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Mucormycosis: A Post Covid Symptom

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Abstract

Mucormycosis is an invasive infection with a high mortality rate even after active management. This infection is caused by a group of filaments molds belonging to the order Mucorales. These Mucorales are decomposers and are found in thedecaying matter, rotten fruits, and vegetables other than the environmental niche, theyreproduce rapidly asexually, it is human pathogenic affecting skin, lungs, brain,gut, and other organs. Mucormycosis is a rare fungal infection, also known as the black fungus which iscaused due to inhalation or ingestion of fungal spores. Immuno-compromised patients are commonly observed to be affected by this infection. The most frequently found Mucorale is*Rhizopus arrhizus*. Initial sites of infection are found to be sinuses, lungs, skin, and gastrointestinal tract.

The recent spread of the COVID-19 pandemic is a major cause of mucormycosis. Several cases of the infection were reported in India and worldwide.In India, mucormycosis associated with COVID-19 increased majorly during the second wave hit.The major causes of COVID-19 associated mucormycosis were diabetes, prolonged use of steroids, cytokine storm, and impact of delta variant. Rhino orbital mucormycosis and pulmonary mucormycosis are the most widely spread types of mucormycosisisassociated with COVID-19.

Keywords: COVID-19, cytokine storm, Rhino orbital Mucormycosis, zygomycosis.

Introduction

Mucormycosis is also known as zygomycosis, an infection caused by fungi belonging to the order Mucorales which comprises 261 species in 55 genera, 38 of which are associated with human infections. The most frequently found is *Rhizopusarrhizus* (formerly *Rhizopusoryzae*)which is associated with human infections. *Lichtheimia, Mucor, Rhizomucor, and Cunninghamella* are also the pathogens that were reported in Mucormycosis including *Saksenaea, Apophysomyces, Cokeromyces, Actinomucor, and Syncephalastrum.* The infection was first reported in 1885 by Paultauf [1-2]. After candidiasis and aspergillosis, Mucormycosis is considered the third most common Angio-invasive fungal infection. The immunosuppressed individuals are commonly affected and it is rarely reported in healthy individuals. In the past decades, Mucormycosis has turned out to be one of the fungal infections with high mortality rates[3-4]. *Rhizopusoryzae* is frequently isolated from patients with Mucormycosis [5-7].

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Pathophysiology

The infection by these fungi is due to the formation of asexual spores.The fungal spores enter the human body through inhalation, ingestion, or direct inoculation and settle in the oral and nasal mucosa. The initial site of infections is observed to be the paranasal sinuses, lungs, skin, and gastrointestinal tract. The foremost risk factors of Mucormycosis are uncontrolled diabetes mellitus resulting in ketoacidosis,malignant hematological disorders, organ or bone marrow transplantation,treatment with corticosteroids, trauma, burns,neutropenia, cancer, etc.

The presence of high concentrations of iron in serum is an important risk factor for Mucormycosis.Patients treated with deferoxamine have a high incidence of Mucormycosisbecause thesefungi use this chelant as a siderophore to obtain more iron. The increased risk of Mucormycosis in patients with ketoacidosis may also be due to the release of iron bound to proteins[8].

History

The term Mucormycosiswascoined by an American pathologist R.D. Baker. In 1885, Arnold Paltaufreported the first case of disseminated Mucormycosis titled "Mycosis mucorina". In 1876, Fürbinger stated that the disease was first observed in cancer patients whose right lung showed fungal hyphae and a few sporangia at hemorrhagic infarct. Over time, more cases were diagnosed, and the occurrence of the disease increased. Mucormycosis infection was observed in immunocompromised individuals during the period of 1980s and 1990s[9].Mucorales can survive high temperatures. They are universal and widely found on organic substrates, including bread, decaying fruits, vegetable matters, crop debris, soil, compost piles, animal excreta, and excavation and construction sites. Sporangiosporesare aerosolized, hence can spread easily making inhalation the major mode of transmission. Mucormycosis is distinguished by the presence of hyphal invasion of sinus tissue in a period of fewer than four weeks [10].

Epidemiology

The prevalence of the infection is difficult to estimate since it is not a reportable disease and the risk varies widely in different populations. A review of 929 cases of Mucormycosis reported between 1940 and 2003 claimed that diabetes mellitus was the most common risk factor found in 36% of cases, followed by hematologic malignancies (17%) and solid organ or hematopoietic cell transplantation (12%) [11]. In a few patients, Mucormycosis was a diabetes-defining illness. In another study conducted in France between 2005 and 2007,in 101 patients diagnosed with Mucormycosis the most prevalent risk factor was hematologic malignancy with an occurrence rate of 50%, succeeded by diabetes and trauma at23% and 18% of patients respectively [12-13].

