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COVID-19 KINDRED MUCORMYCOSIS AND ITS THERAPEUTIC ENDEAVOUR: A BRIEF REVIEW

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ABSTRACT:

Mucormycosis is a fungal infection caused by a group of filamentous moulds in the Mucorales order and Zygomycetes class. Mucormycosis, often known as black fungus disease, is a kind of mucormycosis. This illness primarily affects diabetics and those with impaired immune systems. As patients' immunity decreases as a result of COVID-19 infection, mucormycosis instances rise as a result of inhaling moulds containing industrial oxygen. The major goal of this paper is to give a full overview of mucormycosis, including its epidemiology, pathophysiology, diagnosis, therapy, and relationship to COVID-19.

Between March and June 2021, a thorough literature search was conducted utilising terms such as Mucormycosis, Black fungus, Mucorales, Zygomycetes, Rhizopus, and others in various search engines such as PubMed, Google Scholars, Research Gate, and SCOPUS. Mucormycosis, or black fungus disease, is an uncommon invasive fungal illness with a significant fatality risk if not detected properly. Mucorales frequently prey on endothelial cells in vascular tissue. Mucormycosis is classified into six types depending on their anatomical locations: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. Patients receiving iron overload therapy are more likely to develop black fungus. Imaging analysis, sputum culture, and bronchoalveolar lavage culture are generally used to diagnose and treat mucormycosis. Amphotericin B treatment combined with suitable surgery can boost survival rates by 1.5 times. Mucorales have a wide spectrum of resistance to antifungal medications. However, first-line therapies such as amphotericin B, posaconazole, and isavuconazole are feasible. COVID- To combat the infections, 19 individuals with black fungus are being treated with first-line antifungal medications. In the future, much more research will be required to identify new medicinal therapies.

Keywords: Mucormycosis, Black fungus, COVID-19, Mucorales, Zygomycetes, Rhizopus, Amphotericin B

INTRODUCTION:

'Mycosis' is a scientific term for fungal infections, while the term 'mucor' implies a particular genus of fungi. Formerly named Zygomycosis, Mucormycosis is an all-pervasive and opportunistic sporadic fungal infection ranking third-most in the list of invasive infections after Candidiasis and Aspergillosis. Molds of class- Mucormycetes/Zygomycetes belonging to Mucorales are recognized to induce the infection[1,2]. They live throughout the environment, be it in the soil, on the dead decaying matter, animal excreta, or in the air. Sporangiospores present in the environment enter the body predominantly through inhalation, and uncommonly by ingestion or lesion inoculation. The disease precipitation is liable to the organisms mentioned; *Rhizopus* spp, *Mucor* spp, *Rhizomucor* spp, *Syncephalastrum* spp, *Cunninghamella bertholletiae*, *Apophysomyces* spp, and *Lichtheimia* species. Amongst the Rhizopus spp., *Rhizopus arrhizus* accounts for a majority of the infections followed by Apophysomyces spp.

The trending Severe Acute Respiratory Syndrome - Corona Virus-2 (SARS-CoV-2) pandemic has impacted negatively on the patient's psyche and overall wellbeing. The first wave of COVID-19 infection announced in December 2019 posed a terrifying situation waning public health. Since then, the healthcare providers have been engaged, coping up with the pandemic, but are now challenged with the emergence of co-infections exacerbating patient health. Treatment strategies for the recently surfacing cases of COVID-19 with mucormycosis have not only compromised the patient's life but have also alarmed the pharmacist, globally, to derive appropriate therapeutic solutions and normalize the existing situation. The major threat of Mucormycotic infections is to COVID-19 patients with diabetes mellitus and patients on ventilator systems surrounded by an unhygienic environment. Similarly, systemic corticosteroids, namely dexamethasone, hydrocortisone, prednisone, methylprednisolone, recommended by WHO in treating severe to critical Covid-19 patients helped reduce the mortality rate, however, the increased dosage and prolonged use manifested with predominantly immunosuppressive effects may form a risk to mucormycosis and other invasive infections. COVID-19 linked mucormycosis cases have surged considerably and there is a need to speed up its prompt diagnosis and treatment.

We have summarized the forms, clinical manifestations, risk factors, diagnosis, and current therapies for mucormycosis, which have been briefly discussed through this study in order to provide up-to-date information.

