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REVIEW ARTICLE

A Comprehensive Review of Mucormycosis: A Black Fungus Disease Causing Mayhem in COVID-19 Patients

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ABSTRACT

Mucormycosis is an in frequent devious fungal infection characterized by infarction and necrosis of host tissues that result from invasion of the vasculature by hyphae. The mortality rate of this infection is so high compared to COVID-19, because the maximum death cases were observed due to this infection occurred after post-recovery of COVID-19 or simultaneously. The urge of death cases Mucormycosis is acknowledged as an epidemic in various states of India. As per the numeral cases, this infection is warned as a widespread in more than ten states of India. Madhya Pradesh and Gujarat Government were declared this infection as an epidemic. Mucormycosis is mainly classified as rhino cerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, disseminated, and miscellaneous. The main risk factors related to this disease are diabetic ketoacidosis, organ transplant, steroidal drug, hematopoietic stem cell transplantation, leukemia, and immune compromised body. The main diagnostic tool is the biopsy, computed tomography scan, and magnetic resonance imaging. "Liposomal amphotericin B" is the primary treatment of this infection. Posaconazole oral solution and isavuconazole are also used. Hyperbaric oxygen and iron chelator such as deferoxamine are also useful as adjunctive therapy. A specific test is necessary to decrease the mortality rate and to increase effective therapy.

Keywords: Biopsy, deferoxamine, hematopoietic stem cell transplantation, liposomal amphotericin B, mucormycosis

INTRODUCTION

Mucormycosis is an infrequent devious fungal infection characterized by infarction and necrosis of host tissues that result from invasion of the vasculature by hyphae.

As the whole world is suffering from Coronavirus disease. This is a new disease entity caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2) and the 1st case of it was documented in China in December 2019. Hence, the name of this disease is to be kept with the year of emerging of this disease "COVID-19." After China, it subsequently causing a worldwide pandemic because it transmits humans to humans and the rate of transmission is very fast. During the current pandemic of COVID-19, a gathering of appearances and difficulties have emerged and are being reported.[1]

A surge of *Mucormycosis* is being stated in the course of the arena over the last decades, and its miles extraordinarily rising in growing countries. Three consecutive case collections on mucormycosis had been stated from an unmarried tertiary-care canter in India: 129 instances over 10 years (1990–1999), 178 instances at some stage in the following 5 years (2000–2004), after which 75 instances in 18 months at some stage in 2006–2007.[2]

In A total of 129 cases of zygomycosis, a yearly occurrence of 12.9 cases per year were observed.

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A maximum of 25 cases was reported in the year 1999. Reported ratio was 2.25: 1 of male-to-female. Eighty-one (62.8%) of these cases occurred after the 3rd decade of life and seven (5.4%) were seen in kids <10 years of age.[3]

The 1st case of Mucormycosis after treatment of COVID-19 is seen in a well 33-year-old female who is accessible for transformed psychological level and proptosis. Mucormycosis and orbital compartment syndrome was diagnosed in that woman, in accumulation to COVID-19. Nowadays, mucormycosis occurred after post-treatment of COVID-19 that this is due to inappropriate hygiene or facilities related to the devices used in time of treatment such as oxygen mask. Apart from this, there were many reasons which result in mucormycosis.[99,100]

Mucormycosis at present after the COVID pandemic has infected 7250 people in India. The infection has a result of COVID-19 complications. This mucormycosis is as well-known as the black fungus has been killed 219 people across the country. This infection is spreading day by day and till May 2021, it has infected 8848 people in overall India. In the different states of India, there is a hazardous situation. In Maharashtra, 1500 cases have been stated with 90 deaths. In Gujarat, 1163 cases with 61 deaths have been detected. In Haryana, 268 cases with eight deaths have been reported. In Delhi, 203 with only one death have been reported. In Uttar Pradesh, 169 cases with eight deaths have been registered. In Bihar, 103 cases with two deaths were detected. In Madhya Pradesh, there are 575 cases with 31 deaths have been reported. In Chhattisgarh, 101 cases with one death have been registered. In Karnataka, there are 97 cases that have been registered and the peaceful news is that there is no cause of death from this black fungus infection. In Telangana, 90 cases with 10 deaths have been recorded.[99,100]

