Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 112 (2021) 278–280

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Five probable factors responsible for the COVID-associated mucormycosis outbreak in India

Khaiwal Ravindra [a,*], Ajit Ahlawat [b,*]

[a] Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India
[b] Leibniz Institute for Tropospheric Research, Leipzig 04328, Germany

ARTICLE INFO

Article history:
Received 20 July 2021
Revised 21 September 2021
Accepted 22 September 2021

Keywords:
COVID-19
COVID-associated mucormycosis
diabetes mellitus
steroid overdose
awareness

ABSTRACT

The second wave of COVID-19 due to the delta variant (B.1.617.2) led to a rapid rise in total coronavirus and COVID-associated mucormycosis cases reported from India. Hence, our study explored the possible causes of a rapid upsurge in COVID-associated mucormycosis, which has accounted for over 70% of global cases. Factors associated with the increase in mucormycosis cases in COVID-19 patients include diabetes mellitus, steroid overdose, high iron levels, and immunosuppression, combined with other possible factors, such as unhygienic conditions, prolonged hospitalization, use of ventilators, and leaky humidifiers in oxygen cylinders. These create an ideal environment for contracting mucormycosis. However, these cases could be reduced by disseminating simple preventive measures and creating awareness among the medical society and general public of this rare and deadly contagion of COVID-associated mucormycosis. The identification of early symptoms will also help to restrict the spread of lethal fungal diseases. Furthermore, a collaborative team of surgeons, ophthalmologists, physicians, and otolaryngologists would be required in the hospital wards to accelerate surgeries on severely impacted patients.

Perspective

India has faced a catastrophic COVID-19 second wave due to the delta variant (B.1.617.2), which is known to have a higher viral load. As of June 1, 2021, the total reported cases in India contributed to the majority of worldwide cases, with a peak of over 0.4 million patients on May 7, 2021. Since then, daily new coronavirus cases have been dropping in India, but the rapid rise in COVID-associated mucormycosis (CAMCR) cases has posed another challenge to the country's already burdened healthcare system (Raut and Huy, 2021) Mucormycosis (MCR), also known as black fungus, is an invasive fungal infection generally caused by a group of opportunistic molds called mucormycetes; it is a sporadic but life-threatening infection if handled ineffectively.

According to a previously published study, the overall all-cause mortality rate for mucormycosis cases was found to be 54% (Roden et al., 2005). Variation in mortality rates is affected by the patients' existing conditions, types of fungus, and affected body parts. For example, Roden et al. found the death rate to be 46% among sinus-infected patients, 76% for pulmonary-related infections, and a colossal 96% for disseminated mucormycosis (Roden et al., 2005).

During the ongoing COVID-19 second wave in India, a rapid upsurge in COVID-associated mucormycosis cases has been observed when compared with the first wave. The reasons behind this substantial rise during the second wave need proper investigation. India had reported approximately 14 872 cases of mucormycosis as of May 28, 2021 (Raut and Huy, 2021). The Indian states Maharashtra and Gujarat contributed most mucormycosis cases among active and recovered coronavirus patients (Raut and Huy, 2021). Within Maharashtra state, cities like Nagpur and Pune accounted for almost 33% of Maharashtra's mucormycosis cases.

Several Indian states have already declared a mucormycosis epidemic after a surge in COVID-associated cases and deaths; these include Telangana, Karnataka, Bihar, Chhattisgarh, Madhya Pradesh, Rajasthan, Uttarakhand, Haryana, and Delhi (Raut and Huy, 2021). According to a recent study, approximately 71% of total worldwide mucormycosis cases in COVID-19 patients, from December 2019 to April 2021, were from India (John et al., 2021). The Indian Council of Medical Research (ICMR) has recently provided

E-mail addresses: Khaiwal@yahoo.com, Khaiwal.Ravindra@pgimer.edu.in (K. Ravindra), ahlawat@tropos.de (A. Ahlawat).
* Equal contributions

https://doi.org/10.1016/j.ijid.2021.09.057

some important guidelines relating to COVID-associated mucormycosis (ICMR, 2021). However, these guidelines lack certain points, which should be included as soon as possible to protect against this deadly disease. In order to create more awareness among the medical society and general public of this rare and fatal infection, our study provides details on probable factors causing COVID-associated mucormycosis. The five most probable factors associated with the increase in mucormycosis in COVID-19 patients are described here.