Mucormycosis – Association With COVID-19

Coronavirus disease 2019 (COVID-19) is an infection caused due to severe acute respiratory syndrome Coronavirus2 (SARS-CoV-2). The first occurrence was reported in December 2019 in Wuhan, China. The symptoms ofCOVID-19 have developed and expanded compared to the initial days of the outbreak of the disease, initially dry cough and high-grade fever, advanced to other signs such as shortness of breath, anosmia, ageusia, diarrhea, chest pain, generalized malaise, acute cardiac injury and secondary infections [14]. Centre for disease control and prevention defines coinfections as infections occurring simultaneously with the initial infection whereas superinfections are defined as infections occurring in patients after the recovery from the initial infections Secondary infections can be caused due to bacteria, viruses, mycobacteria, and fungi[15]. Common fungal infections include Aspergillosis,Cryptococcus, Candidiasis, and Mucormycosis[16].

Prevalence Of Mucormycosis In COVID-19 Patients in India

Being a fungal infection, Mucormycosisaffects immune-compromised individuals. The body's Immune response is weakened due to various reasons such as uncontrolled diabetes, COVID-19, HIV/AIDS, other viral infections/diseases, congenital bone marrow disease, severe burns,

and cancer. COVID-19 patients who have received steroids are particularly at risk as steroids subdue the immune system. The fungal spores inhaled are killed by white blood cells in healthy individuals whereas, in an individual whose immune response is suppressed, the body has a low white blood cells count due to less production. In this condition, the spores germinate and grow rapidly, attack the sinuses, spread at a faster rate to the lungs, brain, and central nervous system, and in turn,infect the individual[17].

Cases Reported in India and Worldwide

According to a doctor in Mumbai,at least 40 cases of Mucormycosiswere observed in April 2021 during the second wave of COVID-19 in patients who recovered from COVID-19 and were diabetic. Six of his colleagues reported 58 cases of infections between December and February from Mumbai, Bangalore, Hyderabad, Delhi, and Pune. In most of the cases, the infection was observedwithin 11 to 15 days after recovery from COVID-19 [18].

As of 13th May 2021, in a total of 101 casesof post-COVID black fungus reported worldwide, 95 cases were confirmed whereas 6 were suspected.82 cases were reported from India, 9and 3 cases from the USA and Iran respectively. Mucormycosis in COVID-19 active patients accounted for 59.4% and40.6% of individuals were recovered [19].

Tamil Nadu reported 518 cases and 17 deaths as of June 1st2021 [20]. Gujarat reported 5000 cases and 250 deaths as of June 3rd, 2021, and most cases were reported from Ahmedabad, Surat, and Rajkot. The majority of infections were observed in thepatients administeredsteroids for a prolonged period [21]. The country's capital, Delhi reported 1044 cases till June 3rd2021 among which 92 people recovered fully and 89 casualties occurred [22]. Five districts of Maharashtra namely Pune, Nagpur, Aurangabad, Mumbai, and Nashik reported 57% of the cases. A total of 7,359 cases were reported from Maharashtra of which Pune reported the highest number of 1316 as of June 14th, 2021[23]. The state of Jharkhand reported 79 confirmed and 53 suspected cases in 18 districts as of June 19th, 2021. The state has registered 26 deaths due to Mucormycosis while 50 patients recovered [24].

The Major Causes Of COVID-19 Associated MucormycosisAre -

Diabetes In COVID Patients

Diabetes is a very common chronic disease in adults worldwide. India has the second-largest number of adults in the age category 20-79 years with Diabetes Mellitus.It is observed that 57% of patients have uncontrolled diabetes and 18% have Diabetic ketoacidosis [25].

The binding of SARS-COV-2 on ACE2 receptors results in down-regulation of ACE2 expression on the cells of many organs majorly lungs, intestine, and Pancreas. In the case of the Pancreas, ACE-2/Angiotensin 1-7 plays a vital role in maintaining beta cells which are involved in the synthesis of insulin. The binding of these receptors by the spike protein of the virus increases pro-inflammatory cytokines leading to hampering the immune system [26]. The resultant Immunocompromised state induces the growth of Mucorales.Hyperglycemia stimulates the growth of the fungi and prevents chemotaxis and phagocytic activities. *Rhizopus oryzae* is a common Mucorale that grows profusely by secreting the enzyme ketoreductase which utilizes the ketone bodies common in patients with diabetic ketoacidosis [3].

