Review Article

A Review on Mucormycosis with recent pharmacological treatment

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Abstract

Mucormycosis is antifungal eye infection difficult to manage this infection with limited use of diagnostic tool and therapeutic option, but previous literature studied diagnostic strategies and evaluate the potency of antifungal agent as a treatment option. Mucormycosis was difficult to study on imaging studies. Surgery plus antifungal therapy of high dose yields greater survival rates. Mucorales are most widely resisted to the used as an antifungal agent. Amphotericin -B were kept for de-escalation refractory therapy whereas, patient's intolerant to Amphotericin B.

Keywords: Mucormycosis, amphotericin, antifungal agents,

Introduction:

Mucormycosis, also known as 'Zygomycosis''. It is rare fungal infection produced by the group of molds called mucoromycetes infection is mainly seen in the people, who are on treatment for serious health issue. The fungi mainly found in throughout environment, soil, decaying organic matter. People get contaminated when they are in contacted with the fungal spores. Mucormycosis are developed on skin after fungus attack through a cut, scrape, burn, or other type of trauma[1].

More individual was passionate to Invasive Fungal infection was complicated because drug target sites of eukaryotic pathogen resemble to the human host. Mucormycosis fungal infection, which lead to causes exceeding high mortality. Among the *Mucoraceae, Rhizopus oryzae (Rhizopus arrhizus)* was more common cause of infection. Other isolated agents from *Mucoraceae* family causes a same spectrum of infection include *Rhizopus Microspores* Var. *Rhizopodiformis, Absidia Corymbifera.* Patient of Mucormycosis had been reported after infected with Species[2,3]. According to industrialize countries Mucormycosis incidences increased by 7.3% per year. Diagnosis was difficult because of clinic-radiological and historical lack of diagnostic tool. Secondly it includes treatment was an emergency and owing the Angio invasive and necrotic infection[4,5]. Aim of review is to highlight the Pathophysiology, Clinical manifestation, Diagnosis, and Treatment.

Pathophysiology:

Previous experimental evidence shown that phagocytes as the primary host defense against Mucormycosis. Person who has having low number of phagocytes or impaired phagocyte's function has more chances of causing Mucormycosis. Normal immune cells such as mononuclear and polymorphonuclear phagocytes take up and kill hyphae and spore of the molds, by the generation of oxidative metabolites, cationic peptide defensins and Neutropenia is main causes of Mucormycosis.in diabetes patient with low controlled blood glucose have chronically defective neutrophile function and acidic PH and hyperglycemia of ketoacidosis can cause neutrophil motility and killing fungi and bacteria[6,7].High dose glucocorticoid can also impair phagocytosis and intracellular killing of ingested Mucorales spores and affects ability of mouse bronchoalveolar macrophages to prevent germination and infection induced by intranasal inoculation [8,9]. The exact mechanism of ketoacidosis, diabetes, steroids impair function of these phagocytes remain unknown. The pervious study and recently identified clinical sign causes increase level of serum iron [10,11]. The well-studied virulence mechanism of fungi is capacity to sequester iron form host. iron is an essential cofactor for enzyme in every organism and prokaryotes to complex multicellular vertebrates. Free ion is nonexistent under physiological condition in human, so infecting organism must have mechanism to store iron within the host [12]. In the past two decades it was reported that

patient treated with iron chelator has chances of increased invasive Mucormycosis. *Rhizopus spp.* has capacity to accumulate 8- and 40-fold greater amount of iron provided by deferoxamine to *Candida albicans* [13]. More iron uptake by *Rhizopus Spp.* was correlated with increased with serum. Rhizopus has used model organism to study iron acquisition. *Rhizopus oryzae* grows poorly in serum unless exogenous iron is added and utilized deferoxamine as siderophore to provide iron to the fungus. If serum is acidified to PH Rhizopus can grow fastly, because acidic PH dissociates iron protein complex and makes free iron available for fungal cells. chelation not the mechanism by which deferoxamine enables the Mucormycosis infection. Iron chelators significantly decreased the growth of *Rhizopus*, other function siderophores actually deliver iron to fungal cell and promote growth. patients taking deferoxamine for iron overload related to hemodialysis have significant chance of infection[14]. deferoxamine is a siderophore produced naturally bacteria and function as a xenosiderophore to deliver iron to Rhizopus growing in vitro. Deferoxamine has high affinity for iron and can extract iron from transferrin and ferritin. Rhizopus and deferoxamine made a deferoxamine -iron complex and reduces ferric to ferrous iron during intracellular transport. Rhizopus genome contain siderophore, Mucorales have multiple mechanism to acquire scarce but essential iron ions from an environment that does not easily give them up [15].

