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RESEARCH ARTICLE

POST COVID EFFECTS OF BLACK FUNGUS MUCORMYCOSIS: A REVIEW

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Abstract

Mucormycosis is a disease caused by the fungi belonging to the order mucorales which affects mainly the immunocompromised patients. These fungi are mainly found in soil and in the decomposition of plants and animals from which the sporangiospores are released in the air which are then inhaled resulting in infection based on the host resistance. The cases are increasing in conditions with malnutrition, diabetes, steroid therapy and acidosis. After aspergillosis and candidiasis, mucormycosis is the third most common invasive fungal infection.The common genera that has been identified include mucor, rhizopus, Rhizomucor, Absidia, Apophysomyces, Cunninghamella and sakhsanaea. Five major forms of infection include rhino-orbito-cerebral, pulmonary, disseminated, cutaneous and gastrointestinal.There is a difference in epidemiology of mucormycosis between developed and developing countries. In developed countries even though the disease is uncommon, they are found in patients with diabetes mellitus and hematological malignancies undergoing chemotherapy. While in developing countries they are seen in patients withdiabetes and trauma.

Introduction:-

Covid19 pandemic affected manylivesaroundtheworld. InIndia covid recovered patients were affected by a fungus called black fungi mucormycosis.The severity of the disease dependsupontheimmunity of anindividual. Therearemany fungiinthisworld which can act as an opportunistic pathogen.There are many fungisuchas Aspergillus, Candida, Mucoretc., which can cause infection in human. But the infection caused by Mucormycosisin post covidrecovered patient was found to be a life threatening one. In the review articles we would like to elaborate the habitat, pathogenesis, diagnosis and treatments that are available to treat black fungus and also the effect of black fungusin covidpatients.

Fungus

Fungus is used to cover many organisms together. This group consists of microscopic as well as macroscopic organisms. Microscopic organism which cannot be seen through our naked eyes and can be observed only under the microscope. On the other hand, the macroscopic organisms can be seen through our naked eyes. Fungus can be a unicellular or multicellular organisms.Their mode of nutrition is heterotrophic. Based upon the mode of nutrition fungus can be classified into saprophytes, parasites, symbionts and Predacious Fungi.

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Habitat

Black fungi can occur in greatestenvironments and under penuriousnutrient conditions, where they often grow meristematically (Sterflinger ***et al.,*** 1999). In the pastyear many dematiaceous yeast like cells,emerge asto be, alongwith lichens and cyanobacteria, among the highlysuccessful residentsof marble, limestone, granite, and other rock types in severe or partial lack of waterenvironments (Sterflinger&Krumbein 1997, Wollenzien ***et al.,*** 1997, Sterflinger 1998, Ruibal ***et al.,*** 2005). They have been discoveredin hot arid areasof Arizona (U.S.A.) (Staley ***et al.,*** 1982, Palmer ***et al.,*** 1987), in glacialAntarctic deserts (Nienow&Friedmann 1993, Selbmann ***et al.,*** 2005), in Mediterranean countries such as Italy, Greece, Turkey (Gorbushina ***et al.,*** 2005, Ruibal ***etal.,*** 2005, Sert&Sterflinger 2005), on stone monuments in Austria (Sterflinger&Prillinger 2001), and on granites of the Ivory Coast (Budel ***et al.,*** 2000). Sterflinger&Krumbein (1995) assumedthat the ability to grow meristematicallyprovides the colonies an optimal surface/volume ratio for enhanced stress tolerance. In particular, they resist raised temperatures, poorwater availability (Wollenzien ***et al.,*** 1995), UV radiation (Urzì ***et al.,*** 1995), increasedsalt concentration (Zalar ***et al.,*** 1999) or amalgamations of these factors and morestresses (Selbmann ***et al.,*** 2005, Scott ***et al.,*** 2007).

Pathogenesis

Mucorales infects the head and neck region is Rhino-orbital-cerebral type. This is the most usual type of infection (Parfrey1986.) Initially infection was found in the palate or the paranasal sinuses (one of many small hollow spaces in the bones around the nose), progresses to the orbit and, if not diagnosed early, it will enter into the brain (Yohai RA, Bullock JD, Aziz AA, Markert RJ 1994).

Fever, lethargy, headache, orbital pain, abrupt loss of vision, ophthalmoplegia, proptosis, ptosis, dilated pupil, corneal anaesthesia and clouding, chemosis, periorbital cellulitis, sinusitis, epistaxis, facial palsy, trigeminal nerve distribution sensory loss and seizures (Ferry AP and Abedi S 1983 & Ericsson ***etal.,***1993.)

