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BLACK FUNGUS CAUSES DURING POST COVID-19 COMPLICATIONS

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ABSTRACT

Covid-19 is a human to human transmitted disease which is declared as a global pandemic that causes unhealthy process in the respiratory system and which leads to the damage to the alveolar with severe inflammatory exudation. A covid-19 patient has lower immunosuppressive CD4+T and CD8+T cells and needs mechanical ventilation, hence longer stay in hospitals. Covid-19 patients have been discovered to develop a fungal infection i.e., Black Fungus which is also known as Mucormycosis. Mucormycosis is a rare and fungal infection that suppresses the immune system. There are somany newly developed medications but curing the infection is still a challenge. To initiate the examination of infection molecular diagnostic techniques, PCR (Polymerase Chain Reaction), In Situ hybridizationneeded for the treatment. The management of Mucormycosis depends on underlying factors such as injection of anti-fungal, surgical intervention, and dose of anti-fungal medication.

KEYWORD: Covid-19, Mucormycosis, PCR.

INTRODUCTION

COVID-19 is a human-to-human transmitted illness that produces severe inflammatory exudation and alveolar destruction.Mucormycosis is a fungal illness that has been identified in COVID-19 patients.[1] Mucormycosis is a fungal illness caused by a group of saprophytic fungus belonging to the Mucorales family, which may be found in soil and decaying organic matter including fruit and vegetables.[1] The black yeast Exophiala dermatitidis, a possible cause of brain infections in East Asian patients, has a very low degree of genetic diversity, leading to the conclusion that this species is an emerging pathogen presently undergoing active speciation. In hot, wet settings, such as steam baths, it is discovered to be an oligotrophic fungus. Cladophialophora-, Fonsecaea-, and Ramichloridium-like strains that cause chromoblastomycosis in humans are frequently found on rotten plant material, but the fungal molecular diversity in the environment is much higher than that of the human patient, making it difficult to pinpoint the disease's etiological agents.[2]

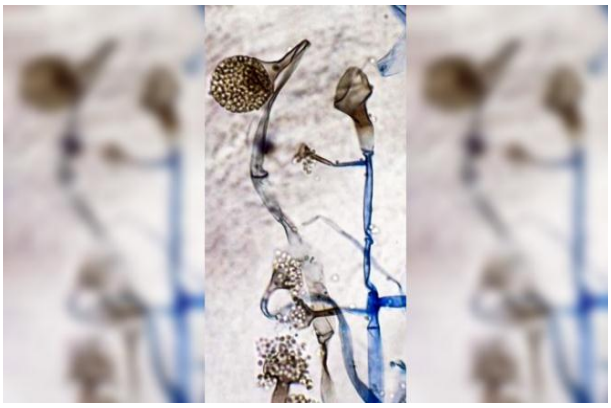


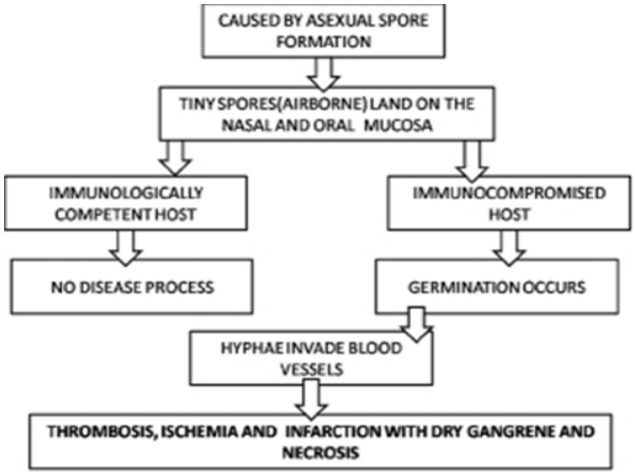
Figure 1: Microscopic view of mucor.

Pathophysiology of black fungus

Mucormycosis is a dangerous angioinvasive illness that causes blood vessels to enlarge.

As a consequence, blood clots develop, obstructing circulation to the distal organ and giving rise to the blackish colour that gives the fungus its name.

