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Review article on A Deadly BLACK FUNGUS (Mucormycosis) And its Association With COVID-19

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ABSTRACT

After first phase of Covid-19, the second wave affects a lot to the Indians with mysterious fungal infection known as Mucormycosis. Mucormycosis is an infection caused by a group of filamentous molds belong to order Mucorales and class Zygomycetes.

Mucormycosis is commonly known as black fungus disease. This infection mainly targets diabetic and immune-compromised patients. As COVID-19 infection declines the immunity of patients, so mucormycosis cases are also increasing due to inhalation of molds containing industrial oxygen.

Here, we reviewed clinical pathogenesis, signs, symptoms and treatment against black fungus.

The conclusion revealed that use of immunosuppressant to combat Covid-19 also increases the risk to get infected with mucormycosis. Patients with hyperglycemia, ketoacidosis, solid organ or bone marrow transplantion, liver cirrhosis, neutropenia are more susceptible to get attacked by Mucormycosis moulds. Early diagnosis, removal of predisposing factors, timely antifungal therapy with surgical removal of all infected tissues and adjunctive therapies are four major factors to eradicate Mucormycosis.

***Keywords*:**
COVID-19
Mucormycosis
Black fungus
Hyperglycemia
Immunosuppressant

1. Introduction

India affects a lot with the worldwide pandemic Covid-19 caused by "Severe acute respiratory syndrome Corona virus-2 (SARS-CoV-2)". [1] First case of COVID-19 was reported in Kerala, India on 30th January 2020, afterwards highest cases i.e. 1 lakhs per day were reported for the year by May 2020.[2]

After mid June recovery of patient's increases successively with decrease in infection rate, further active case dropped to less than 15000 in January 2021. Afterwards second wave was begun in oMarch 2021 with a larger blow of active cases then first wave with deficiency of hospital beds, vaccines, medicines, oxygen cylinders and oxygen. The daily reported cases were reached to around 4.5 lakhs in starting of May 2021.[3] The effect of Covid-19 ranges from mild to moderate to life threatening with some associated disorders such as diabetes mellitus, cardiac diseases and immune compromised conditions.[4,5] Research articles also reported about the development of severe opportunistic infectious diseases like pneumonia, candidiasis, pulmo-nary aspergillosis etc in Covid-19 affected patients.[6,7] There are also reports of development of mysterious fungal infection known as Mucormycosis or Black fungus in Covid-19 patients.[8] Covid-19 patients in India also suffer with this epidemic disease (mucormycosis) with a reported case of 8848 till May 22, 2021.[9] Here the current article reports signs, symptoms, diagnosis, treatment, prevention against black fungus.

Objective:- **The main objective of the present article is to provide a comprehensive review on mucormycosis, its epidemiology, pathophysiology, diagnosis, treatment, and its association with COVID-19.**

2. About Mucormycosis or black fungus

Mucormycosis is also termed as black fungus due to the necrosis of affected tissue of patient's skin which turns it into black. "Mucormy-cosis" is the rarest type of fungal infection in order of importance after candidiasis and aspergillosis. It caused by Mucormycetes belong to the class Zygomycetes having order Mucorales. The mucormycetes mould mainly occurs in soil, leaves, decayed wood, manure etc. Species of Mucoraceae family i.e Rhizopus arrhizus, Rhizopus pusillus, Apophyso-myces elegans, Absidia elegans and Mucor racemosus are most common cause of the disease.[10,11]

3. Clinical pathogenesis

Mucormycetes mould can invade in the susceptible host via nostrils, mouth or burned/disrupted skin which results in rhino-orbito-cerebral, gastrointestinal or cutaneous wound infections.[12]Mucormycosis also results in vascular thrombus and may lead to tissue necrosis.[13]

It is most common in the patients with uncontrolled diabetes and leukemia.The second most preferred site of infection could be lungs and sinuses.