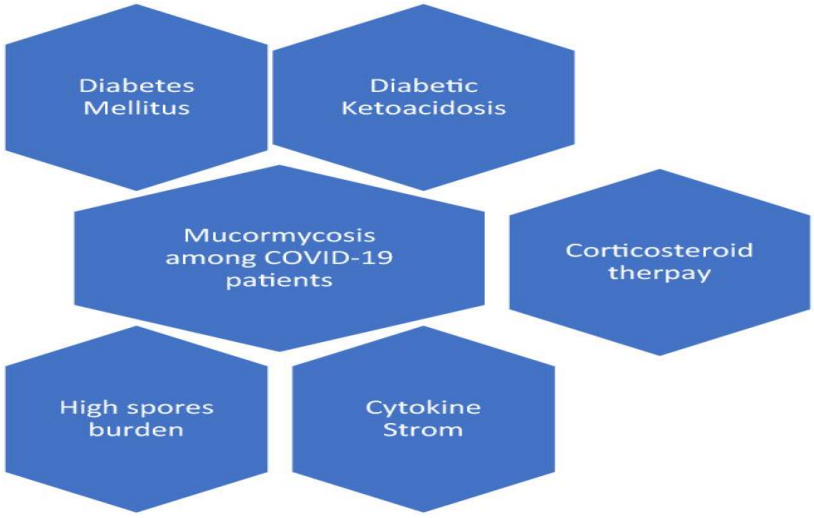

Fig.no.1 Mucormycosis among Covid 19 patients Symptoms

CATEGORIES WITH CLINICAL EXPRESSIONS OF MUCORMYCOSIS:

Mucormycosis in patients appears in different forms depending upon the site of infection. These forms are detailed as given below(1,3–7):

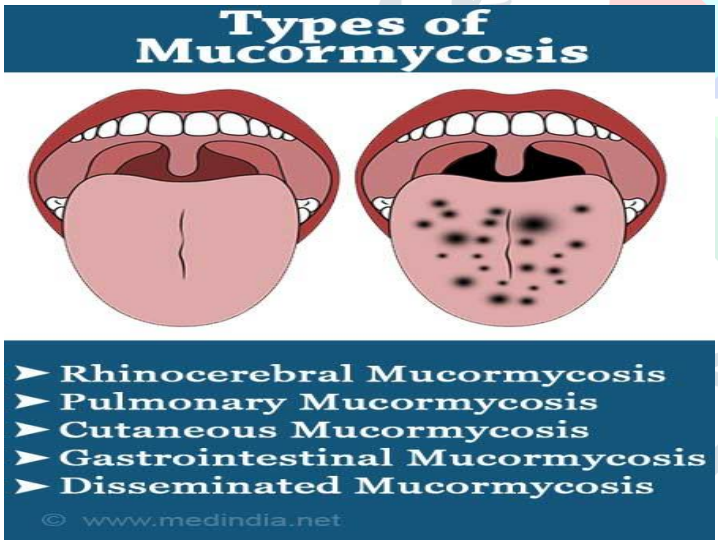

Fig.no.2 Types of Mucormycosis

1. **Rhino-Orbito-Cerebral Mucormycosis (ROCM):**

   This type comprises 33-55% of the overall cases affecting paranasal sinuses, the palate, orbits, sphenoid sinuses, cavernous sinuses, and lastly the brain. Primary symptoms cover fever, headache, nasal congestion, perinasal, and soft tissue swelling, followed by nasal ulceration. Early detection and treatment are preferable otherwise it may cause severe secondary symptoms as spreading to the adjoining tissues causing thrombosis, necrosis, and black nasal eschar. If the infection progresses towards the eyes, exophthalmos, pain in eyes, blurred vision, periorbital discoloration, bulky

extraocular muscles, proptosis may occur and eventually after infecting the cranium it may lead to lethargy, blindness, and seizures resulting in a fatality.

2. **Pulmonary Mucormycosis (PM):**

Lungs get infected by the entry of spores via the respiratory tract in this form of mucormycosis. Symptoms include pyrexia, dry cough, hemoptysis, chest pain, and breathlessness. It progresses causing invasion, thrombosis, necrosis, and infarction of the pleural parenchymal tissues and may spread to the chest wall, pulmonary arteries, mediastinal structures, etc. Pulmonary edema, lung cavitation, pleural infiltration, nodule formation are usual manifestations observed in PM.