The high iron concentration in diabetic patients also aggravates fungal growth [27]. The acidic pH during diabetic ketoacidosis prevents the binding of iron to transferrin which further increases the intracellular iron concentration [3]. Another reason for the high intracellular iron concentration in diabetic patients and individuals suffering from severe COVID-19 is the release of cytokines IL-6. Upregulation of iron results in tissue damage and also enhances the expression of GRP-78 on endothelial cells which act as receptors for the binding of Mucorales28].

Cytokine Storm Due To COVID-19

Pathogen associated molecular patterns (PAMP) are recognized by TLR-7 which activates several signaling pathways and transcription factors such as Janus kinases transducers (JAK/STAT), Interferon response factors (IRF-3,IRF-7), Activator protein (AP-1), Nuclear factors which can induce the secretion of inflammatory cytokines –Interleukins (IL-6, IL-1), Monocyte chemo-attractant protein (MCP-1). Tumour

necrosis factor- α (TNF-α) and Interferon -1 (IFN-1). The adaptive immune response is initiated along with the release of inflammatory cytokines. High titer of cytokines in the bloodstream of patients results in the development of ARDS and multiple organ failure along with an increase in neutrophil count and a decrease in lymphocyte count [29].

Prolonged Usage of Steroids In COVID-19 Patients

Steroids are administered in COVID -19 Patients, especially the ones suffering from diabetes. It results in elevation of blood sugar levels which stimulates the growth of Mucorales [30]. Steroids help in controlling the inflammatory response by entering the cell and preventing the transcription of cytokines.This, in turn, affects the immune system of the patients if given for a prolonged period resulting in an immunocompromised state, due to neutrophilic leukocytosis, lymphopenia (T cells more than B cells), and impaired ability of leukocytes to migrate to the site of infection [31-32].

Impact of DeltaVariant

Although the first wave of COVID-19 in India affected many, the delta variant (B1.617.2) was more infectious during the second wave [33]. According to researchers, the delta variant is suspected as thecause of the surge in Mucormycosis during the second wave since the variant is very infectious and known to destroy the beta cells in the pancreas resulting in diabetes in healthy individuals and hence a cause for Mucormycosis [34]. Hence, the discovery and study of the new variant could explain the rise in secondary fungal infection due to lowering the immune response and functioning.

Rhino-Orbito-CerebralMucormycosis (ROCM) And Pulmonary Mucormycosis-Types of Mucormycosis Associated with COVID-19

ROCM is the most commonly observed type of Black Fungal Infection. Around seventy percent of patients, who contracted ROCM were diabetic [35]. Facial pain and facial swelling along with fever are the common symptoms observed in patients.Theinitial appearance of the inflamed nasal mucosa is followed by the erythematous phase, formation of necrotic eschars, blood vessel thrombosis, and tissue infarction. Progression of the infection to the central nervous system brings forth the development of confusion and disorientation [36]. If the palates are involved, the manifestations will include ulcers on the palate, toothache, and difficulty in the movement of the jaw [35].

Pulmonary Mucormycosis – Usual clinical presentation includes neutropenia,pleural effusion, dyspnea,cough, and nodules[36]. Though reversed halo sign in the peripheral locations of the lung has been identified as a sign of Pulmonary Mucormycosis, it is less specific since it has also been considered a radiological feature of COVID-19.Diagnosis of Pulmonary Mucormycosis associated with COVID-19 is challenging since the more specific manifestation, which is the appearance of the cavitary lung lesions is also found in COVID-19 associated pulmonary aspergillosis [37].

Diagnosis

Histopathological examination of the tissue samples is one of the prime diagnostic tools in detecting Mucormycosisinfection [10].

Treatment

Successful treatment for Mucormycosis includes antifungal medicines like Amphotericin BDeoxycholate, Liposomal Amphotericin B (5-10mg/kg), Amphotericin B lipid complex, Amphotericin B colloidal dispersion, and Posaconazole (400mg bid). Also,the combination of caspofungin and lipid Amphotericin B, a mixture of lipid Amphotericin B and Posaconazole, is suggested[9]. For patients who are intolerant to amphotericin B, alternative drugs are posaconazole or isavuconazole.

Both triazoles are also strongly recommended for salvage treatments [38, 39].

