



Mucormycosis (black fungus/zygomycosis) and COVID-19; Does the coexistence of these two increase mortality?

Mehdi Forouzesh¹, Saman Farshid², Nasrin Ghiasi³, Mahnaz Narimani Zaman Abadi⁴, Rohollah Valizadeh⁵, Tella Sadighpour^{6,7*}, Shahrzad Alimohammadi^{8,9}

¹Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran

²Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran

³Department of Midwifery, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran

⁴Department of Anesthesiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

⁵Student Research Committee, Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

⁶Herbert Wertheim College of Medicine, Florida International University, Florida, USA

⁷American University of Antigua College of Medicine, Antigua and Barbuda

⁸Doctoral School of Molecular Medicine, University of Debrecen, Debrecen, Hungary

⁹Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

*Correspondence to

Tella Sadighpour,

Email: tsadi003@fiu.edu,

tellas@auamed.net,

Tella.90s@gmail.com

Received 14 May 2021

Accepted 4 June 2021

Published online 13 June 2021

Key point

Diabetes and the use of corticosteroids are reported in more than 70% of cases with mucormycosis in patients with COVID-19, thus physicians should have a high suspicion for mucormycosis in these patients. In case of mucormycosis, histopathological confirmation and fungal culture should be considered for differential diagnosis. Once mucormycosis is diagnosed, a combined treating method consisting of antifungals administration like amphotericin B, surgical intervention, and the reversal of the underlying condition must be considered as soon as possible. Coexisting mucormycosis and COVID-19 increase the likelihood of mortality.

Keywords: Mucormycosis, COVID-19, SARS-COV-2, Zygomycosis, COVID-19 associated mucormycosis

Citation: Forouzesh M, Farshid S, Ghiasi N, Narimani Zaman Abadi M, Valizadeh R, Sadighpour T, Alimohammadi S. Mucormycosis (black fungus/zygomycosis) and COVID-19; Does the coexistence of these two increase mortality?. Immunopathol Persa. 2021;7(2):e0x. DOI:10.34172/ipp.2021.xx.



Mucormycosis, an angioinvasive infection, is commonly rare and considered as a secondary infection. It occurs in patients with weakened immune system, diabetic ketoacidosis, as well as those patients who are under long-term use of antibiotics and/or steroids (1). The exact prevalence of mucormycosis is unknown but it shows to be increased as studies report. The prevalence of mucormycosis in India (around 140 people/1000000 population) is eighty times higher than in developed countries. Some new risk factors such as chronic kidney disease and tuberculosis are reported from developing countries (1). Mucormycosis is rare and usually harmless to healthy people but can be fatal to patients with weakened immune systems as Ercan et al reported (2). In general, a person develops mucormycosis after inhaling fungal spores in the air. Infection can also occur due to skin injuries or after eating contaminated food with fungus (3). Ercan et al revealed that mucormycosis can lead to rapid death without treatment in the presence of an underlying disease and can be treated

with surgical debridement combined with intravenous amphotericin B (2). It is difficult to estimate the exact number of patients with mucormycosis as most cases may have been misdiagnosed (1,2). Although mucormycosis is not contagious, it is very difficult to be diagnosed and treated since some mucorales are very resistant to the human immune system. As most of the symptoms that patients experience are during this infection are nonspecific and may be confused with other infections, including other fungal or even viral diseases (3). Mucormycosis manifestations can be presented as sinusitis and then spread to the eyes, optic nerve, and even the brain, and can be accompanied by facial edema, ptosis, and vision loss (4). Most patients with mucormycosis infection caused by mucoraceae family have an underlying disease including diabetes, acquired immunodeficiency syndrome (AIDS), anemia, malnutrition, neoplasm, and immunodeficiency in which their symptoms started with a cold and sinusitis and then were accompanied by pain and swelling in