Rhino-orbito-cerebral mucormycosis can be seen in patients with diabetic ketoacidosis (Lehrer RI, Howard***etal.,***1980), in leukaemia patients (Ferguson ***et al.,***1988), situations like organ and bonemarrow transplant, β-thalassaemia, trauma, burns, deferoxamine therapy and even polypousrhinosinusitis (condition in which mucous membrane lining in the nose) (Garcia-Covarrubias L, Bartlett R, Barratt DM, Wasser-mann RJ 2001)and also affect HIV patients (Hejny C, Kerrison JB, Newman NJ, Stone CM 2001). The development of Rhino-orbito-cerebral mucormycosis can seen in patients more than 4 weeks (HarrillWC, Stewart MG, Lee AG, Cernoch P 1996).

Pulmonary Mucormycosis

The second most common site of involvement of Mucoralesinfection is lungs which is Pulmonary type (Parfrey NA. 1986)**.** Majority of cases is spotted in leukaemia patients. Primary route of infection is inhalation of spores (Bigby TD, Serota ML, Tierney LM Jr, Matthay MA., 1986). Individuals with leukaemia, lymphoma and severe neutropenia are more susceptible and develop pulmonary mucormycosis (Meyer RD, Rosen P, Armstrong D., 1972). Patients with solid tumours (sarcomas, carcinomas and lymphomas) rarely develop pulmonary mucormycosis (Solano T, Atkins B, Tambosis E, Mann S, Gottlieb T., 2000).

Cough, fever, haemoptysisand ⁄ or pleuritic chest pain. (Lee FY, Mossad SB, Adal KA., 1999).Patients who have disorders with blood and bonemarrow can have infection that are exist together with *Aspergillus species*, *Candida species*, bacteria or cytomegalovirus (Maertens J, Demuynck H, Verbeken EK ***et al.,***1999). Pulmonary mucormycosis have a natural tendency to invade blood vessels and produce thrombosis.

Cutaneous Mucormycosis

Break in the skin's integrity from surgery, burns, soiled trauma, motor vehicle accidents, bone-fractures, intravenous lines, insect bites, cactus spine injuries, abrasions, lacerations, biopsy sites, allergen patch testing, contaminated adhesive tapes and intramuscular injections can promote **Cutaneous mucormycosis** (Chakrabarti A, Kumar P, Padhye AA ***et al.,***1997). Itis superficial or deep infection. It is the form of infectionassociatedwithunderlying disease(Vainrub B, Macareno A, Mandel S, Musher DM.1988).

Patients can develop pustules, blisters, nodules, necrotic ulcerations, echthymagangrenosum-likelesionsor necrotizing cellulitis afterthe onset of fungus (Cocanour CS, Miller-Crotchett P, Reed RL, Johnson PC, Fischer RP 1992). Infection starts in thelimb of the body after trauma or priorskin lesions (Caceres AM, Sardinas C, Marcano C ***et al.,*** 1977).

Neutropenic patients with leukaemia or lymphoma comprise the majority of patients with disseminated mucormycosis (having spreadthroughout anorgan orthe body), (Nolan RL, Carter RR 3rd, Griffith JE, Chapman SW 1989). Risk factors include organ transplantation, chemotherapy, corticosteroids and deferoxaminetherapy (medicationthat bindsironandaluminium), (Kontoyiannis DP, Wessel VC, Bodey GP, Rolston VI 2000).

Patients who have undergone organ bone-marrow or peripheral blood stem cell transplantationand individuals withacute granulocytic leukaemia, lymphoma, DKA, nonketotic diabetes mellitus, amoebiasis, typhoid, vitamin B3deficiency, edematous malnutrition, malaria and prematurity can start Gastrointestinal mucormycosis (Vadeboncoeur C, Walton JM, Raisen J, Soucy P, Lau H, Rubin S, 1994.)

They are non-specific and include abdominal pain and haematemesis and melena (Calle S, Klatsky S. 1966).If mucoralesenter into gastric mucosa person can get a gastric mucormycosisinfection that is knownasgastric ulcers. Intestinal mucormycosisis infrequent in the normal host (Keys TF, Haldorson AM, Rhodes KH, Roberts GD, Fifer EZ 1978). Mucormycosis of maxilla (bones forms your upper jaw) in an immunocompetent patient and an uncontrolled diabetic patient (i.e) Oral mucormycosis (Ferguson BJ. 2000)

Stiffness and blood discharge from nose, palatal ulceration, numbness in the middle third of the face and necrotic alveolus. Individuals who lack phagocytes or who have impaired phagocytic function are at higher risk of mucormycosis. Individuals with neutropenia (when a person has low level of neutrophils) are at increased risk for developing mucormycosis (Sugar AM, 2005). So, neutrophils can fight infections by destroying harmful fungi that invade the body. Normal hosts kill Mucorales by the generation of oxidative metabolites and defensins (cysteine-rich cationic proteins) with the help of both mononuclear and polymorphonuclearphagocyte. In the sightof hyperglycemia and low pH, which is found in patients with diabetic ketoacidosis (DKA), phagocytes are unable to function normally and have weakend or damaged chemotaxis and flawed intracellular lethalby both oxidative and non-oxidative mechanisms (Waldorf AR, Ruderman N, Diamond RD. 1984).