Neglected Fungal Coinfection in COVID-19 Patients

Scientific study suggested that SARS-CoV and SARS-CoV-2 belong to the same species and are of similar prevalence, biological, and clinical characteristics. In 2003, the SARS-CoV infection turned into transmitted in China. Moreover, there has been the incidence of fungal contamination in SARS sufferers approximately 14.8–27%, which turned into even superior in brutally sick ones, as much as 21.9–33%, within side the meantime, fungal contamination turned into the primary motive of dying for SARS sufferers, accounting for 25–73.7% in all reasons of dying.[7]

Epidemic

The ministry of health and family welfare has advised states and union territories to mark mucormycosis as a notified ailment under the epidemic diseases act 1897. The declaration behind this is that this infection is leading to extended morbidity and mortality in COVID-19 patients.[99,100]

NAME OF STATES WHICH DECLARED MUCORMYCOSIS AS AN EPIDEMIC

Madhya Pradesh and Gujarat government were acknowledged mucormycosis as the epidemic in the state. Other than these states some states have been notified of this as an epidemic. These states are as follows:

Telangana, Odisha, Rajasthan, Karnataka, Tamil Nadu, Uttarakhand, Bihar, Maharashtra, and Andhra Pradesh.[99,100]

Dr. Nair who works in three hospitals in Mumbai has been observed that the 2nd wave of COVID-19 in India created the worst situation in different cities of the country, and he has seen 40 patients who suffered from black fungus in April 2021. Dr. who is treating patients has been saying that the next wave is so lethal and the different mutations of the corona have been seen with the highest rate of mortality within the very short period. Dr. Nair who has seen 40 patients, many of the patients are a diabetic patient who has been recovered from COVID-19 at home. Eleven patients will be suffered from surgical treatment of the eyes. Between December 2020 and February 2021, Dr. Nair's six colleagues observed 58 patients of mucormycosis as a complication of post-COVID recovery. Moreover, in these cases, a maximum

of the patients observed 12–15 days post-recovery from COVID-19.[99,100]

The Fungi

The term Mucormycosis is interchangeable with zygomycosis. This signified those infections caused by fungi of the phylum *Zygomycota* (which comprises *Mucorales*, *Entomophthorales*, and others). It defines infections activated through *Mucorales*, derived from fungi. *Mucorales* is the order of that fungi. The maximum generally said pathogens in mucormycosis are *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp. (previously of the genera *Absidia* and Mycocladus), observed through *Rhizomucor* spp., *Cunninghamella* spp., *Apophysomyces* spp., and *Saksenaea* spp.[6] Other than *Rhizopus* spp., there were some families isolated from patients of mucormycosis which had an identical spectrum of infection and they were *Rhizopus* microsporus var. rhizopodiformis, *Mucor* species, and *Rhizomucor pusillus*.[5]

Mucor mycosis refers to a cluster of different mycoses caused by one of the ubiquitous, saprophytic fungi of the order *Mucorales*. *Rhizopus*, *Rhizomucor*, and *Absidia* are the organism's maximum usually remoted from sufferers who've Mucormycosis. *Cunninghamella*, *Mortierella*, *Mucor*, *Apophysomyces*, and *Saksenaea* have additionally been recovered from sufferers who have mucormycosis. The *Mucorales* are increasing at a range of temperatures (25°C–55°C); the optimal temperature for the development of clinically significant species of *Mucorales* is 28°C–30°C: Detaches improved from clinical specimens will also cultivate at a temperature of 37°C. The organisms are aerobic and are predicted to grow in 2–5 days of cultivation in the microbiology laboratory.[4]

The zygomycoses are infections triggered by fungi of the class Zygomycetes, comprised the orders *Mucorales* and *Entomophthorales*. *Entomophthorales* are infrequent origins of subcutaneous and mucocutaneous infections recognized as entomophthoromycosis.[5]

These fungi live all over the environment, predominantly in soil and in decaying organic matter, such as leaves, compost piles, or rotten wood.[98]