the face (5-7). The diagnosis of mucormycosis is complex and challenging and is based on a direct examination, culture, and histopathological features. One of the main laboratory methods is the internal transcribed spacer region and can be recommended as a first-line method for species identification of mucorales (1,8). During the COVID-19 pandemic, paying attention to symptoms can help for a timely and proper diagnosis. Dexamethasone, as a steroid, is commonly available that can be used to treat severely ill patients and can reduce the mortality rate in COVID-19 patients. However, this treatment reduces the immune system to fight the infection. In addition, steroids raise the blood sugar level in diabetic patients and create a sugar-rich environment in which the fungus can grow (9-11). We believe that diabetes is associated with a higher mortality rate following getting COVID-19 (12). COVID-19 patients with diabetes are at two times higher risk of developing a severe form of COVID-19 (13). Hence, diabetes is a common risk factor for the severe condition in both COVID-19 and mucormycosis; therefore, the coexistence of these two diseases can worsen the final status of the patient. About 40 to 50% of patients with mucormycosis have diabetes mellitus, and develop ketoacidosis. The study by Pinto et al showed that 88.2% of patients with mucormycosis have diabetes mellitus and 53.3% of them had diabetic ketoacidosis (14). In addition, in India, by 21 May 2021, diabetes was found in 80% of cases with mucormycosis, and the use of corticosteroids was reported in 76.3% of cases with mucormycosis in patients with COVID-19 (15). The best way to deal with mucormycosis infection is to prevent it by appropriate administration of immunosuppressive drugs and control of underlying diseases such as diabetes (16). The high incidence of COVID-19 patients with mucormycosis in India, which is named COVID-19 associated mucormycosis (CAM), shows a great concern on a new pandemic of mucormycosis (17). It is recommended to avoid indiscriminate use of corticosteroids in COVID-19 patients with diabetes because diabetic patients are much more likely to develop mucormycosis (18). Moreover, the risk of secondary infections increases following glucocorticoid treatment. After getting COVID-19, the immune system is damaged and the use of concurrent immunosuppressant may worsen the status of COVID-19 infection (19,20). According to the Centers for Disease Control and Prevention (CDC), the mortality rate of mucormycosis in patients with COVID-19 has reached 54%, which can be presented in different features based on the patient's status and the infection site (21). In countries like India with the second highest rate of diabetes worldwide, the spread of mucormycosis is lethal (22). The early diagnosis of any type of mucormycosis like rhino-orbital mucormycosis in COVID-19 patients is of great importance particularly in those with diabetes or immunodeficiency and receiving systemic corticosteroids. In a case series of COVID-19 patients with mucormycosis,

all patients were died despite receiving enough therapy (23-25). Treating physicians should have a high suspicion for mucormycosis in patients with COVID-19 and diabetes (26,27). In case of mucormycosis infection, histopathological confirmation and fungal culture should be considered for differential diagnosis (28). Therefore, previous medical history is very important in the patients with COVID-19. Additionally, mucormycosis in immunocompromised state facilitates pulmonary mucormycosis (29). Finally, once mucormycosis is diagnosed, a combined method consisting of antifungals administration like amphotericin B, surgical intervention, and the reversal of the underlying condition must be considered as soon as possible (30).

Authors' contribution

Primary draft was prepared by MF, SF, TS and RH. NG, MN, SAM and TS edited the paper. All authors read and signed the final paper.

Conflicts of interest

The authors report no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

There was no financial support.

References

1. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and Diagnosis of Mucormycosis: An Update. *J Fungi* 2020;6:265. doi: 10.3390/jof6040265.
2. Ercan I, Cakir BO, Civelek S, Turgut S. Rhinocerebral mucormycosis: a report of two cases. *Kulak Burun Bogaz Ihtis Derg.* 2005;15:40-4.
3. Petrikos G, Skiada A, Sambatakou H, Toskas A, Vaiopoulos G, Giannopoulou M, Katsilambros N. Mucormycosis: ten-year experience at a tertiary-care center in Greece. *Eur J Clin Microbiol Infect Dis.* 2003;22:753-6. doi: 10.1007/s10096-003-1035-y.
4. Pandey A, Bansa IV, Asthana AK, et al. Maxillary osteomyelitis by mucormycosis: Report of four cases. *Int Infect Dis.* 2011; 15:66-9. doi: 10.1016/j.ijid.2010.09.003.
5. Anaissie EJ, Shikhani AH. Rhinocerebral mucormycosis with internal carotid occlusion: report of two cases and review of the literature. *Laryngoscope.* 1985;95:1107-13.
6. Kauffman CA, Malani AN. Zygomycosis: an emerging fungal infection with new options for management. *Curr Infect Dis Rep.* 2007;9:435-40. doi: 10.1007/s11908-007-0066-4.
7. Turunc T, Demiroglu Z, Aliskan H, Colakoglu S, Arslan H. Eleven cases of mucormycosis with atypical clinical manifestations in diabetic patients. *Diabetes Res Clin Prac.* 2008;82:203-8.
8. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikos G. Challenges in the diagnosis and treatment of mucormycosis. *Med Mycol.* 2018;56:93-101. doi: 10.1093/mmy/myx101.
9. Johnson AK, Ghazarian Z, Cendrowski KD, Persichino JG. Pulmonary aspergillosis and mucormycosis in a patient with COVID-19. *Med Mycol Case Rep.* 2021;32:64-67. doi: 10.1016/j.mmcr.2021.03.006.

10. Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V. Sino-orbital mucormycosis in a COVID-19 patient: A case report. *Int J Surg Case Rep.* 2021;82:105957. doi: 10.1016/j.ijscr.2021.105957.
11. Hoang K, Abdo T, Reinersman JM, Lu R, Higueta NIA. A case of invasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient. *Med Mycol Case Rep.* 2020;29:22-24. doi: 10.1016/j.mmcr.2020.05.008.
12. Ciardullo S, Zerbini F, Perra S, Muraca E, Cannistraci R, Lauriola M, et al. Impact of diabetes on COVID-19-related in-hospital mortality: a retrospective study from Northern Italy. *J Endocrinol Invest.* 2021;44:843-850. doi: 10.1007/s40618-020-01382-7.
13. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr.* 2020;14:535-545. doi: 10.1016/j.dsx.2020.04.044.
14. Pinto ME, Manrique HA, Guevara X, Acosta M, Villena JE, Solís J. Hyperglycemic hyperosmolar state and rhino-orbital mucormycosis. *Diabetes Res Clin Pract.* 2011;91:e37-9. doi: 10.1016/j.diabres.2010.09.038.
15. Awadhesh Kumar Singh, Ritu Singh, Shashank R. Joshi, Anoop Misra. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr.* 2021. doi: 10.1016/j.dsx.2021.05.019.
16. Guevara N, Roy D, Dutruc-Rosset C, Santini J, Hofman P, Castillo L. Mucormycosis--early diagnosis and treatment. *Rev Laryngol Otol Rhinol (Bord).* 2004;125:127-31.
17. Patel A, Agarwal R, Rudramurth SM, Shevkani M, Xess I, Sharma R, et al. Multicenter epidemiologic study of COVID-19-associated mucormycosis, India. *Emerg Infect Dis.* 2021;27(9). doi: 10.3201/eid2709.210934.
18. 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;186:289-98. doi: 10.1007/s11046-021-00528-2.
19. Kumar G, Adams A, Herrera M, Rojas ER, Singh V, Sakhuja A, et al. Predictors and outcomes of hais in COVID-19 patients. *Int J Infect Dis.* 2020;104:287-92.
20. Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, et al. IL-6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. *Front Med.* 2020;7:583897. doi: 10.3389/fmed.2020.583897.
21. What is 'black fungus' that is hitting India's COVID-19 patients? Available from: <https://www.reuters.com/business/healthcare-pharmaceuticals/what-is-black-fungus-that-is-hitting-indias-covid-19-patients-2021-05-24/>.
22. Dyer O. Covid-19: India sees record deaths as "black fungus" spreads fear *BMJ.* 2021;373:n1238. doi:10.1136/bmj.n1238
23. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. *Cureus.* 2020;12:e10726. doi: 10.7759/cureus.10726.
24. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med.* 2021;42:264.e5-264.e8. doi: 10.1016/j.ajem.2020.09.032.
25. Waizel-Haiat S, Guerrero-Paz JA, Sanchez-Hurtado L, Calleja-Alarcon S, Romero-Gutierrez L. A Case of Fatal Rhino-Orbital Mucormycosis Associated With New Onset Diabetic Ketoacidosis and COVID-19. *Cureus.* 2021;13:e13163. doi: 10.7759/cureus.13163.
26. Mekonnen ZK, Ashraf DC, Jankowski T, Grob SR, Vagefi MR, Kersten RC, et al. Acute Invasive Rhino-Orbital Mucormycosis in a Patient With COVID-19-Associated Acute Respiratory Distress Syndrome. *Ophthalmic Plast Reconstr Surg.* 2021;37:e40-e80. doi: 10.1097/IOP.0000000000001889.
27. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *J Fungi.* 2021;7:298. doi: 10.3390/jof7040298.
28. Patil S, Sarate D, Chopade S, Khade M, Dhage S, Kangate S. Emerging Challenge of Mucormycosis in postCOVID Patients. *J Med Cse Rep.* 2021;2:7-10. doi : 10.47310/iarjmcr.2021.v02i03.002.
29. Placik DA, Taylor WL, Wnuk NM. Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia. *Radiol Case Rep.* 2020;15:2378-81. doi: 10.1016/j.radcr.2020.09.026.
30. Alekseyev K, Didenko L, Chaudhry B. Rhinocerebral Mucormycosis and COVID-19 Pneumonia. *J Med Cases.* 2021;12:85-9. doi: 10.14740/jmc3637.