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Review Article

A BRIEF REVIEW ON MUCORMYCOSIS: PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT

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ABSTRACT

Mucormycosis is an invasive fungal infection caused by a group of moulds or spores and specially effects the patients with low ability to fight against diseases. It is not contagious; it can be diagnosed with Computed tomography scan and new advancement in molecular tools are being developed. In this review mucormycosis pathology, diagnosis and its treatment with various antifungal drugs are discussed in brief.

Keywords: Mucormycosis, Rhizopus, Diabetes, Visceral forms, Amphotericin-B.

1. INTRODUCTION

Mucormycosis can also be termed as Zygomycosis, is an invasive fungal infection mainly recognized in the patients with immunological disorder caused by the members of Mucorales and Zygomycotic species. The term was given by an American pathologist R.D. Baker. The infections are categorized by rapid progression and an increased mortality rate is being reported with few therapeutic options [1]. The most common relating agents of mucormycosis are the Mucorales with four genera *Rhizopus, Mucor, Absidia* and *Cunninghamella* and Entomophthorales with two genera *Conidiobolus* and *Basidiobolus*, which differs from each agent clinically and genetically. *Rhizopus oryzae*, is detected as the pathogen causing 70% of the total mucormycosis infection [2].

2. EPIDEMIOLOGY

The agents of mucormycosis are distributed worldwide and are found everywhere in the environment and the inhalation of sporangiospores or inoculation of wounds severe the condition of the patient. It is an opportunistic Infectious disease effecting the immunodepressed patients, especially in case of diabetes, patients with frequent episodes of ketoacidosis, burn and trauma patients, patients requiring iron chelation therapy or chemotherapy. As diagnosis is difficult, the occurrence of this disease is unknown and as a result it cannot be reported as scientific evidence [3-5].

3. PATHOPHYSIOLOGY

Mucorales mainly effect the deep tissues by the means of percutaneous injection and ingestion or inhalation of spores [6]. Persons with impaired or low phagocytes are infected more readily with invasive mucormycosis while the normal immune cells such as mononuclear and polymorphonuclear phagocytes kills the hyphae and spores causing the disease [7]. One of the risk factors is Neutropenia induced by cytotoxic chemotherapy or patients with diabetes have the chances of killing the internalized fungi and bacteria resulting from the acidic pH and hyperglycaemia of ketoacidosis also impairing the neutrophil motility and a patient in high dose of glucocorticoids can also impair phagocytosis and intracellular killing of ingested Mucorales spores [8]. The uptake capacity of iron from the host is the most researched virulence mechanism. Either it is a multi-cellular or prokaryotic organism iron being an important cofactor for a variety of enzymes but in normal physiological conditions iron doesn't exist freely so the infecting fungi must acquire it through sources. For this, the model of iron uptake *Rhizopus* is taken under study which grows poorly under serum unless iron is being provided. It grows rapidly, if the serum is acidified to pH<7.3 probably because acidic pH dissociates the iron-protein complexes and make free iron available for the uptake [9]. To mask this use of iron, chelators will act as one of the options. Patients receiving deferoxamine for iron overload related to haemodialysis have a significant risk for mucormycosis [10], as it has extremely high affinity towards iron and deliver it to *Rhizopus* for its growth *in vitro*. During intracellular transport, *Rhizopus* reduces ferric to ferrous ion from the deferoxamine iron complexes [11]. *Rhizopus* binds to macromolecules of the extracellular matrix with the invasion of the endothelial

cells of the vascular system [12]. GRP78 (cell surface protein) is upregulated during glucose starvation and which potentially acts as a receptor for Mucorales species in humans and permits uptake by and damage to the endothelial cells [13], with secreted proteases and ketone reduction pathway amongst the other virulence factor [14-15]. Exposure to voriconazole in animal models shows increased virulence factor in certain Mucorales taxa [16]. Mortality rate was reported to be as high as 90% or even more with Mucormycosis infection, prior to the administration of amphotericin-B and radical surgery [17]. But it's not the same in the case of AIDS patients [18] thus implying that the T lymphocytes are not that important for hampering the fungal proliferation but only the neutrophils. Deployment of newer azole agents in the future must need to observe that the new agents do not accelerate self-contradictory growth of mucormycosis disease.