Risk Factors

There are some contradictory factors or some cofactor that will increase the risk of an event of this infection and these factors are as follows;[5,11]

- Diabetes mellitus and especially diabetic ketoacidosis
- Malignancy or ongoing session of chemotherapy for various types of tumors
- Leukemia
- Hematopoietic stem cell transplantation (HSCT)
- Organ transplant
- Any kind of central nervous system (CNS)-related disease
- Immunologically compromised body from various sources like in diseases AIDS, COVID, or some kind of malnutrition or administration of heavy steroidal drugs.
- Neutropenia
- Extensive use of corticosteroid
- Iron overload/hemochromatosis (disease-related to iron storage)
- Skin injury induced by surgery, burns, or wounds
- Prematurity and low birth weight
- Use of injection drug Figure 2

Pathogenesis

Infection in humans arises through the breath of spores of *Mucorales* into the respiratory tract. These spores will be gathered in the nasal turbinates or pass from the pulmonary alveoli. Specifics events responsible for hyphal propagation in tissue are largely unknown. The most typical feature of Mucormycosis is the hyphal invasion of blood vessels. This invasion results in a combination of hemorrhage, thrombosis, infarction, and necrosis of tissue. The reasons these fungi tend vasculature are unknown.[4]

Normal hosts can be able to kill *Mucorales* by mononuclear and polynuclear phagocytes through the formation of oxidative metabolites and

cationic peptides [Figure 1]. Experimental studies demonstrate that these phagocytes are the major host defense mechanism against Mucormycosis. Patients with dysfunctional phagocytes are at higher risk for evolving Mucormycosis. Hyperglycemia and acidosis are known to damage the capability of phagocytes to move toward and kill the organisms by oxidative and non-oxidative mechanisms. The exact mechanisms by which ketoacidosis, diabetes, or steroids impair the function of these phagocytes remain unknown.[5]