Conclusion

The emergence of Mucormycosis has become a serious problem during the COVID-19 pandemic. Uncontrolled hyperglycemia and prolonged medication of steroids are the most common conditions among patients with COVID-associatedMucormycosis.Cytokine storm in COVID patients causes an imbalance in the

numbers and types of WBCs which in turn can accelerate the spread of Mucormycosis.The spread of the Delta variant during the second wave of COVID proved to be highly infectious and augmented the spread of Mucormycosis.Early diagnosis and timely management are essential to improve outcomes in pulmonary Mucormycosis.

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References

1. Paltauf A. (1885). Mycosis mucorina, *Arch Pathol. Anat, 102:553-564*.
2. Ribes J.A., Vanover-Sams C.L. and Baker D.J. (2000). Zygomycetes in human disease**,** *Clin Microbiol Rev, 13: 236-301.*
3. Petrikkos G., Skiada A., Lortholary O., Roilides E., Walsh TJ. and KontoyiannisD.P. (2012). Epidemiology and clinical manifestations of Mucormycosis**,***Clin Infect Dis,54 (1): S23-34.*
4. Afroze S.N., KorleparaR. and MadalaJ. (2017). Mucormycosis in a Diabetic Patient: A Case Report with an Insight into Its Pathophysiology,*Contemporary Clinical dentistry8(4): (Oct-Dec): 662–666.*
5. Ibrahim A.S.,Spellberg B., WalshT.J. and Kontoyiannis D.P. (2012). Pathogenesis of Mucormycosis, *Clin Infect Dis, 54(1): S16–S22*.
6. Jeong W**.**, Keighley C**.**, Wolfe R**.**, Lee W**.**L**.**, Slavin M**.**A**.**,Kong D**.**C**.**M**.,**and Chen S**.**C**.** (2019)**.** The epidemiology and clinical manifestations of Mucormycosis: a systematic review and meta-analysis of case reports**,***Clinical microbiology, and infection***,** *25(2019): 26-34***.**
7. Nishanth G., Anitha N., Aravindha B. N. andMalathi L. (2020).Mucormycosis - A review,*European Journal of Molecular & Clinical Medicine, 07 (03): 1786-1791*.
8. Artis W.M., FountainJ. A., DelcherH. K. and JonesH. E. (1982). A mechanism of susceptibility to Mucormycosis in diabetic ketoacidosis: transferrin and iron availability, *Diabetes, 31 (1982): 1109-1114*.
9. Suganya R**.**, Malathi N**.**, Karthikeyan V**.** andJanagaraj V.D. (2019). Mucormycosis: A Brief Review, *J Pure Appl Microbiol, 13(1): 161-165.*
10. Borkar S.G. (2021).Mucormycosis: A Surge in Mucorales Fungal infection in Post-COVID Patients in Indian states and Insight into known and unknown factors, *international journal of global health, 1(3):26-60.*
11. Roden M. M., ZaoutisT.E., Buchanan W.L., Knudsen T.A., Sarkisova T. A., Schaufele R. L., Sein M., Sein T., ChiouC.C., Chu J. H., Kontoyiannis D.P. and Walsh T. J. (2005). Epidemiology and outcome of zygomycosis: A review of 929 reported cases, *Clin. Infect. Dis 41, 634-653.*
12. Lanternier F., Dannaoui E., Morizot G., Elie C., Garcia-Hermoso D., Huerre M., Bitar D., Dromer F. andLortholary O.(2012). A global analysis of Mucormycosis in France (2005-2007), *Clinical infectious diseases, 54(1): S35-43.*
13. Anna S., Loannis P. and Maria D. (2020). Epidemiology and Diagnosis of Mucormycosis: An Update, *J.Fungi, 6(265): 2-20*.
14. Sharma S., GroverM., Bhargava S., Samdani S. andKataria T. (2021). Post coronavirus disease Mucormycosis: a deadly addition to the pandemic spectrum,*Journal of laryngology and autology, 135(5) 442 – 447.*
15. Feldman C and Anderson R (2021) The role of co-infections and secondary infections in patients with COVID –19, *Pneumonia (Nathan) 13(1):5*.
16. Song G., Liang G. and Liu W. (2020). Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China, *Mycopathologia, 185 (4):599 – 606.*
17. Suryanarayanan T.S. andShaanker R.U. (2021). COVID-19, and Black Fungus: What Is Mucormycosis, *Health, Science the wire*.