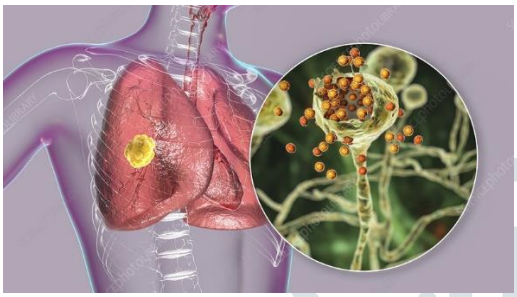

Fig.3 Pulmonary Mucormycosis

3. **Cutaneous Mucormycosis (CM):**

This state usually appears because of traumatic injury, burns, surgery, use of non-sterile dressings, occasionally through intravenous catheter sites, or rarely by the bite of an insect. Affected areas of the skin exhibit swelling, redness, inflammation, hardness, pain, itchiness and the proliferation may result in ulceration, sore formation, thrombosis, necrotizing the overlying tissues augmenting to blackening off the skin .

4. **Gastrointestinal Mucormycosis (GM):**

Within the gastrointestinal tract, the stomach remains the most infected site, the next being colon, small intestine, and esophagus. Contaminated food and mouth breathing are the source to the spore entry. Nearly all cases present abdominal pain, hematemesis (vomiting blood), gastrointestinal bleeding arising from perforations, ulceration into the peritoneum leading to bowel infarction caused by inadequate blood flow, thus leading to hemorrhagic shock.

5. **Disseminated Mucormycosis (DM):**

This is distinct from the others in that all the others are localized forms, whereas this one spreads throughout the body. The widespread infection usually involves lungs, heart, sinuses, spleen, CNS, liver, kidney, skin etc.

6. **Miscellaneous:**

This kind of presentations are typically rare and comprise endocarditis, peritonitis, osteomyelitis and pyelonephritis. Indications vary according to the body system involved.

RISK FACTORS:

The peak incidence of morbidity and death is due to significant risk variables and this illness may often not be that dangerous. However, the following was noted:

