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Mucormycosis: The Deadly Black Fungus – Review

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Abstract

In this era of COVID-19 many things changed in the world. A common cold causing virus caused a worldwide chaos. The death count was further elevated due to a life-threatening super infection which is being called as Black Fungus. Mucorales fungus causes an infection in humans which is called as Mucormycosis. Reports confirm that this super infection was more prevalent in immuno compromised patients. This disease has been characterized to cause endothelialitis and microvascular thrombosis leading to cell death and necrosis. Lymphpenia is seen constantly with this disease and immune suppression is marked due to use of steroids in the treatment of COVID-19. Antifungal medications are used in conjunction with surgical intervention in the treatment of this fungal infections. Isavuconazole was recently approved by FDA to treat invasive aspergillosis and invasive mucormycosis. Mucormycosis has affected the entire world but maximum cases were witnessed in the Asian continent due to very high incidence of diabetes and tuberculosis cases, lack of infrastructure to cure the diseases and highly populated areas. The aim of this review is to overview a etiology, pathogenesis and histopathology of Mucormycosis along with the multi-disciplinary approach required for its treatment.

Keywords: Mucormycosis; Black Fungus; COVID-19; Diabetes Mellitus; Corticosteroids.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with a wide range of opportunistic bacterial and fungal infections. Both Aspergillus and Candida have been reported as the main fungal pathogens for co-infection in people with COVID-19. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India. (1)

Phycomycosis or zygomycosis was first described in 1885 by Paltauf and later coined as Mucormycosis in 1957 by Baker an American pathologist for an aggressive infection caused by Rhizopus. Mucormycosis is an uncommon but a fatal fungal infection that usually affects patients with altered immunity. Mucormycosis is an Angio invasive disease caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunningham Ella and Absidia of Order- Mucorales, Class- Zygomycetes. The Rhizopus Oryzae type is responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino orbital-cerebral (ROCM) form. (2) Mode of contamination occurs through the inhalation of fungal spores which can be attributed to lack of infrastructure in our country to maintain the distance between the patients and use of inappropriately sterilized ventilators. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of year 2019-2020. (3)

Nevertheless, DM remains the leading risk factor associated with mucormycosis globally, with an overall mortality of 46%. Indeed, presence of DM was an independent risk factor (Odds ratio [OR] 2.69; 95% Confidence Interval 1.77e3.54; $P < 0.001$) in a large 2018 meta-analysis of 851 cases of rarely occurring mucormycosis, and the most common species isolated was Rhizopus (48%). While long term use of corticosteroids have often been associated with several opportunistic fungal infection including aspergillosis and mucormycosis, even a short course of corticosteroids has recently been reported to link with mucormycosis especially in people with DM. (4) A cumulative prednisone dose of greater than 600 mg or a total methyl prednisone dose of 27 g given during the month before, predisposes immunocompromised people to mucormycosis. Surprisingly, 46% of the patients had received corticosteroids within the month before the diagnosis of mucormycosis in the European Confederation of Medical Mycology study. Several anecdotal cases are also being reported in grey literature such as the print and electronic media. (5) These finding are unprecedented and carry an immense public health importance, primarily because fatality rate with mucormycosis is pretty high. Especially the intracranial involvement of mucormycosis increases the fatality rate to as high as 90%. Moreover, rapidity of dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 h in the diagnosis could be fatal, the reason 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series.(6) This prompted us to conduct a systematic review of published case reports/series of mucormycosis in people with COVID-19, to know its temporal associations in relation to comorbidities, association with drugs being used in COVID-19 and overall characteristics of patients with its outcome. We additionally postulated a mechanistic explanation as to why mucormycosis could be increasingly linked to COVID-19 and is being reported increasingly from India. A systematic literature search was conducted in

the electronic database of PubMed and Google Scholar from inception until December 2021 using keyword "COVID-19", "SARS CoV-2", AND "Mucormycosis", "Zygomycosis", "Phycomycosis, "Mucorales", "Mucor", "Rhizopus", "Rhizomucor", "Cunningham Ella", and "Absidia". Details of all the cases that reported mucormycosis (both confirmed and suspected) in people with COVID-19 so far, were retrieved. Characteristics of each patient was collected on excel sheet and analyzed on various endpoints and outcomes. Two authors independently checked the veracity of data.