After inhaling fungal spores in the air, Black Fungus usually affects the lungs, although it may also affect the skin.



Flow Diagram of Pathophysiology of Black Fungus

- **How this pathophysiology interferes with the COVID-19 patient treatment???**

The respiratory system is most affected by COVID-19; the most frequent involvement is Rhino-orbito-cerebral presentation.

The fungal spore moves from the peripheral hole in the facial region into the brain through blood vessels.

The black-colored discharge contains necrosed tissue, blood clots, and fungal hyphae as the illness develops.[3]

Mainly where the mucormycosis found??

- Fungi are most often seen in people's kitchens when fruits decay or bread becomes mouldy. Fungi have been around for 400 million years and perform an essential function on the planet. They have aided plants in their transition from aquatic to terrestrial environments, and they continue to assist them in obtaining nutrients from the soil.
- Fungi decompose organic waste and recover nutrients trapped in leaves and wood. Although fungi are abundant in plants, only a tiny percentage of them affect people. The fact that animals, including humans, have developed complex immune systems is one explanation.
- We've mostly seen the black growth on aged fruits and bread. Mucoralean fungus are the first to invade plant matter that has died or decayed. They quickly deplete the small supply of basic carbohydrates before competing with other fungus for more complex carbohydrates like cellulose.
- Mucormycosis may occur when a patient's immune system is weakened and they inhale Mucor spores. This is an uncommon, non-contagious illness that, if not treated promptly, may be disabling or deadly.
- Mucormycosis is more likely to occur in people who have COVID-19, HIV/AIDS, and other viral illnesses, congenital bone marrow disease, severe burns, malignancies, and untreated or irregularly managed diabetes. Because steroids weaken the immune system, COVID-19 patients who have received steroids are more vulnerable.[4]

Cases of fungal infection after COVID-19

1. To put into fact, fungal infection, Chen et al. performed this infection test in China on 99 patients out of which 5/99 were found to have Aspergillusflavus and one case of Candida glabrata, and three cases of C. Albicans.[5]
2. Many patients were treated with anti-fungal medicine but were in vain. Another German study associated with COVID-19 found 6 out of 19 patients infected with black fungal.
3. In the Netherlands, there were fresh new cases of black fungus, infecting 7 with A.fumigatus. In France, there were 5 patients infected with A. flavus by tracheal aspirates culture.[6]
4. Many incidences in that period have found COVID with fungal infection increase from 16-27%, with severely ill patients dying. Most percentage of them with Mucormycosis has died since the beginning of this fungal incidence began.[7] The below figure shows penicillin in Mucormycosis;

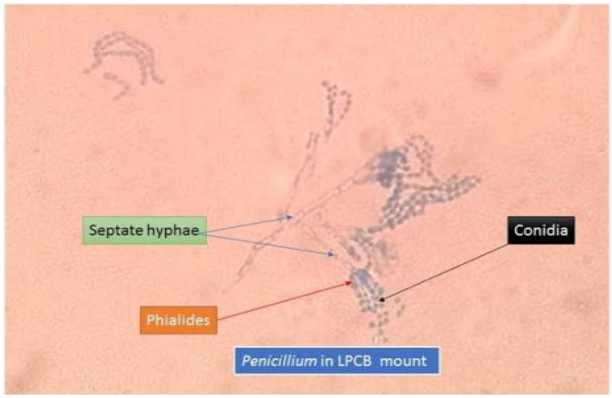


Figure 2: Figure shows penicillin in mucormycosis.

Symptoms

The symptoms include are:

1. Fever,
2. Headache,
3. Reddish and swollen skin near the nose or eyes,
4. Facial pain,
5. Cough producing bloody or dark fluids,
6. Shortness of breath,[8]
7. Centrilobular nodules,
8. bronchial wall thickening,
9. Petri bronchial consolidation with Aspergillus,[8]
10. loss of eyesight,
11. hearing impair,
12. severe heart attack and
13. Brain cell loss.[9]

Source and Development

In this, the explanation of the species, their history, and study of the species.[10] Mucormycosis has common agents such as Rhizopus spp, Mucor spp. Genera of Mucorales varies from country to country. Mucor spp, Lichthemiaspp, and Rhizopussppat 34%, 19%, and 19% are common in Europe. In India, Rhizopus spp is the most common causing disease Apophysomyceselegans, A. variabilis, and Rhizopushomothalliusare emerging. Another species namely Apophysomycesis reported in Mexico. By inhalation of sporangiospores, Mucormycosis is caused.[10]

Mucormycosis has been a center of attention all around the globe. But there seem differences in species and effects on the human body differing from a developed country and developing nations. In a developed nation this disease is less common and seen only in patients with haematological malignancies (HM).