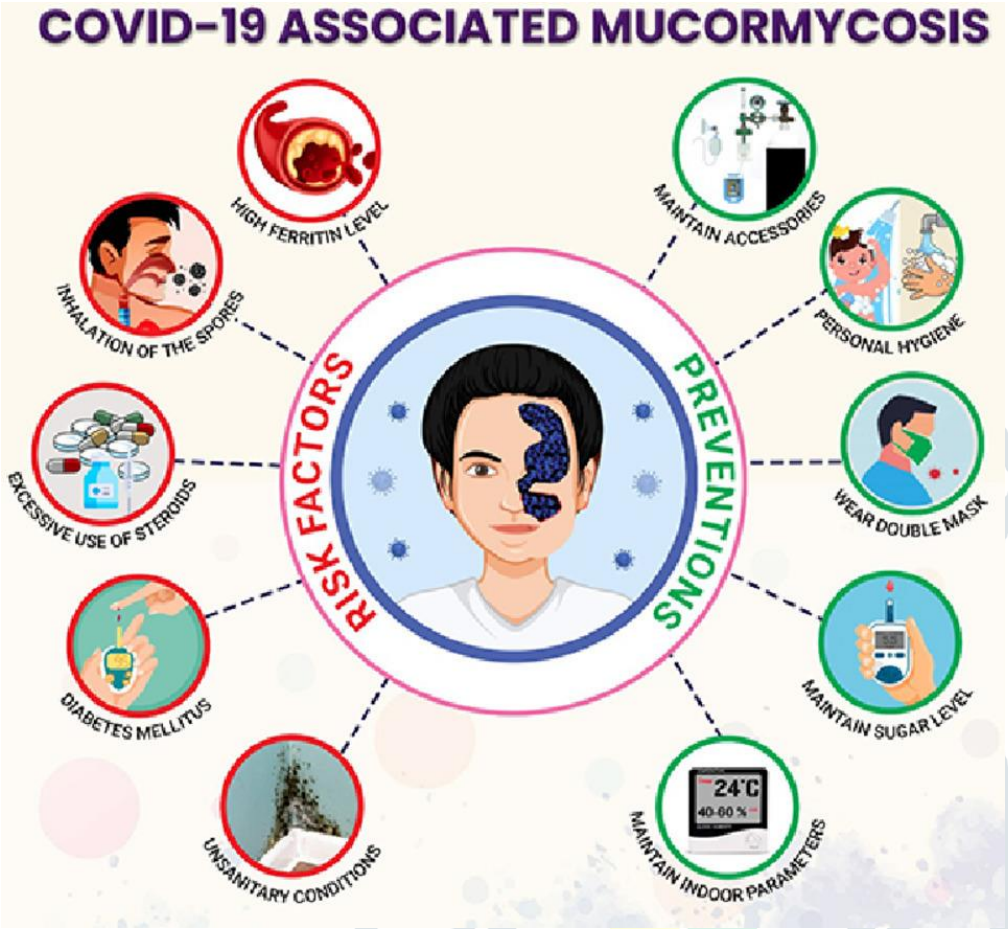

Fig.no.4 Risk Factor of Covid 19 Associated with Mucormycosis

- Patients recovered from COVID-19, who had been administered corticosteroids, showed a significant outbreak of mucormycosis.
- Diabetes mellitus with or without a serious complication of diabetic ketoacidosis has been majorly reported to be the underlying cause of mucormycosis.
- Additionally, hematologic malignancies, solid organ transplant (SOT), immunocompromised patients, renal diseases, patients on deferoxamine therapy due to iron overload, surgical site infections, intravenous drug use, peritoneal dialysis, all account for significant risk factors in commencing as well as intensifying the disease.
- Hematological malignancies involving neutropenia, corticosteroid therapy, hematopoietic stem cell transplant (HSCT), graft-versus-host disease (GVHD) are also risk factors.
- Supplementary predisposing factors constitute skin trauma, broad-spectrum antibiotic drug use, voriconazole prophylaxis, HIV/AIDS, contaminated wound equipment, malnutrition, premature

newbies, chronic kidney disease (CKD), pulmonary tuberculosis, chronic obstructive pulmonary disease (COPD).

These comprehensive list of risk factors are, however, individually or together responsible in contributing to the health burden of the patients.(1,3–16) (34).

EPIDEMIOLOGY

Mucormycosis is a very rare illness, although instances have been on the rise in the last two decades, notably in Belgium, France, Switzerland, and India [3,9,18–20]. According to a research from the National Hospital Discharge Database, between 2001 and 2010, France identified 35,876 individuals with invasive fungal infections (IFIs), with 1.5 percent of IFIs cases being mucormycosis [18]. From 2007 to 2015, 19 instances of mucormycosis were discovered in a single-center research in Spain. Similarly, from 1989 to 2003, three instances of mucormycosis were reported in a tertiary hospital in Geneva, Switzerland, whereas 16 cases were discovered between 2003 and 2008 [20,21]. People on immunosuppressant and voriconazole medications were reported to be more vulnerable to black fungus infection [20].

Mucorales are found all across the world, are thermotolerant, and become quite active when the seasons change. In a case study from Israel, 16 of 19 black fungus cases of rhino-orbito-cerebral mucormycosis (ROCM) were discovered to occur in the fall, while 6 instances of haematological patients were reported to be infected in the months of August to September in Japan [22,23]. Inhalation of fungal sporangiospores or direct injection of pathogens through disturbed skin or mucosa caused this type of infection in humans. There is a definite link between developed and developing nations when it comes to mucormycosis.

In industrialised nations, only patients with diabetes, stem cell transplants, and haematological complications are infected, but in poor countries such as India, it occurs in patients with strokes and uncontrolled diabetes [3,4,10]. Because it's an opportunistic infection, it's quite simple for it to infect persons with a weakened immune system, such as ketoacidosis patients, burn and trauma patients, and patients receiving iron treatment or chemotherapy [1].

PATHOPHYSIOLOGY

Sporangiospore ingestion, inhalation, or inoculation of spores via wounds or trauma, inhalation of saturated oxygen, medical equipment, or an inadequate ventilation system are all examples of how black fungus entered a patient [9,19,20]. Mucorales infection necessitates the presence of phagocytes. Mucormycosis is caused by mould hyphae and spores, which are easily combated by mononuclear or polymorphonuclear phagocytes. As a result, those with a reduced phagocyte count or poor phagocytosis function are more susceptible to black function infections[20]. Excessive chemotherapy might cause neutropenia, which makes you a vulnerable target for this mucormycosis.

Furthermore, patients with impaired neutrophil function owing to poor blood glucose management, acidic pH, or ketoacidosis hyperglycemia may substantially impair neutrophil motility and phagocytic capability [27]. Furthermore, an excessive amount of glucocorticoids might impair phagocytic activity, preventing them from killing ingested Mucorales [1]. The iron metabolism is important in the pathophysiology of mucormycosis [5,24,28,29]. Mucormycosis may take iron from the host in order to survive and multiply, as well as execute a variety of enzymatic functions. Rhizopus oryzae was employed to test iron sequester activity, and it was discovered that mucormycosis grows quickly in iron-rich medium but slowly in iron-depleted serum [30]

According to studies, iron chelators act as an inhibitor of Rhizopus growth by capturing free iron, while others act as a siderophore by transferring iron to fungal cells for their growth. As a result, patients taking iron supplements like deferoxamine for iron overload are more likely to contract mucormycosis[31]. Siderophores are tiny molecular weight compounds produced by bacteria or fungi that have a significant affinity and selectivity for chelating iron molecules. Deferoxamine is a siderophore produced by fungi with a high affinity for iron and the ability to extract iron from ferritin and transferrin in order to utilise it for surviving inside the host [32].