18. BBC news, India Edition, dated 9/05/2021. https://www.bbc.com/news/world-asia-india-57027829
19. Singh A.K., Singh R., Joshi S.R. andMisra A. (2021).Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India,*Diabetes & Metabolic Syndrome 15(4):102146*.
20. The New Indian Express, Tamilnadu Edition, dated 1/06/2021.https://www.newindianexpress.com/states/tamil-nadu/2021/jun/01/tamil-nadu-reports-518-black-fungus-cases-136-of-them-in-chennai-2310423.html
21. The Indian Express, dated 08-10-2020 https://indianexpress.com/article/opinion/columns/COVID-19-global- crisis- local-response-6707887/
22. The New Indian Express, Delhi Edition, dated 03-06-2021. https://www.newindianexpress.com/cities/delhi/2021/jun/03/delhi-reports-1044-black-fungus-cases-89-deaths-so-far-satyender-jain-2311228.html
23. The Times of India, Pune Edition, dated18 - 06- 2021. https://timesofindia.indiatimes.com/city/pune/five-dists-record-57-of-maharashtras-covid-linked-mucormycosis-cases/articleshow/83618336.cms
24. The Times of India,dated 19-06- 2021. https://timesofindia.indiatimes.com/india/jharkhand-on-high-alert-as-mucormycosis-cases-rise/articleshow/83668715.cms
25. JohnT.M., Jacob C.N. andKontoyiannis D.P. (2021). Review When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis, *Journal of fungi (Basel,Switzerland) 7(4):298*
26. Afroze S.N.,Korlepara R. and Rao G.V. andMadala J. (2017). Mucormycosis in a diabetic patient: A case report with an insight into its pathophysiology, *Contemporary clinicaldentistry 8(4):662-666*.
27. VijayabalaG., Annigeri R.J. and Sudarshan R. (2013).Mucormycosis in a diabetic ketoacidosis patient, *Asian Pacific Journal of Tropical Biomedicine 3(10): 830-833*.
28. Ibrahim A.S.(2011). Host cell invasion in Mucormycosis: role of Iron, *CurrentOpinion in Microbiology 14(4): 406-11*.
29. PaseroD., SannaS., Liperi L., Piredda D., BrancaG.P., Casadio L., Simeo R., Buselli A., Rizzo D., BussuF., Rubino S.,TerragniP. (2020). Challenging complication following SARS-CoV-2 infection: a case of pulmonary Mucormycosis, *Infection 49,1055-1060*.
30. First post, dated 2021. https://www.firstpost.com/india/black-fungus-or-Mucormycosis-costly-mistakes-in-COVID-19-treatment-lead-to-new-challenges-9637481.html
31. Petrillo M.G., Bortner C.D andCidlowski J.A. (2016).Glucocorticoids: inflammation and immunity,*The Hypothalamic-Pituitary-Adrenal Axis in Health and Disease. Springer, pp 43-63*.
32. Mishra N et al (2021). A case series of invasive Mucormycosis in patients with COVID-19 infection. *International Journal of Otorhinolaryngology and Head and Neck Surgery 7(5):867-870*.
33. The Times of India, dated 04-06-2021.https://timesofindia.indiatimes.com/india/COVID-19-delta-variant-first-found-in-india-spreads-to-united-kingdom-and-australia/articleshow/83232950.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst. Accessed 4 June 2021.
34. The Telegraph, India Edition, dated 04-06-2021. https://www.telegraph.co.uk/global-health/science-and-disease/indias-black-fungus-wards/
35. Ahmed O. F. (2022). COVID-19 associated with pulmonaryMucormycosis; a case series, *Annals of Medicine and Surgery 76,April 2022,103434*.
36. Linn E., Mou A. and Limper A.H. (2017). PulmonaryMucormycosis: clinical features and outcomes,*Infection 45(4):443-448*.
37. Hoenigl M et al(2022).The emergence of COVID-19 associated Mucormycosis: a review of cases from 18 countries,*The Lancet,Microbe*.
38. Rudramurthy S. M., Hoenigl M., Meis F., Cornely O.A., Muthu V. and Gangneux

J.P. (2021).ECMM/ISHAM recommendations for clinical management of COVID -19 associated Mucormycosis in low- and middle-income countries, *Mycoses64 (2021), pp. 1028-1037*.

39. CornelyO.A, Alastruey A., Izquierdo D., Arenz S.C.A., Chen E., Dannaoui B. and Hochhegger (2019).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, 19 (2019), pp. e405-e421*.

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