Mortality rate associated with lungs infec-tion may be over 60%.[14]

In severe Covid-19 situation patient could develop dysfunction of immune system with decrease in lymphocyte counts and exponentially rise in inflammatory cytokines such as IL-6, IL-1β, IFN- γ, MCP-1, IP-10, IL-4, IL-10 and Tumor necrosis factor (TNF) that leads to hyper-inflammation in the lungs and some patients may leads to death.[15,16]

Due to the severity of hyperinflammation or viral load physicians preferred use of immunosuppressant or steroids as a life saving treat-ment in critically severe patients. A steroid reduces inflammation in the lungs besides these steroids also reduce immunity of the body and in-creases blood sugar level in both diabetic and normal patients.[15]Ac-cording to the physicians immuunosuppresed patients are more likely to be affected with Mucormycosis or Black fungus.[17,18]

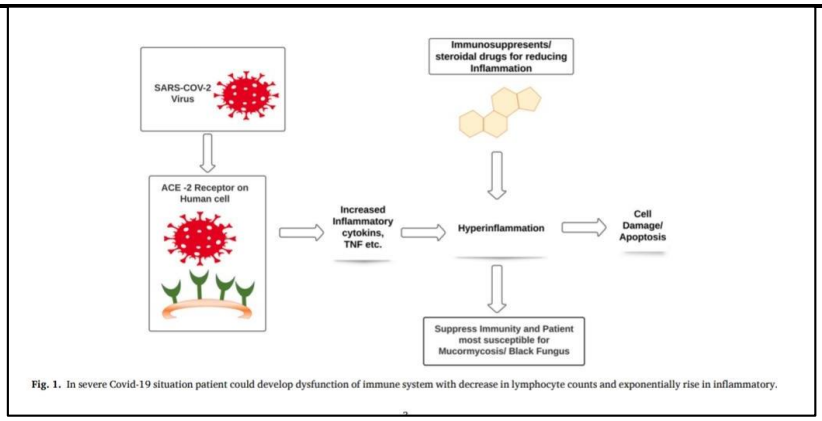

Fig. 1. In severe Covid-19 situation patient could develop dysfunction of immune system with decrease in lymphocyte counts and exponentially rise in inflammatory.

The entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is possible via spike protein available on the envelope which binds with angiotensin converting enzyme 2 (ACE 2), which are avail-able at pancreatic beta cells, lungs, kidney and small intestine. It is possible that entry of virus into pancreatic cells may damage beta cells and leads to insulin deficiency.[19,20] Patients with hyperglycemia and ketoacidosis are more susceptible to get attacked by Mucormycosis moulds.[21,22]Treatment of Covid-19 patient with immunosuppressant having uncontrolled diabetes mellitus and ketoacidosis are also at major

risk for Mucormycosis as it leads to dysfunctional phagocytes causes impaired intracellular killing by oxidative and non-oxidative mechanism.[23]

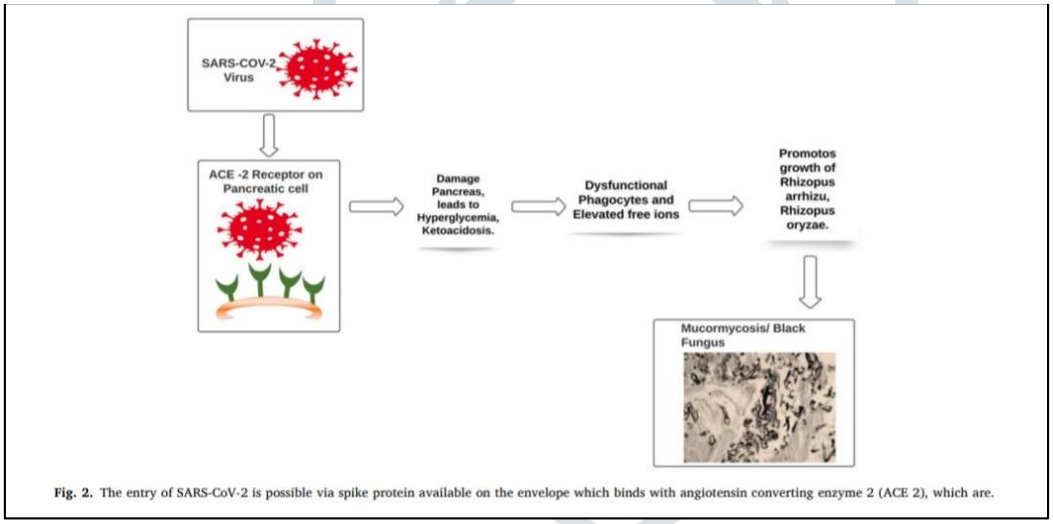

Fig. 2. The entry of SARS-CoV-2 is possible via spike protein available on the envelope which binds with angiotensin converting enzyme 2 (ACE 2), which are.

As discussed above, the probability of the development of Mucor-mycosis mould is mainly associated with patients suffering from dia-betes mellitus, ketoacidosis, decreased immunity and patient's receiveing immunosuppressant/corticosteroids as in case of Covid-19.