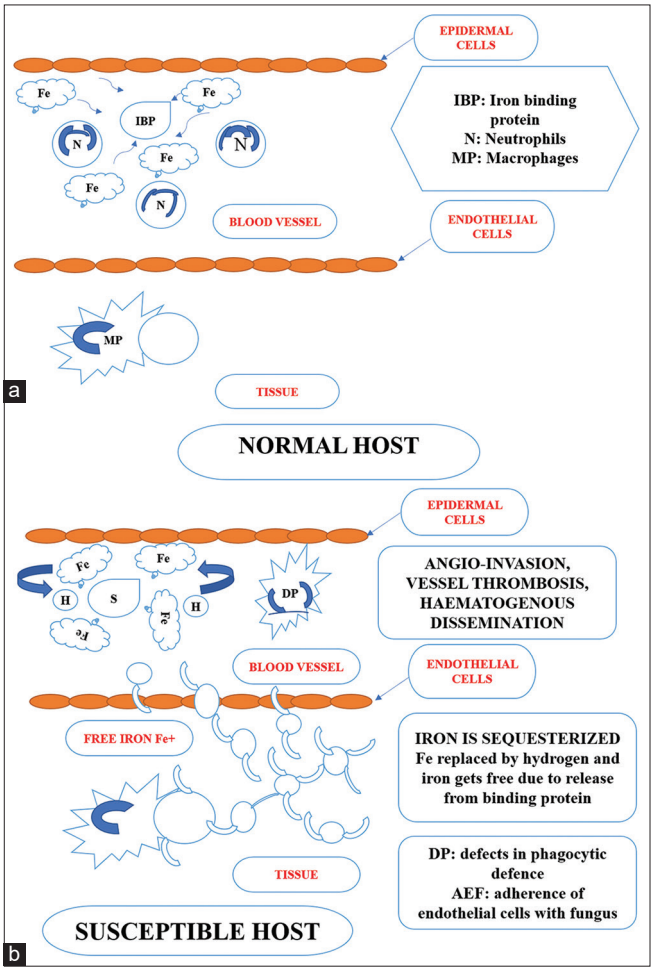

Figure 1: Pathogenetic mechanisms of Mucormycosis. To cause disease, the mediators of Mucormycosis must scavenge from the host sufficient iron for growth, must escape host phagocytic defense mechanisms, and must access vasculature to disseminate. (a) In a normal host, primary defense mechanisms against Mucormycosis include sequestration of iron in serum by specialized iron-binding proteins, phagocytes including circulating neutrophils and tissue macrophages, and endothelial cells. Which regulate vascular tone and permeability. (b) In susceptible hosts, normal defense mechanisms break down. In diabetic ketoacidosis, the acidic pH of the serum causes dissociation of free iron from sequestering proteins. This release of free iron allows rapid fungal growth. Defects in phagocytic defense mechanisms, like neutropenia or functional defects caused by corticosteroids or hyperglycemia, allow a proliferation of the fungus. Finally, adherence to and damage of endothelial cells by the fungus allows fungal angioinvasion and vessel thrombosis and subsequent tissue necrosis and dissemination of the fungal infection

TYPES OF MUCORMYCOSIS

The clinical studies on Mucormycosis have been shown that it may be divided into six separate syndromes: Rhino cerebral, pulmonary, cutaneous, gastrointestinal, CNS, disseminated, and miscellaneous (e.g., bones, kidney, heart, and mediastinum).[4,5]

Rhino Cerebral Mucormycosis

It is the furthermost common form of Mucormycosis and it is responsible for about 1/3rd and half of all cases of Mucormycosis. The infection is spread to the brain from the sinus. About 70% of rhinocerebral cases were found in patients having diabetic ketoacidosis. After diabetes, it also occurred in the patients of renal transplant, neutropenic cancer patients, HSCT, and solid organ transplant. The initial signs are sinusitis/periorbital cellulitis and include eye or facial ache and facial numbness, and sooner or later the onset of conjunctival suffusion, blurry vision, and tender tissue swelling. Fever may and may not be present and rise in the level of WBC. Untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function and proptosis. Signs and symptoms such as bilateral proptosis, chemosis, imaginative and prescient loss, and ophthalmoplegia, a threatening signal that shows the development of cavernous sinus thrombosis. Improvement of a black, necrotic eschar, is an ultimate degree contamination signal of contamination. Infection once in a while extends from the sinuses into the mouth and produces painful, necrotic ulceration of the difficult palate. Progressive imaginative and prescient loss and in the long run blindness came about due to contamination. A bloody nasal discharge is the first emblem that infection has attacked through the turbinates and into the brain.[5]

Pulmonary Mucormycosis

This type of infection happens most commonly in leukemic patients who are getting chemotherapy or in patients experiencing hematopoietic stem cell transplants. Neutropenic patients or persons having stem cell transplants are also the high-risk candidates of this infection. It often occurs in post engraftment and is strongly related to graft versus host disease. Patients having diabetic ketoacidosis may also undergo this infection. Symptoms include dyspnea, cough, and chest pain in most cases fever also. Angioinvasion consequences in cell death of parenchyma tissue, which can also additionally subsequently cause cavitation and hemoptysis, which can be deadly if the main blood vessel is involved, lobar consolidation, remoted masses, nodular disease, and cavitation. Wedge-shaped infarcts of the lung are seen in the radiographical analysis.

Cutaneous Mucormycosis

It is far usually located in sufferers who have sustained trauma (in those instances the fungi are placed into the pores of skin and deeper subcutaneous layers) or who have had bandages implemented to the pores and skin. Patients with an excessive chance of rising this contamination are people with the distraction of protecting the cutaneous barrier every day. The negotiators of this contamination are classically not able of penetrating intact pores and skin. Still, burns, traumatic disruption of skin, and persistent maceration of skin enable the organisms to penetrate deeper tissues. Insulin injection or catheter insertion sites, infected surgical dressings, and infected tape used to steady an endotracheal tube in a "ventilated" affected person are true reasserts of this contamination. It is competitive domestically and penetrates from the cutaneous and subcutaneous tissues into the adjoining fat, muscle, fascia, or even bone. That turned into the number one sort of vascular contamination. Secondary vascular invasion may also result in hematogenous disseminated contamination of the deep organs.