Inhalation of Mucoralessporangiosporesby immunocompetent patient does not result in the development of mucormycosis because their body is able to recognize antigens and act against them. In comparison, corticosteroid-immunosuppressed (steroids work by decreasing the inflammation and reducing the activity of the immune system) or individuals with DKA die of progressive pulmonary and hematogenously disseminated infection (Lamaris GA, Ben-Ami R, Lewis RE, Chamilos G, Samonis G, Kontoyiannis DP, 2009). Overuse, misuse of steroids is the major cause behind mucormycosis (Dr.RandeepGuleria, director of the AIIMS).

Diagnosis

Early diagnosis of mucormycosis is importantas it can increase the rate of survival and can reduce surgical resection, suffering and disfigurement. Mucor can be cultured on both bacterial and fungal cultures at a temperature of 25-55°C (Forbes BA, Sahm DF, Weissfeld AS, 1998). Mucorales present in clinical specimen can grow at a temperature of 37°C (Sugar AM. 1992) forming fluffy, grey or brownish colonies. In patients with hematological malignancies only 23-50%cases are diagnosed with ante mortem of mucormycosis. Direct microscopy of bronchoalveolar lavage with transbronchial biopsy may increase the yield of diagnosis. Culturing of the specimen has less sensitivity as it shows negative in 50% of the mucormycosis cases. Molecular based assays in the diagnosis of mucormycosis include polymerase chain reaction (PCR) (Nagao K, Ota T, Tanikawa ***et al.,*** 2005), restriction fragment length polymorphism analyses (RFLP) (Machouart M, Larche J, Burton ***et al.,*** 2006), DNA sequencing of defined gene regions, melt curve analysis of PCR products (Kasai M, Harrington SM, Francesconi ***et al.,*** 2008). Majority of the molecular assays either focus on the internal transcribed spacer or 18S rRNA genes. (Alvarez E, Sutton DA, Cano ***et al.,*** 2009).

Treatment

The diagnosis and treatment for mucormycosis should be started at earlier stage to reducethe mortalityrate. Mucormycosis has developed a high resistance towards most of the antifungal drugs. The most effective against the mucormycosis is amphotericin Bexcept for Cunninghamellaand Apophysomyces (SalasV, Pastor FJ, Calvo E ***et al.,*** 2012). Theantifungal agents used for mucormycosisis polyene whichis mostpreferred. Even though amphotericinBdeoxycholatehasbeenused manyyears, a lipid formulation ofamphotericin B deoxycholateare lessnephroroxic andcan beadministratedforlongerperiodwith higher dosage when compared to amphotericin B deoxycholate(Walsh ***et al.,*** 1998).

Effect of Black Fungus on Covid Patients

In post-COVID-19 stage Black Fungus is observed as secondary infection in COVID-19 infected patients. Mucormycosis affect nose, eyes, brain and sinuses recovering COVID-19 patients should look for medical help when they haveswelling in the face, pain and numbness, Unusual (bloody or black-brown) discharge from the nose, Swollen eyes, Nasal or sinus congestion, black lesions on nasal bridge or upper inside of the mouth (ICMR guidelines). Limitthe usage ofsteroidsfor 5 to10 days to mildto moderate dosagetopeoplein early-stage or with mild COVID-19infections can prevent the patients from mucormycosis. Early diagnosis of mucormycosis is essential as fungi has invasive ability into blood vessels, embolizing to distant organs, including the brain.

Conclusion:-

More cases of mucormycosismay be due to increasing numbers of immunocompromisedpatients. Thereare no specific clinical or radiological features makingdiagnosis more difficultand challenging. Diagnostic optionsare limited with variable results. The risk factors are diabetes mellitus, burns, iron overloaded, transplantation, chemotheraphy, intravenous drug use. The imaging studies of mucormycosis are plain X-ray, CT Scan, MRIScans andChest CT/MRI. Mucormycosis carries mortality rate of 50-85%.PosaconazoleandIsuvaconazole can be tried duringtreatment. Duration of treatment is highlyindividualized.

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