Aetio-pathogenesis

An etiology behind germination of Mucorales spores are in association with the ideal environment created by certain conditions in COVID patients. (3,7)

They are:

1) Low oxygen (hypoxia),

2) High glucose (diabetes, new onset hyperglycemia, steroid-induced hyperglycemia),

3) Acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]),

4) High iron levels (increased ferritins) and

5) Decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.

Mucormycosis is an angiopathic illness characterized by endothelialitis and microvascular thrombosis leading to tissue necrosis and infarction. It is the third most common invasive mycosis after candidiasis and aspergillosis, which is caused by a fungus of the Zygomycetes class. Asexual spores of the fungus when inhaled they land on nasal and oral mucosa causing an immediate inflammatory response. (8) In immune-competent host the disease usually does not progress. In immune-compromised host these spores germinate and hyphae formation begins. These hyphae invades blood vessels leading to angioedema and thereby causes ischemia, necrosis and thrombosis. Thrombosis and septicaemia due to pool of bacteria that invade necrosed tissue are the major reasons for high mortality rate. (9)

Inhalation of fungal spores is the predominant route of infection in the sinus. Most Mucorales produce spores that are small enough (3–11 mm) to reach the distal alveolar spaces. Sinusitis can be caused by larger spores (>10 mm) lodged in the nasal turbinates. Even in immunocompetent hosts, inhalation of a high spore inoculum, such as during construction in polluted air ducts, can cause subacute sino-PMs. As a result, mucormycosis is uncommon in individuals with a good innate immune response, but it can be deadly in neutropenic patients. Patients on high-dose steroids are another high-risk category for mucormycosis because glucocorticoids impede macrophage migration, ingestion, and phagolysosome fusion. (10)

Diagnosis

The 1950 Smith and Krichner (11) criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include: (i) Black, necrotic turbinate's easily mistaken for dried, crusted blood, (ii) Blood-tinged nasal discharge and facial pain, both on the same side, (iii) Soft peri-orbital or peri-nasal swelling with discoloration and induration, (iv) Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and, (v) Multiple cranial nerve palsies unrelated to documented lesions.

In relation to COVID, rhino orbital cerebral type and pulmonary type of mucormycosis are most commonly associated variants. For the diagnosis of rhinoorbitocerebral mucormycosis a method was

developed. An examination must be conducted on all COVID positive hospitalised patients to check for multiple cranial nerve palsies, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache or acute vision loss. (4,7,12)

Upon visual inspection, infected tissue may appear normal during the earliest stages of spread of the fungus. Infected tissue then progresses through an erythematous phase, with or without oedema, before the onset of a violaceous appearance and, finally, the development of a black, necrotic eschar as the blood vessels become thrombosed and tissue infarction occurs. (13) Palatal involvement is usually the result of the direct extension of disease from the maxillary sinus and in the distribution of the sphenopalatine and greater palatine arteries. Pain and swelling precede oral ulceration, and the resulting tissue necrosis can result in palatal perforation. Infection can sometimes extend from the sinuses into the mouth and produce painful, necrotic ulcerations of the hard palate. (2,11,14) If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function and proptosis. Marked chemosis may also be seen. The infection may rapidly extend into the neighbouring tissues. (15)

Clinically, it is difficult to tell the difference between pulmonary aspergillosis and fusariosis. The reverse halo sign on a computed tomography (CT) scan is a very good indicator of pulmonary mucormycosis. (16)

Magnetic Resonance Imaging is useful in identifying the extent of the disease in intadural, intracranial, cavernous sinus or cavernous portion of internal carotid artery. (16,17)

Histopathology

The presence of fungal hyphae typical of mucormycetes in biopsies of afflicted tissues or bronchoalveolar lavage (BAL) in individuals with pulmonary mucormycosis leads to a definite diagnosis. (18) Histopathology is a critical diagnostic technique because it separates the presence of fungus as a pathogen in the material from a culture contaminant and is required to determine whether blood vessel invasion has occurred. Neutropenia is the most common cause of pulmonary mucormycosis. Giant cell invasion, thrombosis and eosinophilic necrosis are pathological hallmark of the disease. (19)