Gastrointestinal Mucormycosis

This type of infection in the gastrointestinal tract is very infrequent. It mostly arises in malnourished patients (especially in infants/children) and can also arise through ingestion of the fungi. It is largely seen in premature neonates. Necrotized enterocolitis was seen in neonates who are suffering from this infection. This infection is rare in the case of neutropenic adults, immune-compromising situations, including AIDS, systemic lupus erythematosus, and organ transplantation. The stomach, ileum, and colon are the sites involved in this infection. Hepatic Mucormycosis has been seen in the person who is taking herbal medications. The symptoms may vary and depends on the site of infection. Intra-abdominal abscess, non-specific abdominal pain, nausea, and vomiting are greatest common symptoms. Fever and hematochezia may also occur.

Mucormycosis Related to CNS

The major route of this infection is a direct allowance through the nasal/paranasal sinuses. It is supposed that infection is primarily blowout hematogenous in IV drug abusers who was suffering from Mucormycosis of the CNS. This infection always arises in patients who are suffering from other medical conditions like AIDS. This infection is invaded in the bloodstream.[4]

Disseminated Mucormycosis

It originates from any primary site of infection. Pulmonary mucormycosis in strictly neutropenic patients has the maximum occurrence of dissemination. Less frequently, dissemination can arise from the gastrointestinal tract, the sinuses, or cutaneous lesions, the former happening predominantly in burn patients. The furthermost common site of dissemination is the brain, but metastatic lesions may likewise be found in the spleen, heart, skin, and other organs.

Miscellaneous

Mediators of the *Mucorales* can infect virtually anyone's site. Brain obsession in the non-appearance

of sinus infection, endocarditis, and pyelonephritis occur infrequently, mostly in intravenous drug abusers. Other is in bones, mediastinum, trachea, kidneys, and peritoneum associated with dialysis. Other rare forms of this infection include syndrome of vena cava and external otitis.[5]

Mortality

The overall mortality rate for all type of mucormycosis ranges from 40 to 80% with variable rates and it depends on the basic conditions and sites of infection. The highest survival rates are recorded in patients with a healthy immune status. The poorest prediction is observed in patients having hematological malignancies and HSCT recipients and patients with extensive burns. Disseminated disease, such as mucormycosis of CNS, is frequently associated with mortality rates >80%. Minor mortality is seen with localized sinus or skin infection, where the previous tissue-based diagnosis is often possible and surgical debridement may result in a cure. Mortality rate is maximum in neonates and immune-compromised patients having gastrointestinal mucormycosis and delay in diagnosis results in polymicrobial sepsis. Improved survival is a result of earlier diagnosis and multidisciplinary treatment methods including aggressive surgical intervention.[6]

The worldwide death rate of pulmonary mucormycosis is about 50–70% but is less than 95% if it is the portion of a disseminated process. The cutaneous and subcutaneous illness might be cause necrotization, which has a death rate leading 80%. The mortality rate related with dissemination of brain will be lead to 100%. Even without CNS participation, disseminated mucormycosis has a death rate which is superior than 90%. In patients experiencing HSCT, the 1-year mortality is higher than 95% due to a blend of fundamental disease and graft-versus-host disease.[5]

Diagnosis

As this disease is too lethal, hence, the early diagnosis of this infection is very much needed, because, in some cases, there was diagnosis done after the post-mortem of body. Suspected patients with Mucormycosis must be referred instantly to a facility with the peak care level. Attack on blood vessels is a main pathologic indicator of Mucormycosis, areas of vasculitis with thrombosis, hemorrhage, and infarction are significant signs in the differential diagnosis of Mucormycosis. Tissue damage is a symbol of the disease. Section of lungs, respiration tract, and pores of the skin of aspergillosis inflamed sufferers are the same as the ones visible in sufferers who have mucormycosis. Culture, pathological examination, and biopsy of the specimens are the only definitive way to differentiate between Mucormycosis and aspergillosis.[6]