First, diabetes mellitus is the most common risk factor linked to an increase in mucormycosis in India (Singh et al., 2021) — accounting for a 46% mortality rate worldwide (Jeong et al., 2019). In 2018, a meta-analysis consisting of 851 cases of mucormycosis was conducted, which indicated the presence of diabetes mellitus as an independent risk factor (odds ratio = 2.69; 95% CI = 1.77–3.54; $p < 0.001$) (Jeong et al., 2019). India was ranked second in overall contribution to the world's total population with diabetes mellitus. Moreover, diabetes mellitus was significantly reported in over 50% of mucormycosis cases in India. In a recently published study on mucormycosis in India, 57% of patients had uncontrolled diabetes mellitus and 18% had diabetic ketoacidosis (Prakash et al., 2019).

Second, an excessive intake of steroids has been identified as a significant risk factor for mucormycosis. Since the recovery trial revealed that steroids reduced mortality in those COVID-19 patients on oxygen or who required mechanical respiration, steroids have become widely used. Even patients who did not have hypoxia (low blood oxygen) or who did not require hospitalization were frequently given heavy doses of steroids. In most cases, people with black fungus had self-medicated themselves on unauthorized steroids after their oxygen concentration levels had dropped. The deadly combination of steroids and a failed immune system due to COVID-19 had increased immune defense breach. Endothelialitis, which is seen during severe COVID-19, is another plausible link between COVID-19 and mucormycosis (Ackermann et al., 2020).

Third, unsanitary conditions could have increased the risk of developing mucormycosis infections. Many patients received additional oxygen via an oxygen concentrator in their homes due to the unavailability of hospital beds during the mammoth COVID-19 second wave. In most oxygen concentrators, frequent use of distilled water for supplemental humidification is needed as a moisture source when using a refillable humidifier bottle. The distilled water may serve as a potential source for pathogenic organisms, such as bacteria and mold. Moreover, there could be significant contamination in the pipes used for oxygen cylinders (Malik et al., 2021). The long-term stay of immunosuppressed patients in intensive care units employing these pipes and oxygen cylinders could have increased infections.

Fourth, high ferritin levels could be associated with a rise in mucormycosis cases in India. A change in iron metabolism has been found to occur in severe COVID-19 cases (Perricone et al., 2020). Higher ferritin levels can lead to an increase in intracellular iron, resulting in the production of reactive oxygen species, which will cause tissue damage. In cases with strong infection, cytokines excite the synthesis of ferritin and downregulate iron export, leading to an overloading of intracellular iron and thus aggravating the whole process, with excess free iron released as a result of tissue damage (Edeas et al., 2020). The overloading of intracellular and excess free iron could be a specific risk factor for mucormycosis (Ibrahim et al., 2012). Furthermore, following the rapid rise in mucormycosis, wide-scale shortages of amphotericin B, the mainstay therapy for mucormycosis, are being reported.

Fifth, poor indoor ventilation supports the prolonged airborne spread of fungal spores present in the surrounding environment. A recent study has identified mucormycosis infections originating from hospital linen supplied by a company with poor indoor ventilation, resulting in high humidity and dusty conditions (Cheng et al., 2016).

To summarize, diabetes mellitus, steroid overdose, high iron levels, and immunosuppression, combined with other factors such as unhygienic conditions, prolonged hospitalization, use of ventilators, and leaky humidifiers in oxygen cylinders, combine to create an ideal environment for contracting mucormycosis. Moreover, many patients infected with the delta variant experience severe immune suppression, compromising the host response and increased the risk of developing further opportunistic infections, including those caused by molds, leading to a higher risk of adverse outcomes in cases of delayed diagnosis and inadequate treatment.

In order to prevent mucormycosis transmission, treatment routines such as antifungal remedies and surgical debridement are recommended (Bala et al., 2015). A previously published study found that surgery combined with medical treatment with amphotericin B produced superior results (odds ratio = 0.2; $p < 0.04$) compared with amphotericin B alone (61.5% vs 10.3% patient survival) (Bala et al., 2015). In addition, the aim should be to identify possible sources of mold indoors and mitigate them immediately. Indoor air temperature and humidity checks should be performed regularly, specifically on those days when humidity exceeds 60%, which increases the chances of mold growth. The indoor temperature and humidity should be maintained at 24°C and 40–60%, respectively, to minimize both the risk of mucormycosis as well as coronavirus infection (Ahlawat et al., 2020a,b; Moriyama et al., 2020; Dabisch et al., 2021). Air filters present in the air-conditioning systems should be changed in a timely manner (Hartnett et al., 2019).