The developing countries paint a different picture; it is common in patients with uncontrolled diabetes mellitus or trauma. In India, Mucormycosis is seen in 14 out of 100000 patients. In Europe and the US, it is seen in 0.01 per 100000 populations.[11]

The percentage associated with Mucormycosis in rhino-orbito- cerebral pulmonary are 27%, 20%, and 18%. In Europe it is 27%, 32%, 26%. Considering patients with HM is less compared to patients in India with DM. In Mexico, 72% of people were associated with diabetes underlying malignancies, sinus and pulmonary.[12]

Infections from Mucorales are usually rapid; they were initially reported in farmers from China. Some reports show they are opportunistic fungus-like Mucorirregularis that have completely different epidemiology. Their infections are highly chronic but without any risk factors affecting only skin and tissue cells.[13]

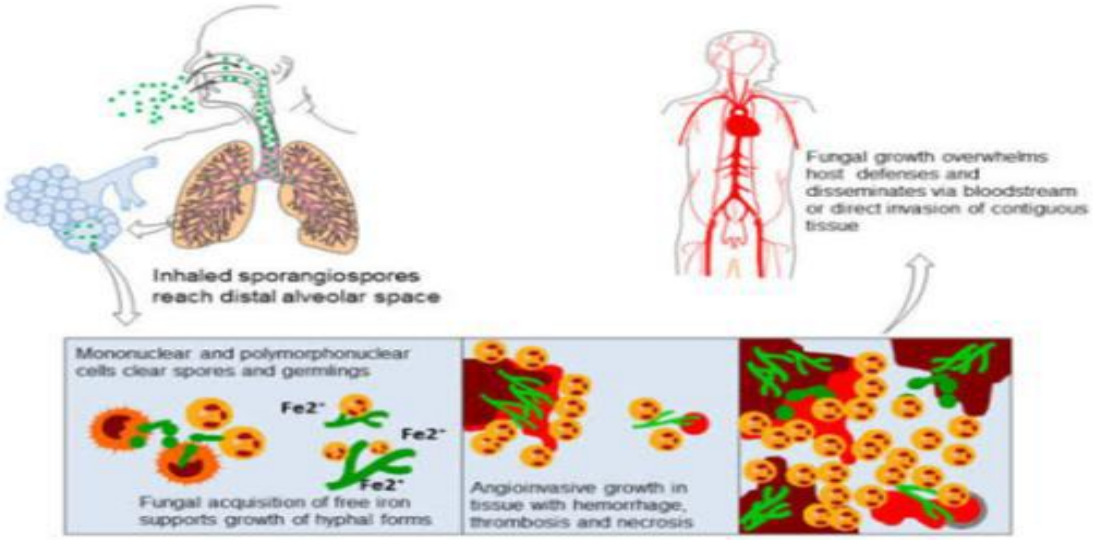


Figure 3: Formation of mucormycosis inside.