The source of developing or inoculation of Mucormycosis moulds is mainly accompanied by contamination with water and soil.[24] In case of Covid-19 probably the source could be water for humidifier during ox-ygen therapy before inhaling inside by the patients. The infection can be

life threatening and has a mortality rate of 38–80%.

4. Signs and symptoms

During treatment or post Covid-19 patient's complaint for fever, headache, and reddish swollen skin over nose and around eyes all are the major signs and symptoms of Mucormycosis.[25,26] Patients also re-ported visual abnormalities, eye swelling, ocular pain, facial edema and breathe shortening. Diabetic patients also reported for the symptoms of diplopia which is also the sign of infection.[27] In scientific terminology sinus pain, proptosis, periorbital swelling, orbital apex syndrome and ulcer of the palate and cranial nerve palsy are the major symptoms of Mucormycosis infection.[28]

5. Diagnosis

Diagnosis of mucormycosis is a challenging task but based upon identification of characteristic symptoms, detailed patient history, thorough clinical evaluation and specialized tests dedicated physician can diagnose it. Mucormycosis doesn't respond to any antigen detection test as galactomannan antigen test is available for detection of aspergillosis.[29] Histopathology of infected tissue is also used to distinguish the Mucorales from Aspergillus

6. Conditions prone to get easily infected with black fungal infection/mucormycosis:

There are several health conditions of people who are more prone to developed mucormycosis for example poorly controlled diabetes mellitus, hematological malignancies with neutropenia, solid organ transplant recipients, hematopoietic stem cell transplant recipients, rheumatic or autoimmune disease, chemotherapy or immunosuppression, peritoneal dialysis, human immunodeficiency virus infection, malnutrition, overload of iron in body, burns, trauma and people who used voriconazole as a medication in past [30,31]. Jeong W. et al. said that a meta-analysis was done from 600 publications, from the year 2000 to 2017, which contains 851 worldwide cases of mucormycosis with the following risk factors such as diabetes mellitus (40%), trauma (33%), hematological malignancies (32%), diabetic ketoacidosis (20%), neutropenia (20%), no underlying disease (18%), solid organ transplant recipients (14%), burns (11%), natural disease (5%) [30]. The most common risk factor for mucormycosis in Asia is diabetes mellitus while in NorthAmerica and Europe, organ transplant and hematological malignancies is the most common risk factors [30,32].

7. Treatments related to black fungal infection/mucormycosis:

Early diagnosis is the main key to control mucormycosis. The successfulness of treatments mainly relies on early and timely diagnosis along with prevention of predisposing factors associated with mucormycosis.. Prevention of spreading of infection to other organs by surgical debridement of the infected tissue is another method to treat mucormycosis specially in case of rhino-cerebral or soft tissue involvement [33,34]. Early high dose systemic anti-fungal treatment produces greater than 1.5-fold higher survival rates in patients [35,36]. Mucorales are naturally resistance to almost most of the anti-fungal medication, therefore choice of anti-fungal medication is very difficult [37]. The main initial therapy for mucormycosis is, the lipid formulations of amphotericin B (LFAB) [33].

FDA approved triazole isavuconazole (ISAV) for the treatment of mucormycosis in adult populations while posaconazole also possesses activity against mucormycosis. For induction and salvage therapy both POSA and ISAV are used[38]. According to the report of a single-center study in between 1989 to 2006 containing 70 patients of mucormycosis with hematological malignancies with neutropenia, administration of amphotericin B (AmB) based therapy after 6 days of initial infection leads to increase in two-fold mortality rate at twelve weeks after diagnosis of mucormycosis [84]. In case of both safety and efficacy LFAB is always better than AmB deoxycholate. The first line therapy for mucormycosis is always a high

dose of LFAB i.e. 5 to 10 mg/kg/day for minimum 6 to 8 weeks. Sun HY et al.mentioned that in case of rhino-orbital cerebral zygomycosis in solid organ transplant patients, death rate among patients treated with LFAB was found to be only 15.7% while it was 59.6% in case of AmB deoxycholate treated patients. For those patients who were unable to tolerate AmB, the combination treatment of posaconazole and caspofungin was found to be effective due to potential synergistic effects between two drugs.[40]

CONCLUSION

Mucormycosis is a rare invasive fungal invasion which mainly occur in patient with diabetes, immunocompromised and iron overload treatment. Recently, it has been found in the body of SARS-CoV-2 infected patients with higher mortality rate.