TECHNIQUES USED FOR DIAGNOSIS OF MUCORMYCOSIS

Radiography

In person who is suffering from hematologic malignancy and traced as pulmonary Mucormycosis, a pulmonary computed tomography (CT) scan suggested the finding of reversed halo sign, an area of ground-glass opacity surrounded by a circle of association on thoracic CT, and vascular occlusion in CT pulmonary angiography. Diabetic patients represent pain on face, inflammation of paranasal sinuses, exophthalmos, paralysis of motor nerve of eye, and newly diagnosed amaurosis. CT and magnetic resonance imaging (MRI) of cranial are strongly suggested to determine the presence of sinusitis. If sinusitis is identified, endoscopy is strongly suggested to identify mucormycosis. If the disease of the eye/brain is suspected, then MRI should be shown instead of a CT scan due to considerably greater sensitivity. A biopsy is the only potential diagnosis for mucormycosis when it was confirmed in a patient having fundamental malignancy. Then, cranial, thoracic, and abdominal studies are used to find the extent of disease. Given the quick development of mucormycosis, weekly CT scans are mostly endorsed, particularly in unstable patients.[6]

Histology

Mucormycosis is seen by the use of direct microscopy of specimens. First, staining with

fluorescent calcofluor white/blankophor is done. To verify an infection, non-pigmented hyphae displaying tissue invasion ought to be uncovered in tissue sections stained with hematoxylin-eosin, periodic acid-Schiff stain, or Grocott-Gomori's me then a mine-silver stain. Histopathologically, *Mucorales* hyphae have an inconstant width of 6–16 μm, but perhaps up to 25 μm, and are non-septate or pauci-septate. In tissue, the hyphae appear ribbon-like with an irregular pattern of branching. Hemorrhagic infarction, coagulation necrosis, infiltration through neutrophils, and perineural invasion are usual capabilities of acute lesions, whereas, a pyogranulomatous swelling with an incidence of giant cells, hyphae covered by the Splendore–Hoeppli phenomenon, are chronic lesions which describe deeply eosinophilic material neighboring the pathogen are seen. Since there is very much similarity between aspergillosis and mucormycosis infection; hence, the perfect detection should be needed to avoid misidentification. For this proper, identification of fungal species must be needed. This should be done using an immunohistochemistry examination. The use of monoclonal antibodies preferred for this as these are so specific. PCR techniques on either fresh or formalin-fixed paraffin-embedded tissue are highly specific.[6]

Culture

The culture of the specimens is endorsed for genus and species identification and antifungal susceptibility testing. Homogenization of tissue must be avoided formerly culturing. Cultivation at 30°C and 37°C separately is mostly suggested. Direct microscopy of specimen and use of fluorescent dyes on specimens is strongly suggested. Septation, branching angle, and hyphal width were observed.[6]

Molecular-based Technique

In the non-appearance of a standardized test, the use of molecular methods fresh clinical material and paraffin sections both used for the discovery of mucormycosis is moderately maintained. Fresh material is selected over paraffin-embedded tissue because formalin can cause damage in DNA. Detection of DNA in serum as well as in other body fluids is very auspicious but due to lack of standardization supported with moderate strength only.[6]

Genus and species identification

Identification of genus and species is used for the improved epidemiologic understanding of mucormycosis. Molecular identification techniques are preferred over morphology. For the finest technique of molecular, identification is "internal transcribed spacer" sequencing is powerfully supported. Matrix-assisted laser desorption ionization with time-of-flight (MALDI-TOF) recognition is commonly suggested since it trusts largely on internal databases, and many workshops does not have that capacity.[6]

Treatment

Four factors are critical for eradicating mucormycosis: Rapidity of diagnosis, reversal of the fundamental predisposing factors, suitable surgical debridement of infected tissue, and proper antifungal therapy. Early diagnosis is vital. Moreover, small lesions can often be surgically removed before they progress to include serious structures or disseminate.[5]

For patients having neutropenia or those who are suffering from GVHD, Posaconazole delayed-release tablets as primary prophylaxis is to be recommended.[6] First-line treatment is taken with high-dose "liposomal amphotericin B" is required essentially, whereas IV isavuconazole and IV posaconazole or delayed-release posaconazole tablets are recommended as moderate strength. Both triazoles are strongly endorsed as salvage treatments. Amphotericin B deoxycholate is not endorsed, as it produces vast toxicity, but it may be the only option in either case of resistance with polyene or with triazole or unavailability of these first-line drugs.