Rhizopus uses deferoxamine as an iron source during intracellular transport by inducing a receptor that traps deferoxamine-iron complexes and inhibits the conversion of ferric to ferrous iron[1]. Mucormycosis has a unique method for invading endothelial cells in the circulatory system, which allows infection to spread from one region of the body to another. GRP78 receptors on cell surfaces are increased during glucose deprivation and operate like Mucorales receptors in humans to kill endothelial cells [33].

DIAGNOSIS:

Clinical expressions of mucormycosis are similar to that of aspergillosis, hence diagnosis of this disease is troublesome. So far, certain diagnostic pathways are available to start quick and appropriate treatment. The diagnosis and diagnostic tools can be portrayed as given below (5,17–20):

I. **Medical examination:**

For a preliminary diagnosis, it is necessary to understand the patient's medical history for underlying conditions and to determine the symptoms of mucormycosis. This directs the physician to which tests need to be performed.

II. **Histopathological & Cytopathological studies:**

Patient samples such as damaged tissues, sputum, nasal discharge, surgical removal of infected skin (in case of cutaneous mucormycosis) may be forwarded for tissue examination and microbiological testing. For determination of fungal strains, hematoxylin-eosin (H and E), Periodic acid Shiff (PAS) or Gomori methenamine silver stains may be applied in fungal culture tests. Further, if the patient turns out to be positive for fungal culture, studies of the hyphae may be performed with potassium hydroxide wet mount and observed under a fluorescent microscope with suitable stains.

III. Radiological imaging techniques:

In order to get more exhaustive information regarding the spread of the disease, several imaging techniques may be pragmatic and include:

A. Plain orbit or sinus radiography

B. Computed Tomography (CT)

C. Magnetic Resonance Imaging (MRI)

D. Angiography/Surgical Exploration

PREVAILING TREATMENTS:

It would be effective to implement medical and surgical therapy simultaneously, especially in ROCM and PM types of Mucormycosis. Reliable treatment to mucormycosis is paramount to recuperate from the disease. This may include one or multiple treatments prescribed concomitantly, as the case may be. Current recommended therapies given are as follows:

1) **Dilution of the predisposing factors-** This may be achieved with anti-diabetic medications to overcome hyperglycemia, declining the steroid intake, termination of immunosuppressive drugs, administration of iron should be put on hold, interferon treatment to boost immune system, cytokines, granulocyte transfusion to control neutropenia, cytokine therapy, etc.
2) **Surgical debridement:** Getting rid of the infected dead tissues through surgical procedures and wound cleansing not only prevents proliferation of infection but also helps in wound healing. The surgical intervention may vary, corresponding to the forms of mucormycosis.
3) **Antifungal therapy:**

   Primary standard antifungal drug treatment is employing broad spectrum polyene **Amphotericin-B (AmB)**. By the reason of high dosage and toxicity associated with conventional AmB, intravenous liposomal preparations of AmB (L-AmB) and AmB lipid complex (ABLC) are recommended meeting decreased dose and high therapeutic index. Another drug **Posaconazole** administered orally may be incorporated into the drug regimen as 800mg in 2-4 doses daily. **Isavuconazole** in the form of Isavuconazonium sulfate, a prodrug, has proven its antifungal potential in vitro and may be advised to patients dealing with mucormycosis. In some cases, **Caspofungin** might be preferred in multiple antifungal treatment, however, less evidence of combined effects has been proved till date. The dosing regimen as prescribed by the physician must be followed for a minimum of 3 weeks.
4) **Hyperbaric oxygen therapy (HBOT)**

   It is the last resort required to treat oxygen starving tissues in alarming situations where even after all the treatments, the patient's condition gradually degrades. It comprises 100% oxygen at the pressure of 2.0-2.5 atm for 1.5 hours and 1-2 times every day for up to 10-20 days(1,2,5,10,17,18).