In response to the need to control the mucormycosis spread, the Indian government, with state government support, has acted quickly in an attempt to control the situation. This has included the production of guidelines, making arrangements for separate rooms in hospitals to manage mucormycosis cases, and acquiring essential drugs, i.e. amphotericin B (Raut and Huy, 2021). The Indian government and ICMR also need to consider the additional solutions provided in this paper, on an immediate basis, in order to curb this deadly disease. Furthermore, disseminating information and providing key materials to the general public will help to prevent an upsurge in mucormycosis cases in COVID-19 patients, and reduce mortality.

Lastly, there is a need to create awareness about fungal diseases among clinicians and the public in order to help identify the early symptoms and restrict the spread of lethal fungal diseases (Ravindra and Mor, 2021). A collaborative team of surgeons, ophthalmologists, physicians, and otolaryngologists (ENT) will be required in hospitals to accelerate surgeries on severely impacted patients.

Funding source

None.

Ethical approval

Not required.

Conflicts of interest

None.

Acknowledgments

The authors thank the Department of Community Medicine and School of Public Health, PGIMER, Chandigarh. The graphical abstract was adapted from the infographic

booklet 'COVID-19 Associated Mucormycosis' available at https://www.care4cleanair.com/awarnessmaterial.

References

Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine 2020;383(2):120–8.

Ahlawat A, Mishra SK, Birks JW, Costabile F, Wiedensohler A. Preventing Airborne Transmission of SARS-CoV-2 in Hospitals and Nursing Homes. International Journal of Environmental Research and Public Health 2020;17(22):8553. doi:10.3390/ijerph17228553.

Ahlawat A, Wiedensohler A, Mishra SK. An overview on the role of relative humidity in airborne transmission of SARS-CoV-2 in indoor environments. Aerosol and Air Quality Research 2020b;20(9):1856–61.

Bala K, Chander J, Handa U, Punia RS, Attri AK. A prospective study of mucormycosis in north India: experience from a tertiary care hospital. Medical Mycology 2015;53(3):248–57.

Cheng VC, Chen JH, Wong SC, Leung SS, So SY, Lung DC, Lee WM, Trendell-Smith NJ, Chan WM, Ng D, To L. Hospital outbreak of pulmonary and cutaneous zygomycosis due to contaminated linen items from substandard laundry. Clinical Infectious Diseases 2016;62(6):714–21.

Dabisch P, Schuit M, Herzog A, Beck K, Wood S, Krause M, Miller D, Weaver W, Freeburger D, Hooper I, Green B. The influence of temperature, humidity, and simulated sunlight on the infectivity of SARS-CoV-2 in aerosols. Aerosol Science and Technology 2021;55(2):142–53.

Edeas M, Saleh J, Peyssonnaux C. Iron: innocent bystander or vicious culprit in COVID-19 pathogenesis? International Journal of Infectious Diseases 2020;97:303–5.

Hartnett KP, Jackson BR, Perkins KM, Glowicz J, Kerins JL, Black SR, Lockhart SR, Christensen BE, Beer KD. A guide to investigating suspected outbreaks of mucormycosis in healthcare. Journal of Fungi 2019;5(3):69.

Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clinical Infectious Diseases 2012;54(suppl_1):S16–22.

Indian Council of Medical Research (ICMR), 2021. Evidence based advisory in the time of COVID-19 (screening, diagnosis and management of mucormycosis). May 9, 2021. https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis_ADVISORY_FROM_ICMR_In_COVID19_time.pdf (accessed June 1, 2021).

Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SA. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clinical Microbiology and Infection 2019;25(1):26–34.

John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. Journal of Fungi 2021;7(4):298.

Malik VS, Ravindra K, Singh M. COVID-19 and increasing demand for medical oxygen: can impurity be a problem? Environmental Science and Pollution Research 2021. doi:10.1007/s11356-021-16385-x.

Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. Annual Review of Virology 2020;7:83–101.

Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y, Gerli R. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. Immunologic Research 2020:1–12.

Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, Pamidimukkala U, Jillwin J, Varma S, Das A, Panda NK. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Medical mycology 2019;57(4):395–402.

Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? The Lancet. Respiratory Medicine 2021.

Ravindra K. and Mor S., 2021. COVID-19 associated mucormycosis. https://www.care4cleanair.com/awarnessmaterial (accessed Sept 20, 2021).

Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clinical Infectious Diseases 2005;41(5):634–53.

Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2021.