First-line antifungal monotherapy

In several cases, "liposomal amphotericin B" is used in the treatment of black fungus with

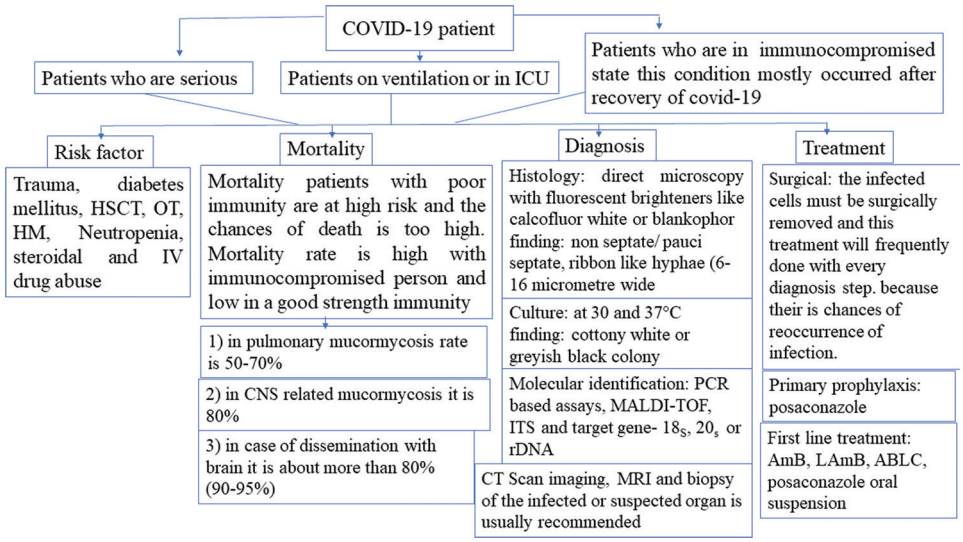

Figure 2: Diagnostic and therapeutic pathway of invasive mucormycosis

extensive success. Daily doses of this are ranged from 1 to 10 mg/kg per day. Those who are taking high doses will be showing increased response rates. It is dose-dependent activity. Patients who are taken 10 mg/kg in a day had considerable serum creatinine increases that were mostly reversible. Doses >10 mg/kg everyday did not show higher blood concentrations. In CNS involvement, animal models show that the use of LAmB at 10 mg/kg per day is appropriate. Moreover, in the nonappearance of CNS involvement, lipid complex of amphotericin B with a dose of 5 mg/kg per day is required to treat successfully. In a kidney transplant, the receivers 'amphotericin B lipid complex 10 mg/kg in everyday is to be given. Amphotericin B deoxycholate was the drug of choice from the ancient time, where the discovery of amphotericin B is not be done. It is effective, but its use is limited by its considerable toxicity.

The action of isavuconazole was like AmB. Isavuconazole was licensed in USA for 1st line treatment of this infection. By dissimilarity with other mold-active azoles, isavuconazole is less hepatotoxic, although it can result in shortening the QTc interval. Posaconazole oral suspension has been used successfully in first-line treatment. Recently, its oral bioavailability is seen in a delayed-release tablet with improved exposure. Moreover, this study is playing a good role to give moderate therapy for this infection. Amphotericin B deoxycholate use is neglected whenever alternatives are available.

The median period of isavuconazole as the first-line or as salvage treatment is 84 days IV/oral route. Sometimes both routes may al souse for treating. In several posaconazole oral suspension experimental studies, treatment period ranged from 1 week to 3 years, the mean period was almost 6 months.

Azoles

Itraconazole is the only marketed azole drug that has *in vitro* activity against *Mucorales*. Posaconazole is more effective than itraconazole but less efficacious than amphotericin B deoxycholate.