Treatment

Most antifungals, including voriconazole, are resistant against Mucorales fungus in vitro. Amphotericin B is the most active medication except for some Apophysomyces and Cunningham Ella strains. (1,3,4,7,11,14,15) Use of liposomal Amhotericin B along with hyperbaric oxygen have proven to successfully irradicate the infection in many cases. The lipid-based formulation of this drug has shown better capillary and cerebro-spinal fluid penetration and reduced nephrotoxicity. Itraconazole and terbinafine have been tried by many authors but they proved to be effective against selected strains. Posaconazole and isavuconazole are being used in certain research institutes along with polyene and/or caspofungin for management of mucormycosis. (11,14) Isavuconazole is a newly discovered triazole having antifungal action against mucorales and other fungal species. Finally, the experimental medication VT-1161, a fungus-specific inhibitor of CYP51, has shown in vitro efficacy against Mucorales, including R. oryzae. Voriconazole prohylaxis for transplant recipients, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound

patients following trauma has been advocated by many authors. (17,18,19)

Aggressive early surgical debridement of the infected craniofacial tissues is the most crucial step in successful management of ROCZ mucormycosis along with medicinal treatment. This includes resection of involved tissues of the face, including skin and muscle, any skin of the nose that is involved, maxillary and ethmoid sinuses, necrotic tissue of the temporal area and infratemporal fossa, and orbital exenteration. (17,19)

Despite recent advancements in diagnosis and treatment, Mucormycosis is a life-threatening infection with a high death rate.

Conclusion

Mucormycosis is a life-threatening infection that most often affects immunocompromised patients and that, despite vigorous multimodal therapy, has a high death rate. Diabetes mellitus is the most common underlying illness worldwide, according to new findings. Considering the fact that India is the world capital for Diabetes, there is a higher risk of this infection in our population. The diagnosis of mucormycosis is still difficult. Although molecular techniques are advancing, histopathology, direct inspection, and culture remain important tools. The rhino-orbital-cerebral cavities were the most often affected in the patients, and DM was the most prevalent underlying illness. Unfortunately, in third-world countries, the use of steroids further complicates the immune suppression situation. Early diagnosis and treatment can reduce comorbidities and mortality rate significantly.

References

1. Kubin CJ, McConville TH, Dietz D, et al. Characterization of bacterial and fungal infections in hospitalized patients with COVID-19 and factors associated with HealthCare-associated infections. Open Forum Infect Dis; 2021;8(6)1-10.

2. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an Update. J Fungi 2020;6(4):265-84.

3. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus 2020 Sep 30;12(9):10726-31.

4. Sargin F, Akbulut M, Karaduman S, Sungurtekin H. Severe rhino cerebral mucormycosis case developed after COVID 19. J Bacteriol Parasitol 2021; 12:386-389.

5. Waizel-Haiat S, Guerrero-Paz JA, Sanchez-Hurtado L, et al. A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19. Cureus 2021; 13:163-9.

6. Patel A, Kaur H, Xess I, et al. A multicenter observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect 2020;26(7):10-15.

7. Karimi-Galougahi M, Arastou S, Haseli S. Fulminant mucormycosis complicating coronavirus disease 2019 (COVID-19). Int Forum Allergy Rhinol. 2021; 11:1029–30.

8. Ackermann M, Verleden SE, Kuehn elm, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-8.

9. Seaton RA, Gibbons CL, Cooper L, Malcolm W, McKinney R, Dundas S. Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. J Infect. 2020; 81:952–60.

10. 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.

11. 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. Clin Microbiol Infect.2019;25:26–34.

12. Zhang X, Tan Y, Ling Y, Lu G, Liu F, Yi Z, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature. 2020; 583:437–40.

13. Walther G, Wagner L, Kurzai O. Outbreaks of mucorales and the species involved. Mycopathologia. 2020; 185:765–81.

14. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Melling Hoff SC. 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. 2019;19(12):405-21.

15. Nath S, Baidya DK. Mucormycosis in COVID-19: Is Zinc a Silent Killer in India? Indian Journal of Critical Care Medicine: Peer-reviewed. Indian J Crit Care Med. 2021;25(9):1079-84.

16. Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP. Therapy of mucormycosis. J Fungi. 2018;4(3):90-5.

17. Honavar SG. Code mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol. 2021;69(6):1361-5.

18. Rocha IC, Hasan MM, Goyal S, Patel T, Jain S, Ghosh A, Cedeño TD. COVID-19 and mucormycosis syndemic: double health threat to a collapsing healthcare system in India. Trop Med Int Health. 2021;26(9):1016-8.

19. Chakrabarti A, Singh S. Management of Mucormycosis. Curr Fungi Infect Reports. 2020; 29:1-3.