4. CLINICAL MANIFESTATIONS OF MUCOR-MYCOSIS

Infections in humans occur mainly in two forms: 1) Superficial and Visceral and 2) Localized and Disseminated.

The characteristic superficial form is seen in external ear, finger nails and skin. On the other hand, Visceral forms are manifested as pulmonary, gastrointestinal and rhino cerebral types. These spores enters either through cutaneous or respiratory route (E.g.,contamination with spores while taking soiled food or by tainted needles) [19]. Tissue necrosis resulting from angioinvasion and thrombosis into the affected tissue is the main sign of the disease which may lead to even death if the underlying risk factors are corrected or any surgical excision if possible is made or treated with proper antifungal therapy [6].

Visceral forms	Underlying host risk factor	Pathogenesis of disease	Clinical manifestations	Mortality rate
Pulmonary	Neutropenia, induction chemotherapy, lung transplantation	Hyphal invasion of pulmonary blood vessels which can lead to haemorrhage, thrombosis, ischemia	Prolonged high fever, airway obstructions	66% or higher depending on level of immunosuppression
Gastrointestinal	Premature neonates, diabetes mellitus, malnourished children	Alcoholic drinks derived from corn, ingestion of spore contaminated fermented milk, dried bread products	Appendiceal,cecal or ileac mass or gastric perforation	85%
Rhino orbital cerebral	Diabetes mellitus, solid organ transplant	Begins in the paranasal sinuses after inhalation of sporangiospores	Sinusitis, facialnumbness, blurryvision, headache	50% or higher

5. DIAGNOSIS OF MUCORMYCOSIS

The diagnosis is difficult based on imaging studies, sputum culture, or needle aspirate but can be diagnosed with a proper high index of suspicion to begin the appropriate diagnostic workup and treatment. By histological analysis or by tissue culture from the site of infection proven invasive fungal infection can be detected, and presence of a host factor under treatment with corticosteroids for 3 weeks or more, or recently diagnosed with neutropenia can induce Probable invasive fungal infection [20]. Conventional radiological techniques are not specific in the diagnosis of pulmonary mucormycosis in contrast, the use of high-resolution computed tomography (CT) and magnetic resonance imaging can be useful for the diagnosis of rhino-orbital-cerebral, pulmonary, and disseminated diseases [21]. Laboratory techniques such as molecular methods and fluorescent in situ hybridization, PAS stains, direct examination, histopathological examinations can be used to detect the invasive mucor in the patient [22]. Diagnosis can be also be done by a biopsy of the tissues infected whereas a bronchoalveolar lavage (BAL), biopsy, or both may be done in case of a patient with pulmonary disease. Tissue discharges as well as swabs are unreliable in case of mucormycosis infection [23]. With the advancement in technology new molecular tools have also been developed to identify mucormycosis directly from tissue samples; fresh tissue

is preferred over paraffin-embedded tissue because formalin damages DNA [24, 25].

6. TREATMENTS

6.1. Polyene Antifungals

Amphotericin B is the first choice of drug for the treatment of mucormycosis which acts by binding to the sterols, preferentially ergosterol which provides rigidity and structure to the cell making the cell to leak, disturbing the growth of the colony. If administered in high dose, the cell will die, the therapeutic dose recommended is 1 to 1.5 mg/kg/d. A review of 170 cases with patients of sinus mucormycosis showed increased survival rate from 50% to 70% with a combination of surgical debridement and amphotericin deoxycholate (ABD) [26] and 41 patients with rhino-orbital-cerebral mucormycosis survived with the combination therapy of surgical and ABD with a mortality rate of 52% [27].