Echinocandins

Caspofungin is the 1st member of novel echinocandin class of antifungal drugs, but it is having less activity against the agents of mucormycosis. The study shows that the combination of caspofungin (1 mg/kg/day) with ABLC (5 mg/kg/day) was synergistic.[5]

Successful therapy for mucormycosis includes a coordinated surgical and medical approach. Extensive surgical session is the most important step of treating the sick person who has mucormycosis. The goal of surgery should be to remove all devitalized tissue. Debridement may have to be repeated daily for several days.

Novel iron chelators

The relevant function of iron metabolism within side the pathogenesis of mucormycosis indicates the opportunity of making use of powerful iron chelators as adjunctive antifungal therapy. Deferoxamine becomes correctly used.[5]

Other adjunctive therapy

Hyperbaric oxygen might be a valuable aid to the standard surgical and medical antifungal therapy of mucormycosis, mainly for patients having rhinocerebral disease. It is thought that hyperbaric oxygen may be beneficial for treating mucormycosis at the side of fashionable remedy due to the fact better oxygen strain improves the cap potential of neutrophils to kill the organism. Furthemore, excessive oxygen strain inhibits the germination of fungal spores and the increase of mycelia *in vitro*. Cytokines that activate phagocytic activity are consisting of gamma interferon and granulocyte-macrophage colony-stimulating factor. They will boom the cap potential of phagocytes to kill marketers of Mucormycosis *in vitro*.[5]

DISCUSSION

Mucormycosis is an infrequent devious fungal infection characterized by infarction and necrosis of host tissues that result from invasion of the vasculature by hyphae. The incident rate of mucormycosis varies from 0.005 to 1.7 per million population.[96] The worldwide mucormycosis case death rate is 46%.[97] This infection is difficult to diagnose. Initial diagnosis and treatment are crucial, as a suspension of even 6 days is related with a doubling up of 30-day mortality from 35 to 66%. In lack of early diagnosis and destructive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is poor. High suspicion for this disease must be considered in patients who are immune compromised.

CONCLUSION

Mucormycosis is an increasingly most common problem in immune compromised patients. The predictable number of cases in India seems to be alarmingly high with uncontrolled diabetes is the most important risk factor. It is an occasional but emerging fungal infection with a high mortality rate. India is having the second largest population country in Asia, after China. As India is still developing, the challenges may increase with overcoming this disease. Mortality is very high with this infection, because, in 2020 –21, the total death case is low as compared to the death rate from black fungus after post-COVID recovery. 1 doctor is taking care of almost 1000 patients. It is very problematic for physician to taking care of every patient with various factors. Increased mortality is just because one single factor is the lack of a specific diagnostic test for the infection-causing organism; mucormycosis is as similar as aspergillosis; hence, accurate diagnosis is very much needed. In most cases, this infection has been diagnosed either post-mortem of the body or in the last stage of infection. In such a situation, it is impossible to overcome this infection. Polyene like amphotericin B is required as it is the firs-line of treatment of this disease. Proper inventory in the overall country is very much required. Manufacturing of amphotericin B should be increased as the demand of the situation. CT scan, MRI, biopsy still playing a dynamic role in the diagnosis of this infection.

FUTURE PROSPECTS

Mucormycosis is a life-threatening infection. Hence, the very specific diagnostic tool and very specific vaccine kind of treatment are required. Many challenges are required to overcome and recover overall outcomes related with invasive mucormycosis. Genome sequencing and molecular tools for studying the *Rhizopus* species are exploring at present and expecting this area of study will be expanding with innovation and discovery. On the other side (diagnostic), in the coming 5 years, the field of molecular diagnostics for mucormycosis will further expand. PCR-based tests hold promise with newer and improved targets derived from basic research studies of the pathogenesis of mucormycosis such as the CotH gene. New targets such as fucomannan using serologic testing approach has the potential for identifying infection

rapidly as a point of care test. MALDI-TOF-based libraries when updated will be a significant resource for rapid and precise identification of mucormycosis. Although, molecular tests will significantly improve the field of Mucormycosis diagnostics, the isolation of the fungus from the culture of body fluids/tissue and histopathology will probably remain the gold standard.

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CONFLICTS OF INTEREST

Authors do not have any conflicts of interest to declare.

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