Mucorales virulence factor that have link to pathogenesis. Mucormycosis has speciality for attack on endothelial cell of vascular system and capability to spread disease from primary site of infection. Rhizopus binds to macromolecules of the extracellular matrix culture. Surface proteins was upregulated during glucose starvation and potentially act as receptor of Mucorales in human and permit uptake and damage to endothelial cells. Virulence factor of Mucorales include secreted protease and ketone reduction pathway certain taxa within Mucorales appear to express increased virulence on animal model applied to voriconazole [16].

Diabetic ketoacidosis has wide chances of developing rhinocerebral Mucormycosis conclusion proved that systemic acidosis had increased level of serum iron due to release of iron from binding site of protein acidosis condition. If we collect sera from patient with diabetic ketoacidosis support to increased *Rhizopus oryzae* in presence of acidic PH and not in presence of alkaline PH. Acidic sera contain increased level of serum iron. Simulated acidotic condition decreased the iron binding Potency of Sera obtain from normal human suggested that acidosis is temporary disrupt the potency of transferrin to bind on iron site. Patient having diabetic ketoacidosis has developed susceptibility for Mucormycosis and increased serum iron[17].

Mucormycosis infection was virtually uniform in extensive angioinvasion with vessel Tissue necrosis. Angioinvasion is related with the potency of Organism to hematogenously disseminate from infection to another target organ. Penetrate through endothelial cell is critical steps in the organism pathogenic strategy. *R. orgyzae* spore but not pregerminated spores have ability to adhere to subendothelial matrix protein including laminin and type IV collagen in vitro. But recent study proves that R. oryzae spores adhere to subendothelial matrix protein better than R. oryzae hyphae [18]. Spores and hyphae adhere equivalently to human umbilical endothelial cells. The unequal adheres of spores and germ tube adherence to subendothelial matrix protein but equivalent adherence to endothelial cell indicates that R. oryzae adhesins to endothelial cells are likely distinct from adhesin used to bind to subendothelial matrix protein. The pregerminated R. oryzae damage endothelial cells in vitro. Damage is independent of serum factors and requires phagocytosis of R. oryzae by endothelial cells. R. oryzae viability was not required for endothelial cell damage, but phagocytosis required for the dead R. oryzae causing damage. if we administered 4 doses of heat killed R. oryzae blastospores result in 40% death rate in mice. Precise mechanism of tissue injury was remaining unclear [19].

Clinical presentation:

According to previous study it was clear that Mucormycosis results in thrombosis infraction /Necrosis. It was generally occurred in the patient with host defense and increased serum iron in rare cases observed in the normal hosts [20]. In many cases infection results in death, treatment with a combination of surgical debridement and antifungal therapy was initiated promptly [21].

Table 1: Clinical Revelation of Mucormycosis.

Types of Mucormycosis	Observed risk Factor	Pathogenesis of Disease state	Clinical manifestation	Mortality rate
Rhino-orbital cerebral [21].	Diabetes, Malignancy, organ transplant	After inhalation of sporangiospores spread to involved the palate, sphenoid sinus, cavernous sinus and brain tissue.	Eye and facial pain, facial numbness, blurry vision, acute ocular motility changes, acute headache.	50%
Pulmonary [22].	Neutropenia, induction chemotherapy, lung transplantation.	Hyphal invasion of pulmonary blood vessel which lead to hemorrhage, thrombosis, ischemia.	Prolonged high-grade fever, nonproductive cough, airway obstruction from endobronchial.	Higher depending on level of immune-suppression
Gastrointestinal [23].	Premature neonates, malnourished children, diabetes mellitus.	Ingestion of spore contaminated porridges, dried bread product, alcoholic drinks from corn.	Appendiceal, ileac mass, gastric perforation, neutropenic patients having present fever.	85%
Cutaneous [24].	Trauma /burn skin in	Occurred due to direct	Varies from localized	25% in case I

	susceptible host	inoculated spores into the skin, caused by dissemination by internal organ to the skin.	disease with gradual onset to progressive, leads to gangrene.	series.
Disseminated [25].	Iron overload, profound immunosuppression, profound neutropenia.	In Mucormycosis organ can be transfer hematogenously to another organ, lung site is most related with dissemination.	Counting on the location of disease and Position of vascular invasion.	20%

Recent Pharmacological treatment:

Current WHO guideline for Mucormycosis recommended that antifungal treatment, surgical debridement, correction risk factors, surgical debridement has involved in all necrotic area for rhino-oculo-cerebral infection and procedure are suggested for improve outcome. Treatment of pulmonary Mucormycosis was unclear. In European country prove that surgical treatment decreased mortality rate by 79%.

