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Mucormycosis A Brief Review

Varun Gupta Fauzia Imtiyaz Aditi Dubey Nadiya Imtiyaz Ajinkya Aher

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ABSTRACT
Mucormycosis is an angioinvasiveinfection that occurs due to the fungi Mucorales. It is a rare disease but increasingly recognized in immunocompromised patients. It can be categorized into rhino-orbito-cerebral, cutaneous, disseminated, gastrointestinal, and pulmonary types.
Overall increased mortality rate is reported,even with agressive treatment, the main aim and purpose of this review related to overview and pathogenesis of mucormycosis, fatality of rhinocerebralmucormycosis, recent advances in diagnostic and treatment methods.
Keywords: Haemoptysis, Dyspnoea, Hematogenously, Iron Chelators

I. INTRODUCTION:

Mucormycosis or black fungus is a serious, rare life threatening fungal disease which is caused by group of moulds called mucormycetes. Fungi which causes mucormycosis belong to family Mucoraceae and the class of fungi is Zygomycetes. The most common cause of this infection is believed to be **Rhizopusoryzae.**[4][8]
This usually occurs in patients who are immunocompromised due to various reasons like diabetes, organ transplantation or take medicines that lower the body's ability to fight germs and sickness. Mucormycosis was previously called Zygomycosis.[9]

TYPES OF MUCORMYCOSIS

1. RHINOCEREBRAL MUCORMYCOSIS-

It is one of the most common form of this infection which affects most of the people. In most of the cases diabetic patients are found to be most affected or people with weak immunity like those who went for organ transplantsymptoms of this type includes sinusitis or cellulitis, facial pain, numbness, blur vision, swelling of tissue.[2]

Symptoms starts to appear from eye with bilateral proptosis, vision loss, opthalmoplegia.it also affects cranial nerves five and seven which causes facial sensation loss or numbness and can also effect pupilary dilation. The first indication could be bloody nasal discharge which is sign that infection has reached to brain.[7][21]

Diagnosis- the diagnosis is mainly done through CT scan, magnetic resonance imaging(MRI) can also be used but in CT scan patients with early symptoms can be detected which is not possible with MRI.[21][22]

2. PULMONARY MUCORMYCOSIS-

It is mucormycosis of lungs and occurs mainly in patients undergoing chemotherapy or leukemia patients. The people who are affected have neutropenia and are taking broad spectrum antibiotics. Patient who are diabetic can also be affected by pulmonary mucormycosis even though it is less common.[9][10][12]
It develops in consequence of hematogenic, lymphogenic spread or inhalation. Common symptoms are chest pain, dry cough, dyspnoea, necrosis of parenchyma tissue leading to haemoptysis which is fatal.([10][48]
Diagnosis can be done by chest CT scan. Some indication of this infection can also be seen in chest X ray. If proper treatment is not taken hematogenous dissemination to the contralateral lung can occur.[48]

3. CUTANEOUS MUCORMYCOSIS

People most commonly affected with this type of mucormycosis are the ones with disruption of normal protective cutaneous barrier. Cutaneous lesions may also arise in diabaetic and immuonocompromised patients. It may penetrate from cutaneous to sub cutaneous tissues into the muscles and sometime bone. Secondary vascular inavation may also occur which further leads to hematogenously disseminated infections.[5][11][18]
Most of the cases of this infection has happened due to voriconazole therapy. Similar occurrence has been described with one more drug therapy that is itraconazole.[11][28]
Diagnosis- If there is confirmationof infraction in some organs then diagnosis can be done.[5][18]

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4. MISCELLANEOUS FORMS

Mucormycosis can occur in any part of the body. Some cases show mucormycosis in trachea, kidney, bones peritoneum associated dialysis. It is not common in AIDS patients although there are some cases in these population also.[13]

Pathogenesis

Germination of sproes and formation of hyphae marks the beginning of the infection.[30]

Patients with diabetes(type 2 specifically) and immunocompromised individuals (with low phagocyte count) fall prey for the fungus.[9][12][58]

Neutrophils inhibit the germination of the spores where as mononuclear and polymorphonuclear phagocytes of normal hosts kill mucorales by generation of oxidative metabolites and cationic peptides(effectors activated by microbial pathogens) and defensins(host defense peptides expressed in neutrophils[23]

Diabetic ketoacidosis, a condition characterized by hyperglycemia and decreased blood ph, impairs the function of phagocytes due to which effective chemotaxis and microbial killing mechanism by oxidative and non oxidative mechanisms is impaired exact mechanism is not known.[9][12][23][58]

Mucorales exploit such an immunosupressed and physiologically impaired state of an individual and exhibit virulence, the characteristic one being ability to acquire iron from the host.[9][23][24]

