Lancet Glob Health. 2021 June 2;9(9):e1203-4. doi: 10.1016/S2214-109X(21)00252-7, PMID 34089644.
22. Self-medication linked to black fungus risk. The New Indian Express [cited Jun 22, 2021]. Available from: http://newindianexpress.com/states/kerala/2021/may/22/self-medication-linked-to-black-fungus-risk-2305885.htmlDate, May 22:2021https://www.
23. Gandra S, Ram S, Levitz SM. The "black fungus". In: India: the emerging Syndemic of COVID-19–Associated mucormycosis.
24. Demand for vitamins, zinc supplements soars in second wave. Do They Help Prevent Covid;19(May 21):2021.
25. The mistakes in our mucormycosis approach. The New Indian Express [cited Jun 22, 2021]. Available from: http://newindianexpress.com/opinions/2021/jun/02/the-mistakes-in-our-mucormycosis-approach-2310511.htmlDate, June 02:2021https://www.
26. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, *et al*. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: The COVID A to Z randomized clinical trial. JAMA Network Open. 2021 February 1;4(2):e210369-. doi: 10.1001/jamanetworkopen.2021.0369, PMID 33576820.
27. Medical oxygen – available and yet not [cited Jun 22, 2021]. Available from:, Apr 21, 2020 https://timesofindia.indiatimes.com/blogs/blunt-frank/medical-oxygen-available-and-yet-not-available.
28. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, Mirhendi H, *et al*. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. Mycoses. 2021 February 16;64(8):798-808. doi: 10.1111/myc.13256, PMID 33590551.
29. Banerjee M, Pal R, Bhadada SK. Intercepting the deadly trinity of mucormycosis, diabetes and COVID-19 in India. Postgrad Med J. 2021 June 7. doi: 10.1136/postgradmedj-2021-140537, PMID 34103372.
30. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta diabetol. 2010 September 1;47(3):193-9. doi: 10.1007/s00592-009-0109-4, PMID 19333547.
31. Ceriello A, De Nigris V, Prattichizzo F. Why is hyperglycaemia worsening COVID-19 and its prognosis? Diabetes Obes Metab. 2020 October;22(10):1951-2. doi: 10.1111/dom.14098, PMID 32463166.