The antifungal therapy was limited and Mucorales was inherently resisting Antifungal Agents. Limited antifungal susceptibility data and scarcely available MIC testing reduced the antifungal infection [27].

There are some critical factors include rapid diagnosis, reversals of predisposing factors, and apposite antifungal agent therapy. small focal lesion can remove before they developed to critical structure or disseminate. Correcting and controlling predisposing problem is needed treatment outcome. Immunosuppressive therapy particularly steroids should consider when Mucormycosis is diagnosed. [28].

Rapid progress of Rhinocerebral Mucormycosis Causes death, when fungus penetrate the cranium, headache or visual changes considers for the evaluation of nasal endoscopy to run out Mucormycosis. Radiographic finding of clinical progression and negative imaging study did not provide diagnostic maneuvers. Clinical suspicion was high. Tissue appear in endoscopy may lag behind invasion, mucosa can appear pink and active during the initial phase of fungal invasion, if suspicion of disease was high, and thickened extraocular muscles was warranted to make diagnosis [29].

Time is important in Mucormycosis because Rhinocerebral disease may present with mental disease and appear stable and urgency for diagnosis was frequently underappreciated. Initial spread of fungus to the brain may asymptomatic. Fungus had penetrated through cranium and entered in intracranial vasculature; death increased substantially. Initially patient was on an antifungal therapy was not definitive therapy; surgery may a key to treatment strategy. Sensitivity of organism consider, so that patient on the Amphotericin B may receive complete ineffective therapy in diagnostic period. Clinical suspicion was high and workup should be proceeded on an emergency basis, even if patient appears stable. Delayed diagnosis shows worse outcome [30].

Importance of surgery in Mucormycosis:

In Mucormycosis antifungal therapy required to control the infection. Mucormycosis having a susceptibility to antifungal agents, strain may be highly resistant to Amphotericin B, angioinvasion, thrombosis result in poor penetration of anti-infective agent to the infection. Causative organism was susceptible to therapy in vitro,

antifungal agent may be ineffective in vivo. Surgery is need for tissue necrosis occurred in Mucormycosis which not be prevented by killing the organism. Surgical debridement of infected tissue should perform on the urgent basis. Repeated detection of the sinuses and orbit may need to ensure that necrotic tissue had been derided and infections have not progressed. Previous study suggested that Rhinocerebral, cutaneous, pulmonary Mucormycosis 65% patients cured with surgery. Pulmonary Mucormycosis, surgical treatment also improve outcome compared with antifungal therapy. Mortality rate of patients treated with antifungal agents was 68% and 11% in patient treated with antifungal agent plus surgery. Localized cutaneous Mucormycosis given with aggressive surgical agent has mortality of 10% [31].

Antifungal therapy:

There is problem for clinician to choose medicine in treating Mucormycosis was available for clinical trial. A barrier to clinical trial was the abysmal rate of success of monotherapy. Due to decreased cure rate consider that unethical to separate the randomize patient in a clinical trial to any ''less intensive '' regimen due to this reason prospective interventional trial not performed. Lacking knowledge of the clinical trial, physician depends upon anecdotal ace report; retrospective reviews and unpublished observation determine the first line therapy of disease [32]. Report is intrinsically subjected to publication and allow to no comparison of the relative efficacies of various treatment strategies, animal models was essential to provide well-controlled comparative analyses of antifungal therapies. Animal models are developed to study infection in vivo include intravenous, intranasal and intrasinus in mice models. Including this newly added included neutropenic, corticosteroid and deferoxamine -treated mouse models and deferoxamine - treated guinea pig model was reported [33]. Species used in these models include R. Oryzae, R. Microspore, Mucor, Absidia Spp. This is no advantage for evaluating different antifungal regimen, and no model completely, accurately recapitulates the normal route of Mucormycosis infection. Due to lack of clinical trial for Mucormycosis, these models are essential to evaluate advantages of different antifungal strategies [34].