Iron is a growth factor in hosts as well as pathogens and pathogens acquire multiple mechanisms for acquiring iron from the host, particularly the level of unbound serum iron plays a crucial role in patients with diabetes ketoacidosis predisposing to mucormycosis[9]

In mammals, iron is bound to host carrier proteins like transferrin, ferritin and lactoferrin, which prevents iron availability to the pathogen and is a major host defense against microbes and mucorales as r. oryzae grow poorly in normal serum levels [1][9][30]

Clinical observation specified that patients with diabeticketoacidosis have elevated levels of free iron in their serum and such iron rich serum supports growth of r.oryzae at acidic ph[9][12]

In addition, acidosis disrupt the capacity of iron binding of seru, results in impaired transferrin binding to iron, proton mediated displacement of ferric ion from transferrin is fount to be the main cause[9][35]

Contrary mechanism of accumulating iron is via siderophores(molecules used by an organism which binds and transports iron in microorganisms), bacterial siderophore include deferoxamine strips ferric iron from transferrin and attaches on the mold through an inducible receptor and finally the iron is transported intracellularly by active reduction of ferric to soluble ferrous form.[1][30][35]

Thus patients undergoing dialysis who are treated with iron chelator deferoxamine are susceptible to mucormycosis, also patients with myelodysplastic syndrome are prone to mucormycosis due to iron overload resulting from repeated blood transfusions another mechanism form obtaining iron is from hemoglobin which also explains the angioinvasive nature of R.oryzae[9][37][45]

Iron further enters fungi by the aid of high affinity iron permease (expressed by ftr1 gene) , present in fungi as a part of reductive system containing surface reductases which reduce ferric to more soluble ferrous ion, the ferrous ion so formed is then captured by protein complex consisting of multicopper oxidase and ferrous permease[13][51][66]

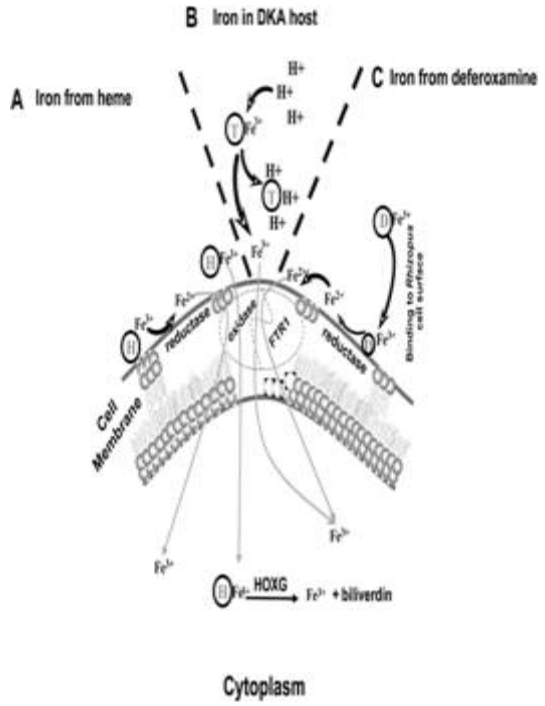

Figure 1.1 Entry of Organism Into Host Cell

Treatment

Factors eradicating mucormycosis:

1. Rapidity of diagnosis
2.treatment of predisposingunderlying conditions.
3. surgical debriment of infected tissue (if possible).
4. antifungal therapy.

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Early diagnosis may help in surgical excision of focal lesion before the infection spread

Role of surgery

Mucormycosisis rapidly progressive, antifungal therapy alone is often inadequate to control the infection. Numerous agents of mucormycosis vary in susceptibility to the antifungal therapy ; some strains may be highly resistant to amphotericin B. Furthermore, the hallmark angioinvasion, thrombosis, and tissue necrosis of this disease result in poor dissemination of anti-infective agents to the site of infection. Therefore, even if the causative organism is susceptible to the surgery is necessary due to the massive amount of tissue necrosis occurring during mucormycosis, which may not be prevented by killing the organism. Surgical debridement of infected and necrotic tissue should be performed on an urgent basis.[28][36][41][47]

In rhinocerebralmucormycosis, early surgical excision of the infected sinuses and appropriate debridement of the retro-orbital space can often prevent the infection from extending into the eye, thereby obviating the need for enucleation and resulting in extremely high cure rates .Repeated surgical exploration of the sinuses and orbit ensures that all necrotic tissue has been debrided and the infection has not advanced. Nonetheless, the observational clinical data support the concept that surgical debridement is necessary to optimize cure rates.[26][32][52][57]