It has been observed that, due to extensive shortage of sterile oxygen, rapid supply of industrial oxygen was provide to save the patient due to which pathogens of mucormycosis is entered into the immunocompromised patients due which along with COVID-19 they also suffer from black fungus.

Therefore, treatment and diagnosed for COVID-19 patients become troublesome. People on treatment for iron overloading such as Deferoxamine are more likely to get affected by black fungus. Among six form of black fungus based on location, rhino-cerebral and pulmonary has higher mortality rate of patients. Since, Amphotericin B was extensively used for treatment, but if it fails then combination of posaconazole and caspofungin was found to be effective due to potential synergistic effects. More reliable and efficient drug therapy are very much necessary to deal with this kind of complex disease.

REFERENCES

1) Ramteke S, Sahu BL. Novel coronavirus disease 2019 (COVID-19) pandemic: considerations for the biomedical waste sector in India. Case Studies in Chemical and Environmental Engineering. 2020;2:100029. https://doi.org/10.1016/j. cscee.2020.100029.

2) Andrews MA, Areekal B, Rajesh KR, et al. First confirmed case of COVID-19 infection in India: a case report. Indian J Med Res. 2020 May;151(5):490–492. https://doi.org/ 10.4103/ijmr.IJMR_2131_20.

3) https://en.wikipedia.org/wiki/COVID-19_pandemic_in_India.

4) Gandhi RT, Lynch JB, Rio CD. Mild or moderate covid-19. N Engl J Med. 2020;383: 1757–1766. https://doi.org/10.1056/NEJMcp2009249.

5) Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Prato SD. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020;8:782–792. https://doi.org/10.1016/S2213-8587(20) 30238-2.

6) Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic fungal infections in the epidemic area of COVID-19: a clinical and diagnostic perspective from Iran. Mycopathologia. 2020;185:607–611. https://doi.org/10.1007/s11046-020-00472-7.

7) Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant Candida auris infections in critically Ill coronavirus disease patients, India, April–July 2020. Emerg Infect Dis.2020;26:2694–2696. https://doi.org/10.3201/eid2611.203504.

8) Sarkar S, Gokhale T, Choudhury SS, Deb AK. COVID-19 and orbital mucormycosis. Indian J Ophthalmol. 2021;69:1002–1004. https://doi.org/10.4103/ijo.IJO_3763_20.

9) 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 Oct-Dec;8 (4):662–666. https://doi.org/10.4103/ccd.ccd_558_17.

10) https://rarediseases.org/rare-diseases/mucormycosis/.

11) https://punemirror.indiatimes.com/news/india/india-reports-8848-mucormycosis -cases/articleshow/82864576.cms.

12) Mohindra S, Mohindra S, Gupta R, Bakshi J, Gupta SK. Rhinocerebral mucormycosis: the disease spectrum in 27 patients. Mycoses. 2007;50:290–296. https://doi.org/ 10.1111/j.1439-0507.2007.01364.x.

13) Rapidis AD. Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: perspectives from a maxillofacial surgeon. Clin Microbiol Infect. 2009;15 (Suppl. 5):98–102. https://doi.org/10.1111/j.1469-0691.2009.02989.x.

14) Spellberg B, Edwards Jr J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18(3): 556–569. https://doi.org/10.1128/CMR.18.3.556-569.2005.

15) Zhou Q, Chen V, Shannon CP, et al. Interferon-α2b treatment for COVID-19. Front. Immunol. 2020 May 15;11:1061. https://doi.org/10.3389/fimmu.2020.01061.

16) Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. Clinica Chimica Acta. 2020 Oct;509:280–287. https://doi.org/10.1016/j.cca.2020.06.017

17) Shang Y, Pan C, Yang X, et al. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. Ann. Intensive Care. 2020;10:73. https://doi.org/10.1186/S13613-020-00689-1.

18) Pak J, Tucci VT, Vincent AL, Sandin RL, Greene JN. Mucormycosis in immunochallenged patients. J Emerg Trauma Shock. 2008;1(2):106–113. https://doi. org/10.4103/0974-2700.42203.

19) Bourgonje AR, Abdulle AE, Timens W, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J. Pathol. 2020;251:228–248. https://doi.org/10.1002/path.5471.

20) Zou X, Chen K, Zou J, Han P, Hao J, Han Z. The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. Front Med. 2020;14:185–192. https:// doi.org/10.1007/s11684-020-0754-0.

21) Maertens J, Demuynck H, Verbeken EK, et al. Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplant. 1999;24:307–312. https:// doi.org/10.1038/sj.bmt.1701885.

22) Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851–856. https://doi.org/ 10.1086/313803.

23) Ahmadikia K, Hashemi SJ, Khodavaisy S, 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. 2021:1–11. https://doi.org/10.1111/myc.13256, 00.

24) Novak Babic M, Gunde-Cimerman N, Vargha M, et al. Fungal contaminants in drinking water regulation? A tale of ecology, exposure, purification and clinical relevance. Int J Environ Res Public Health. 2017;14(6):636. https://doi.org/10.3390/ ijerph14060636.

25) AK AK, Gupta V. StatPearls Publishing; 2021 Jan. Rhino-orbital Cerebral Mucormycosis. [Updated 2021 May 1]. In: StatPearls [Internet]. Treasure Island (FL) https://www.ncbi.nlm.nih.gov/books/NBK557429/. Available from:.

26) https://science.thewire.in/the-sciences/covid-19-and-black-fungus-what-is-muco rmycosis/.

27) Spellberg B, Edwards Jr J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18(3): 556–569. https://doi.org/10.1128/CMR.18.3.556-569.2005.

28) Mukherjee B, Raichura ND, Alam MS. Fungal infections of the orbit. Indian J Ophthalmol. 2016;64(5):337–345. https://doi.org/10.4103/0301-4738.185588.

29) Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev. 2000;13:236–301. https://doi.org/10.1128/CMR.13.2.236.

30) Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports [Internet]. Vol. 25, Clinical Microbiology and Infection. Elsevier B.V.; 2019 [cited 2021 May 30]. p. 26–34. Available from: https://pubmed.ncbi.nlm.nih.gov/30036666/

31)MAH,DMT. Mucormycosis in diabetes. Am J Crit Care[Internet].1997[cited2021May 30];6(5):363–7. Available from: https://pubmed.ncbi.nlm.nih.gov/9283673/

32.) Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, et al. A prospective multicenter study on mucormycosis in India: epidemiology, diagnosis, and treatment. Med Mycol [Internet]. 2019 Jun 1 [cited 2021 May 30];57(4):395–402. Available from: https://pubmed.ncbi.nlm.nih.gov/30085158/

33). Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect [Internet]. 2014 [cited 2021 May 30];20(S3):5–26. Available from: https://pubmed.ncbi.nlm.nih.gov/24479848/

34.) Giudice G, Cutrignelli D, Sportelli P, Limongelli L, Tempesta A, Gioia G, et al. Rhinocerebral Mucormycosis with Orosinusal Involvement: Diagnostic and Surgical Treatment Guidelines. Endocrine, Metab Immune Disord Targets [Internet]. 2017 Feb 22 [cited 2021 May 30];16(4):264–9. Available from: https://pubmed.ncbi.nlm.nih.gov/28017141/

35). Chamilos G, Luna M, Lewis RE, Bodey GP, Chemaly R, Tarrand JJ, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: An autopsy study over a 15-year period (1989-2003). Haematologica [Internet]. 2006 [cited 2021 May 30];91(7):986–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16757415/

36). Skiada A, Petrikkos G. Cutaneous zygomycosis [Internet]. Vol. 15, Clinical Microbiology and Infection. Blackwell Publishing Ltd; 2009 [cited 2021 May 30]. p. 41–5. Available from: https://pubmed.ncbi.nlm.nih.gov/19754756/

37.) Almyroudis NG, Sutton DA, Fothergill AW, Rinaldi MG, Kusne S. In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antimicrob Agents Chemother [Internet]. 2007 Jul [cited 2021 May 30];51(7):2587–90. Available from: /pmc/articles/PMC1913247/

38). Dannaoui E. Antifungal resistance in mucorales. Int J Antimicrob Agents [Internet]. 2017 Nov 1 [cited 2021 May 30];50(5):617–21. Available from: https://pubmed.ncbi.nlm.nih.gov/28802855/

39). Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis [Internet]. 2008 Aug 15 [cited 2021 May 30];47(4):503–9. Available from: https://pubmed.ncbi.nlm.nih.gov/18611163/

40) Sheybani F, Naderi HR, Sarvghad MR, Ghabouli MJ, Arian M. How should we manage a patient with invasive mucoromycosis who develops life-threatening reaction to amphotericin B? Report of two cases and literature review. Med Mycol Case Rep [Internet]. 2015 [cited 2021 May 30];8:29–31.
Available from: /pmc/articles/PMC4366442/.