Polyenes:

Randomized trial unable to explain optimal antifungal treatment. Amphotericin B deoxycholate since 50-year use as an antifungal agent bactericidal resistance saw in isolated liposomal Amphotericin B less toxic than Amphotericin. High dose of Amphotericin B in animal model superior in clinical study. Amphotericin B lipid complex inferior to CNS penetration vs. Liposomal Amphotericin B in one rabbit study not superior for placebo or amphotericin at high dose [35]. There was no investigational prove is available for the itraconazole toxicity profile. Study suggests that Posaconazole more

effective in Screening model. Bacteriostatic in vitro model when combine with polyene but no data available for the activity inferior to amphotericin in murine models. Amphotericin B deoxycholate and its lipid derivatives has activity against Mucormycosis. Various species has a good susceptibility towards amphotericin so, dose of amphotericin B deoxycholate is 1 to 1.5 mg/kg. The molecular basis of drug resistance in this organism was an area of interest for future research. Lipid formulation of amphotericin was significantly less nephrotoxic can be safely administered at higher dose for long period. Use of high dose for lipid-based amphotericin also increases cost enormously. Several case report of patient with Mucormycosis has documented successfully outcome with Amphotericin B lipid complex [36].

In murine model of R. oryzae infection in diabetic ketoacidosis mice contain high dose liposomal Amphotericin was consider to be more effective than Amphotericin B deoxycholate and having doubling survival rate. In patient having haematological malignancies if handle with amphotericin survival rate is 67% when it gets compared with 39% survival rate when patient given with amphotericin B deoxycholate. Based on combination of clinical data and poor success rate with Amphotericin B and animal data showing liposomal Amphotericin B over Amphotericin B deoxycholate, therefore in develop symptoms of Mucormycosis high dose of lipid formulation Amphotericin was preferred initially antifungal treatment[37]. Study had performed on rabbit liposomal Amphotericin B penetrated brain parenchyma at level more than 5 time of Amphotericin B lipid complex. In opposite to liposomal Amphotericin B and Amphotericin B lipid complex didn't improve survival rate when compared with Amphotericin B deoxycholate in our murine model of disseminated R. oryzae infection [38].

In the recent studied the effect of liposomal Amphotericin B in clinical Mucormycosis. No clinical data and review of effect of Amphotericin B lipid complex was set in the comparable data. The efficacy of Liposomal Amphotericin B vs Amphotericin B lipid complex can't made for Mucormycosis. form pharmacokinetic studied, animal data, retrospective clinical data for first line use of high dose liposomal Amphotericin B for Mucormycosis particularly for case of CNS disease with Amphotericin B lipid complex consider as alternative antifungal agents. Therefore, in case of life threatening Mucormycosis infection and immediate initiation of liposomal Amphotericin B at dose of 10mg/kg/day [39].

Azole:

Previous study found out research report for treatment with Itraconazole, further animal studies reveal that Itraconazole is infective against *Rhizopus* and *mucor spp*. susceptible *in- vitro*. Drug did not show activity *in-vivo* against hypersusceptible strain of *Absidia* because of itraconazole were not consider first line agent against, but it considered as adjunctive therapy [40].

Voriconazole approved broad spectrum triazole, was not active against Mucorales *in-vitro.* Investigational triazoles have promising in vitro activity against Mucormycosis. in animal model it was proved that Posaconazole was superior than Itraconazole but less efficacious than Amphotericin B deoxycholate. Posaconazole therapy is effective for refractory Mucormycosis. Successful development was seen rhinocerebral disease with amphotericin and heart/kidney transplant patient who didn't reponse to Amphotericin therapy. More data are

need for the evaluating whether, Posaconazole or Amphotericin is useful.

Echinocandins:

Caspofungin was used as antifungal drug having less activity against agents of Mucormycosis, when evaluated in vitro. In-vitro Caspofungin activity against mold remain unclear. Research was found that Caspofungin plus Amphotericin B lipid Complex was shown synergistic action. This combination improved survival rate by 50%. The study suggests that echinocandins consider as second agent. More study of utility of echinocandins is needed [42].

Other therapy:

Other therapies include hyperbaric oxygen is beneficial due its higher oxygen pressure improves the ability of neutrophils to kill the organism adjunct to the standard surgical and antifungal therapy of rhinocerebral disease. High oxygen pressure reduced the germination of spores and growth of mycelia in vitro [43].

Second alternative therapy for the Mucormycosis includes cytokine therapy. Cytokine therapy at phagocytic activity include granulocyte macrophages colony-stimulating factor, has ability of phagocytes to kill the agents in vitro [44].

Conclusions:

Mucormycosis was a developed in immunocompromised patient. In Mucormycosis iron important in organism pathogenesis. The reaction between Mucorales and endothelial cells beginning to understood the pathogenic feature of disease novel to therapeutic intervention in the feature. Currently there are some novel and alternative treatment used. Combination of lipid-based amphotericin, echinocandin or itraconazole and compassionate use of Posaconazole and its potential for combination therapy with polyenes and Caspofungin are meritorious for study.

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