Diagnosis and Possibilities

1. Positron emission tomography-computed tomography (PET/CT) is used to identify Black fungus with fluorodeoxyglucose (FDG).
2. The Endobrochial ultrasound-guided injection is a useful diagnostic tool for Mucormycosis.
3. CT scan (Computerized tomography) that indicates Mucormycosis is the reversed halo sign (RHS), when sequential thoracic CT scans are performed in more than 100 patients RHS was observed in 92 patients during the initial stage of the disease. Hence we conclude RHS on CT scan is a strong indicator of the presence of pulmonary Mucormycosis.[14]
4. Galacrmanna and 1, 3- beta-D-glucan marker was used to detect the fungal growth.[15]
5. The two drugs most effective for treating Mucormycosis are Amphotericin B and Posaconazole.[16]
6. The suggestion by the European conference for such harsh invasion is lipid formulation of Amphotericin B. The suggested dose is 5mg/kg/day up to 10mg/kg/day for injection in the central nervous system. The results conducted on patients with Mucormycosis showed a response rate of 78% in week 1 to 87% on week 12.[16]
7. Posaconazole and Isavuconazole are used as maintenance therapy dosages recommended by ECMM at a dose of 200 mg q6h of oral.
8. Another option is salvage treatment, combining effects of liquid amphotericin B and caspofungin or Posaconazole, impact showed survival rates much higher on patients with rhino orbital cerebral Mucormycosis.
9. Final treatment can be done with the usage of the drug VT-1161, an inhibitor with selective activity against fungus. They are Ergo sterol synthesis inhibitors and prove an additional asset to fight Mucormycosis.[17]

Culture techniques

In this, Laboratory work and culture on Petri dishes are the effective clinical tools for Mucormycosis.

Tissue histopathology shows inflammation regions, in some cases, these are absent in immune-suppressed patients. In cases of nerve cells, perineural invasion is present when done by tissue histopathology, but that is not the best method always, tissue differentiation is most effective to differentiate between hypea of Aspergillus and hypea of Mucorales. It distinguishes all fungi and helps in pathogen of specimen in laboratory culture containment.[18]

It is observed that Mucorales grow up to 3-7 days on fungal media, namely potato dextrose agar and Saboraud agar incubated at 25 degrees. In some cases, it aids in the yield of culture, because hypea are friable and get damaged easily.

The main target of this culture in situ hybridization is the 5s and 18s ribosomal RNA sequence, hence a specific mouse monoclonal anti- Rhizomucorantibidy is employed to target analysis and to react strongly on Mucorales and Entomophthorales.[19]

➢ **Identification of species in the culture technique**

Identifying species is more important for a better understanding of the epidemiology of Mucormycosis. Mucorales fungi differentiate from Aspergillus fungi on culture and provide a high level of accuracy in fungal identification.

a) Test kits used are ID32C combined with positive melezitose assimilation detects L.remosa.
b) Another one is the matrix-assisted laser desorption/isolation time of flight (MALDI-TOF) along with mass spectrometry.
c) The serology used is ELIZA assays immunoblots and immunodiffusion tests that are invasive towards Mucorales and Mucormycosis.
d) Molecular assays such as PCR restriction fragment length polymorphism analysis (RFLP), DNA sequencing of defined genes, and melt curve analysis were part of assays that help in the analysis of Mucorales. They targeted internal transcribes 18s rRNA genes.[20]

DISCUSSION

- Black Fungus called Mucormycosis is complicating the treatment and recovery of COVID-19 patients. Many patients tested has 2 weeks history of COVID-19 before and after admission in ICU, a CT scan a valuable tool for corona patients revealed, slight mold infections in the chest region but slight reversible halo, ground-glass opacities also observed.[21]

- Presently influenza and Aspergilliosis trials show GM in serum and bronchoalveolar lavage fluid in mycological criteria to overcome imperfect culture limitation & sensitivity of aspergillus.[22]

- The patient reported the presence of fungus, increasing the risk for IPA (Pulmonary Aspergilliosis). Viral infections like influenza or cytomegalovirus infections increase the risk for IPA. There are overexpression f anti-inflammatory cytokines, T-helper cells, and cell-mediated immune response which isimpaired. This impairment is due to mold in COVID-19 patients admitted to ICU. Hence discussion concludes IPA occurrence in COVID19 patients.[23]

CONCLUSION

Mucormycosis is a rare disease but a burden on immune-compromised patients. Newly Developed medications have several pathogeneses but the cure to Mucormycosis is still a challenge. Any condition that dysregulates the immune system predisposes one the opportunistic infection and COVID-19 being a disease of immune dysregulation provides a breeding ground for fungal infection increasing both mortality & morbidity.

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