CONCLUSION:

Mucormycosis is a serious fungal infection and a subject matter which compels us to emphasize it in every aspect. With the upsurge of COVID-19 associated mucormycosis, it has become inevitable for us to understand the etiology. Detection of mucormycosis is puzzling, so is the prognosis and diagnosis. Newer diagnostic tools and molecular techniques are the need of the hour in this contemporary state of the pandemic. Treatments have indeed diminished the mortality rate, novel treatments to completely manage the condition are still questionable and influenced by elements such as unrevealed risk factors, degree of infection, patient conditions, etc. Researchers and clinicians are responsible for thorough study of cases, to figure out possible alternatives or choices of diagnosis and treatments and ultimately share their understanding with society at the earliest. Timely prognosis and prompt management are quintessential to ameliorate outcomes in mucormycosis.

REFERENCES:

1. Ganescu O, Anderson M, Kankakee. Rare Disease Database. 2019;1–10. Available from: rarediseases.org/rare-diseases/osteomyelitis/
2. Sipsas N V., Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP;Therapy of mucormycosis. Vol. 4, Journal of Fungi. MDPI AG; 2018;Pg. 90. doi: https://doi.org/10.3390/jof4030090
3. Mehta S, Pandey;A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus. 2020;12(9):10–4. doi:10.7759/cureus.10726.
4. Serris A, Danion F, Lanternier F. Disease entities in mucormycosis. J Fungi 2019 Mar 1 [cited 2021 May 27];5(1):23. https://doi.org/10.3390/jof5010023.
5. Jaju MR, Sagar RV, Srivastav SK, Singh R, Kumar KV, Faisal M. Different types of mucormycosis: case series. Int J Res Med Sci. 2020 May 26;8(6):2284. DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20202281
6. Singh S, Pal N, Chander J, Sardana R, Mahajan B, Joseph N, et al. Mucormycosis caused by Syncephalastrum spp.: Clinical profile, molecular characterization, antifungal susceptibility and review of literature. Clin Infect Pract. 2021 Jul;11:100074. https://doi.org/10.1016/j.clinpr.2021.100074
7. 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 27]. p. 26–34. DOI: 10.1016/j.cmi.2018.07.011

8. European Journal of Molecular & Clinical Medicine MUCORMYCOSIS-A REVIEW. Volume 07, Issue 03, 2020 pg no.1786-1791.
9. MUCORMYCOSIS - A REVIEW. [cited 2021 May 27]. Available from: https://ejmcm.com/article_3450.html. *2020*, Volume 7, Issue 3, Pages 1786-1791

- Pandey A, Kaur G. Mucormycosis revisited: Case report with review of literature. J Dent Spec. 2020 [cited 2021 May 30];8(1):39–44. DOI https://doi.org/10.18231/j.jds.2020.010

10. Reid G, Lynch JP, Fishbein MC, Clark NM. Mucormycosis. Semin Respir Crit Care Med 2020 Jan 30 41(1):99–114 DOI: 10.1055/s-0039-3401992
11. Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bougnoux ME, Lecuit M, et al. Healthcare-associated mucormycosis. Clin Infect Dis. 2012 Feb 1 [cited 2021 May 28];54(SUPPL. 1):S44–54. DOI: : https://doi.org/10.1093/cid/cir867
12. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Vol. 9, Microorganisms. MDPIAG; 2021 [cited 2021 May 27]. p.g no 1–12. DOI: 10.3390/microorganisms9030523.
13. Suganya R, Malathi N, Karthikeyan V, Janagaraj VD. Mucormycosis : A Brief Review. J Pure Appl Microbiol [Internet]. 2019 [cited 2021 May 30];13(1):161–5. DOI: 10.22207/JPAM.13.1.16
14. 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 Clin Res Rev [Internet]. 2021 May 21 [cited 2021 May 30]; DOI https://doi.org/10.1016/j.dsx.2021.05.019
15. Pilmis B, Alanio A, Lortholary O, Lanternier F. Open Peer Review Recent advances in the understanding and management of mucormycosis [version 1; referees: 2 approved]. 2018; doi: 10.12688/f1000research.15081.1.
16. Pandilwar PK, Khan K, Shah K, Sanap M, Unnikrishnan A, Nerurkar S. CASE REPORT-OPEN ACCESS Mucormycosis: A rare entity with rising clinical presentation in immunocompromised hosts. Int J Surg Case Rep [Internet]. 2020 [cited 2021 May 30]; pg.no.77:57–61. DOI: : https://doi.org/10.1016/j.ijscr.2020.10.075.
17. Karanth M, Taniere P, Barraclough J. A rare presentation of zygomycosis (mucormycosis) and review of the literature. J Clin Pathol [cited 2021 May 30];58:879–881. DOI: 10.1136/jcp.2004.021816.
18. Agrawal R, Yeldandi A, Savas H, Parekh ND, Lombardi PJ, Hart EM. Pulmonary mucormycosis: Risk factors, radiologic findings, and pathologic correlation. Radiographics [cited 2021 May 30];40(3):pg no 656–666 DOI: 10.1148/rg.2020190156.

19. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J. Emerging invasive zygomycosis in a tertiary care center: Epidemiology and associated risk factors. Int J Infect Dis [cited 2021 May 30];14(SUPPL. 3). 2020; pg no 656–666.

20. Guinea J, Escribano P, Vena A, Muñoz P, Martínez-Jiménez MDC, Padilla B, et al. Increasing incidence of mucormycosis in a large Spanish hospital from 2007 to 2015: Epidemiology and microbiological characterization of the isolates [cited 2021 May 30]; 12(6):e0179136. DOI: https://doi.org/10.1371/journal.pone.0179136.

21. Talmi YP, Goldschmied-Reouven A, Bakon M, Barshack I, Wolf M, Horowitz Z, et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol - Head Neck Surg [cited 2021 May 30];127(1):22–31. DOI: 10.1067/mhn.2002.126587.

22. Funada H, Matsuda T. Pulmonary mucormycosis in a hematology ward. Intern Med [Internet]. 1996 [cited 2021 May 30];35(7):540–544 10.2169/internalmedicine.35.540.

23. Chinn RYW, Diamond RD. Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: Relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis.[cited 2021 May 30];38(3):1123–1129. DOI 10.1128/iai.38.3.1123-1129.1982.

24. Ibrahim AS, Kontoyiannis DP. Update on mucormycosis pathogenesis [Internet]. Vol. 26, Current Opinion in Infectious Diseases. Curr Opin Infect Dis; 2013 [cited 2021 May 30]. Pg.no 508–515. Available from: doi: 10.1097/QCO.0000000000000008

25. Ibrahim AS, Gebremariam T, Lin L, Luo G, Husseiny MI, Skory CD, et al. The high affinity iron permease is a key virulence factor required for Rhizopus oryzae pathogenesis. Mol Microbiol [cited 2021 May 30];77(3):587–604;doi:10.1111/j.1365-2958.2010.07234

26. Ibrahim AS, Spellberg B, Edwards J. Iron acquisition: A novel perspective on mucormycosis pathogenesis and treatment Vol. 21, Current Opinion in Infectious Diseases. NIH Public Access; 2008 [cited 2021 May 30]. p. 620–625.;doi:10.1111/j.1365-2958.2010.07234

27. Boelaert JR, Fenves AZ, Coburn JW. Deferoxamine Therapy and Mucormycosis in Dialysis Patients: Report of an International Registry. Am J Kidney Dis [cited 2021 May 30];18(6): pg.no.660–667. doi:10.1111/j.1365-2958.2010.07234.

28. De Locht M, Boelaert JR, Schneider YJ;Iron uptake from ferrioxamine and from ferrirhizoferrin by germinating spores of rhizopus microsporus. Biochem Pharmacol [cited 2021 May 30];47(10):1843–50. DOI: 10.1016/0006-2952(94)90314-x
29. Roden MM, Zaoutis TE, Buchanan WL, et al;Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):pg.no.634–653. DOI: 10.1086/432579
30. Alanio A, Desnos-Ollivier M, Garcia-Hermoso D, et al. : Investigating Clinical Issues by Genotyping of Medically Important Fungi: Why and How? Clin Microbiol Rev. 2017;30(3):671–707;DOI: 10.1128/CMR.00043-16.
31. Ashraf S .Ibrahim;Kerstin Voelz,et al; The mucormycete–host interface; Current Opinion in Microbiology of 2017, (40):40–44 DOI NO. https://doi.org/10.1016/j.mib.2017.10.010
32. A. Skiada, C. Lass-Floerl, N. Klimko, et al; Challenges in the diagnosis and treatment of Mucormycosis; Medical Mycology,2018,56,S93-S101, DOI 10.1093/mmy/myx101
33. Umang Arora, Megha Priyadarshi, Varidh Katiyar et.al, Risk factors for Coronavirus disease-associated mucormycosis; Journal of Infection 84 (2022) 383–390 DOI https://doi.org/10.1016/j.jinf.2021.12.039
34. Amanda Werthman-Ehrenreich; Mucormycosis with orbital compartment syndrome in a patient with COVID-19; American Journal of Emergency Medicine 42 (2021) 264.e5–264.e8 ; DOI:- https://doi.org/10.1016/j.ajem.2020.09.032
35. Asim Azhar , Wajihul Hasan Khan,et al; Mucormycosis and COVID-19 pandemic: Clinical and diagnostic approach; Journal of Infection and Public Health https://doi.org/10.1016/j.jiph.2022.02.007
36. Vidya Krishna, Jaymin Morjaria, Rona Jalandari ,et.al; Autoptic identification of disseminated mucormycosis in a young malepresenting with cerebrovascular event, multi-organ dysfunction and COVID-19 infection; 27 May 2021; http://dx.doi.org/10.1016/j.idcr.2021.e01172
37. Ranga Swamy Sirisati,C. Srinivasa Kumar,et.al, Identification of Mucormycosis in post Covid-19 case using Deep CNN; Turkish Journal of Computer and Mathematics Education; Vol.12 No.09 (2021), 3441- 3450