In patients with pulmonary mucormycosis, surgical treatment plus antifungal therapy also greatly improves outcome compared to the use of antifungal therapy alone.Finally, localized (nondisseminated) cutaneous mucormycosis treated with aggressive surgical debridement and adjunctive antifungal therapy has a mortality of <10% A similar experience has been described with isolated renal mucormycosis. However, because surgical debridement of necrotic tissue is often highly mutilating, if the patient survives the acute phase of the disease, major reconstructive surgery may be necessary.[10][13][36][48][69]

Antifungal therapy

A major hindrance in choosing antifungal therapy is lack of available clinical trials

An added barrier to clinical trials of mucormycosis is the appalling rate of success of monotherapy. Due to low success rate, it might be considered unscrupulous to randomize patients in a clinical trial to any “less intensive” regimen

Polyene: amphotericin b has shown activity against a broad causative species of mucormycosis ,amphotericin B deoxycholate and its lipid derivatives,

recommended dose of amphotericin B deoxycholate has been 1 to 1.5 mg/kg/day which results in a very high toxicity rate.

The lipid formulations of amphotericin are significantly less nephrotoxic than amphotericin B deoxycholate and can be safely administered at higher doses for a longer period of time. However, the use of increased dosing for lipid-based amphotericin also increases costs enormously also the available animal data showing superiority of liposomal amphotericin B over amphotericin B deoxycholate[21][34][46][51][58]

Azoles.

Itraconazole is the only marketed azole drug that has in vitro activity against Mucorales but ineffective in vivo.

In experimental animal models of disseminated mucormycosis, posaconazole is more efficacious than itraconazole but less efficacious than amphotericin B deoxycholate[38][64][65]

Studies proved that R. oryzae expresses the target enzyme for caspofungin and in the murine model of disseminated mucormycosis, caspofungin did have limited activity against R. oryzae . Furthermore, it came to light that the combination of caspofungin (1 mg/kg/day) plus amphotericin B lipid complex (5 mg/kg/day) was synergistic.While either therapy alone mediated no survival benefit, the combination significantly improved survival

These data recommend that echinocandins may have a part as a second agent, particularly in combination with a polyene, in serious cases of mucormycosis.[34][47]

Miscellaneous:

1.the gene encoding high-affinity iron permease (FTR1) is expressed by R. oryzae during murine infection and inhibition of FTR1 gene expression by RNA-I, or reduction of FTR1 copy number by gene disruption reduces the virulence of the fungus in animal models of mucormycosis ,

passive immunization with anti-Ftr1p immune serum protected mice with DKA from infection with R. oryzae

Thus, FTR1 is a crucial virulence factor for R. oryzae, and anti-Ftr1p passive immunotherapy represents a promising strategy to improve outcomes of deadly mucormycosis.

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2. Study reports have suggested that hyperbaric oxygen may be a valuable adjunct to the standard surgical and medical antifungal therapy of mucormycosis, predominantly for patients with rhinocerebral disease,
higher oxygen pressure improves the ability of neutrophils to kill the organism
Additionally, high oxygen pressure inhibits the germination of fungal spores and growth of mycelia in vitro however the outcome of patients with mucormycosis remains to be established through appropriately controlled prospective clinical trials.[22][26][41]

3. The role of adjunctive cytokine therapy for mucormycosis has been understudied. Cytokines that activated phagocytic activity, such as gamma interferon and granulocyte-macrophage colony-stimulating factor, increase the ability of phagocytes to kill agents of mucormycosis in vitro.[3][43]

II. CONCLUSION

Mucormycosis is a life-threatening fungal infection characterized by host tissue infarction and necrosis that occurs mostly in immunocompromised patients, is associated with an cumulative incidence and mortality in spite of the availability of therapeutic tools.

Decisive whether the patient has invasive aspergillosis or mucormycosis could be thought-provoking at the bedside, new tools of molecular biology have been developed to obtain earlier diagnosis and start optimal medico-surgical treatment.

The vital role of iron in the organism's pathogenesis has only lately been determined. The interaction between the Mucorales and endothelial cells is also beginning to be understood. Both of these pathogenetic features of disease may be amenable to novel therapeutic intervention in the future.

Currently, novel regimens for the treatment of mucormycosis include combination lipid-based amphotericin plus either an echinocandin or itraconazole or both. As well, compassionate-use posaconazole is currently available, and its potential for combination therapy with a polyene, caspofungin, or both is admirable for study, novel iron chelator therapy may be useful as an adjunct to standard antifungal therapy. Finally, reversal of predisposing conditions, and aggressive surgical debridement remain cornerstones of therapy for this deadly disease.[35][47][51][64][65][66]

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