6.2. Triazoles

Triazoles is the largest class of antifungal agents clinically used, and acts by inhibiting the 14-α-demethylation of lanosterol in the ergosterol biosynthetic pathway, which leads to the depletion and replacement of ergosterol with toxic 14-α-methylsterols, altering fungal membrane permeability as well as inhibiting membrane bound enzymes involved in cell wall synthesis [28]. Of the second-generation triazoles, only Posaconazole and isavuconazole display appreciable activity against the Mucorales, with the addition of an α-*O*-methyl group to the chemical structure extends the spectrum of these drugs to include *Aspergillus species* and other filamentous fungi [29-30].

6.3. Posaconazole

It is structurally similar to itraconazole and is administered to patient with amphotericin-B resistant [28]. various study was conducted for the administration of the Posaconazole in the treatment of mucormycosis. A dose of 800mg/d was administered as oral suspension and results were seen to be effective with a 50% survival rate [31-33]. However it displays a variation in the pharmacokinetics results and provide a less bioavailability than expected and if administered with proton pump inhibitors reduces the AUC and its peak plasma concentration resulting in the poor absorption of the Posaconazole [34-38]. It can be improved by designing the drug with delayed release mechanism with the same dose as oral suspension or IV dose of 300mg which gives the peak plasma concentration 2 to 4.5 times as compared to the oral single dose of 800mg [39-40] but the proper impact of both the dosage of IV and delayed release is still under research [41].

6.4. Isavuconazole

Isavuconazole, a broad spectrum triazole structurally similar to fluconazole, is the only azole antifungal approved for the treatment of invasive mucormycosis. Currently it is available as isavuconazonium sulphate, a prodrug which is rapidly metabolized by serum butyl cholinesterase to its active form. The approved dose is 372mg (equivalent to 200mg isavuconazole) given every 8 hours for 6 doses, followed by 372mg daily [42]. *In vitro*,isavuconazole has displayed activity, though variable, to *Lichtheimia, Rhizopus, Mucor*, and *Cunninghamella* spp. Wide minimum inhibitory concentration (MIC) ranges with the lower end of reported MIC ranges being similar to those reported with Posaconazole [43]. According to Spellberg et al., high mortality rate especially with haematology patients can be noticed with recent availability of monotherapy and hence proposed the choice of "Combination therapy" for Mucormycosis [44].

6.5. Echinocandins and Combination Therapy

Although echinocandins have no inherent activity against mucormycosis, there is some early evidence that they may augment polyene therapy. The cell wall component β-1,3-glucan is inhibited and this differs this therapy from the mechanism of action of polyenes. This activity in filamentous fungi is largely fungistatic. Study suggests that echinocandins may be added to a polyene backbone for enhanced therapeutic success, particularly in *Rhizopus*spp. And rhino-orbital-cerebralmucormycosis [45-46]. The mechanism of action may be similar to some species expressing the target component for echinocandins.

7. SUMMARY

The mucormycosis is most likely to infect the persons with low immunity and the treatments available are effective to the disease but the drugs have minimum routes of administration and its safety data regarding the drug-drug interactions and adverse effects.

8. CONCLUSION

Based upon the above discussion it is seen that mucormycosis is an infection treatable with amphotericin-B as the first choice of drugs as well as

combination therapy of surgical debridement is a possible treatment with low mortality rate. As seen recently, it has been seen a rapid growth in India as "black fungus" or mucormycosis amid the covid-19 outbreak and has been declared as an epidemic. While other treatment remains as option which need a detailed study and clinical report on its efficacy. The disease needs to be diagnosed in early stage to reduce the mortality rate and further improvement and research is to be carried regarding this deadly fungal infection. As per BBC news in an article stated that India reported nearly 9000 cases of black fungus. The western states of Gujarat and Maharashtra have reported more than half of the reported cases with a mortality of 50% and in a study of 100 patients 83 of them are suffering from diabetes.

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