38. Mohammed Muqeetadnan, Ambreen Rahman, Syed Amer,et al; Pulmonary Mucormycosis: An Emerging Infection; Hindawi Publishing Corporation Volume 2012, Article ID 120809, 3 pages doi:10.1155/2012/120809

39. Kathy Hoanga,, Tony Abdob, J. Matthew Reinersmanc,et al; A case of invasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient;Medicalreportmycology2020;22-24 https://doi.org/10.1016/j.mmcr.2020.05.008

40. Vetriselvan Subramaniyan, Shivkanya Fuloria,et al;COVID-19-associated mucormycosis and treatments; Asian Pacific Journal of Tropical Medicine 2021; 14(9): 401-409; doi 10.4103/1995/7645326253.

41. Nurettin Bayram ,et al ;Cemal Ozsaygılı;Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations; Japanese Journal of Ophthalmology (2021) 65:515–525; https://doi.org/10.1007/s10384-021-00845-5

42. Zahra Heydarifard, Moslem Safaei , Sevrin Zadheidar,et al; Mucormycosis infection in severe COVID- 19 patient with multiple underlying health condition; 2021;9:e05009 DOI:10.1002/ccr3.5009

43. Mahdi Fakhar Ali Sharifpour,Zakaria Zakariaei1,et al; Rhino- orbito- cerebral mucormycosis in a post- COVID- 19 diabetic patient: Rare case from Iran; 2022;10:e05506. DOI: 10.1002/ccr3.5506

44. Awadhesh K Singh, Ritu Singh ,et al; Comments on: Rise of the phoenix: Mucormycosis in COVID-19 time; 2021:1; DOI 10.4103/ijo.IJO_1423_21

45. Neeti Gupta and Saurabh Dembla,et al; Cranial nerve involvement in mucormycosis in post-COVID patients: ; 2021:1; (2022) 53:28 DOI https://doi.org/10.1186/s43055-022-00700-8

46. Vijay Kumar Chennamchetty ,Sowmya Adimulapu, et al; Post-COVID pulmonary mucormycosis; Indian Journal of Immunology and Respiratory Medicine 2021;6(1):62–66 ;DOI https://doi.org/10.18231/j.ijirm.2021.014 2581-4214

47. Awadhesh Kumar Singh a, Ritu Singh,et.al, Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India; Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 102146; DOI https://doi.org/10.1016/j.dsx.2021.05.019 1871-4021

48. Amanda Werthman-Ehrenreich, Mucormycosis with orbital compartment syndrome in a patient with COVID-19: American Journal of Emergency Medicine 42 (2021) 264.e5–264.e8; DOI https://doi.org/10.1016/j.ajem.2020.09.032

49. Daniela Pasero, Silvana Sanna, et.al, A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis; Springer; Infection (2021) 49:1055–1060 https://doi.org/10.1007/s15010-020-01561-x.

50. Valliappan Muthu . Shivaprakash M. Rudramurthy,et.al, Epidemiology and Pathophysiology of COVID-19- Associated Mucormycosis: India Versus the Rest of the World; Mycopathologia (2021) 186:739–754 https://doi.org/10.1007/s11046-021-00584-8

51. Naveen Kumar Choudhary, Amit K. Jain, Rupesh Soni, Neha Gahlot, Mucormycosis: A deadly black fungus infection among COVID-19 patients in India; Clinical Epidemiology and Global Health 12 (2021) 100900; https://doi.org/10.1016/j.cegh.2021.100900

52. Seyed Ahmad Seyed Alinaghi, Amirali Karimi, Alireza Barzegary, Zahra Pashaei, et.al, Mucormycosis infection in patients with COVID-19:A systematic review; Sci Rep.2022;5:e529 https://doi.org/10.1002/hsr2.529.