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A Review on Mucormycosis

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Abstract:
Mucormycosis is a opportunistic fungal infection that occurs in patients who are immunocompramised. The fungus which causing mucormycosis belongs to the class, zygomycetes and the order of mucorales. It is highly life-threatening mycotic infection that is characterised by angioinvasion, infarction, and tissue necrosis. The risk factors include uncontrolled diabetes mellitus in ketoacidosis, various forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation etc. The diagnosis is challenging and treatment should start as early as possible to decrease mortality. Diagnosis is based on symptoms such as, in case of sinusitis, sinus biopsies are required. Ear, nose and throat endoscopy should be done. Molecular identification of mucormycosis can help in confirming diagnosis and identify the fungus from genus to species level. Different techniques are as follows: DNA probes targeting 18S subunit, ITS1 sequencing after PCR with pan-fungal primers, 18S-targeted semi-nested PCR and real time PCR targeting cytochrome b gene. The therapeutic approach should be multimodal including anti-fungal agents, surgical debridement, and correction of underlying symptoms predisposing the patient to disease.

Key Words: mucormycosis, mucorales, ketoacidosis, angioinvasion, pan-fungal primers, ITS1 sequencing, surgical debridement.

Introduction

Definition:

Mucormycosis also called zygomycosis is a rare life-threatening fungal infection caused by exposure to mucormyetemolds characterised by headache, one-sided facial swelling, black lesions on nasal bridge or upper inside of mouth that quickly become more severe that occurs in patients who are immunocompromised because of diabetic ketoacidosis, neutropenia, organ transplantation, and/or increased serum levels of available iron.

Types of Mucormycosis:

Rhinocerebral(sinus & brain) mucormycosis is an infection that occurs in sinuses that spreads to the brain.

Pulmonary (lung) mucormycosis is the common type of infection that occurs in people with cancer and in people who had an stem cell or a organ transplant.t

Gastrointestinal mucormycosis is common in young children than adults especially in premature and low birth weight infants who had antibiotics, surgery or medications that lower the body's ability to find germs and sickness.

Cutaneous (skin) mucormycosis- it occurs when the fungi enter the body through a break in the skin. It is most common in the people with weekend immune systems.

Disseminated mucormycosis- it occurs if the infection spreads throughout the blood stream that affect any another part of the body. It mainly affects brain in addition to other organs such as spleen, heart & skin.

Etiology:

It is an infectious disease caused by a fungus belongs to the class of zygomycetes and the order of mucorales and the species most frequently isolated from patients are Apophysomyces *variabilis,* Cunninghamella *bertholletiae,* Lictheimia *corymbifera,* L.*raosa,* Mucor *circinelloides,* Rhizopus *arrhius(oryzae),* R. *Microsporus,* Rhizomucor *pusillus,* and Saksenae *vasiformis.*

Immunosuppressant patients(such as transplantation, HIV, patients on chronic steroids, anti-rheumatic medications, cancer.

Uncontrolled diabetes mellitus especially with diabetes ketoacidosis.

Epidemiology:

It is an Angio-invasive fungal infection associated with high morbidity & mortality. The rise of mucormycosis infection has been perceived globally, but it is very high in Asian continent especially in india and china among patients with uncontrolled diabetes mellitus. A study shown that 88% of patients with Rhino-orbito-cerebral mucormycosis had diabetes mellitus, 32-40% with pulmonary mucormycosis had haematological malignancy followed by diabetes, 5.4-14% with renal mucormycosis, 13% with disseminated mucormycosis.

Clinical Presentations:

Uncontrolled diabetes with ketoacidosis.

Cerebral extension with high mortality.

Rhino-orbito-cerebral mucormycosis: Non-opthalmic symptoms- fever, headache, facial swelling, nasal discharge, epistaxis, sinusitis, nasal ulceration, tooth ache, hemiplegia, facial numbness, facial nerve palsy, bone destruction, altered mental status.

-Ophthalmic symptoms- eye pain, decreased vision, opthalmopegia, proptosis, chemosis, ptosis, orbital cellulitis, periorbital discolouration and necrosis.

Pulmonary mucormycosis- fever, persistent cough, pleuritic chest pain, dyspnoea, haemoptysis. Imaging studies show lung infiltration and consolidation, multiple nodules, pleural effusion, thickly walled cavities, hilar or mediastinal lymphadenopathy, air crescent sign, pneumothorax.

Cutaneous mucormycosis-initially, lesions are indurated plaques that are erythematous to purple that becomes necrotic, other presentations include targetoid lesions, ulcers, tender nodules, purpuric lrsions, swollen and scaly plaques.

Gastrointestinal mucormycosis- abdominal pain, gastrointestinal bleed, abdominal distension, diarrhoea

Renal mucormycosis- fever, flank pain, anuria or haematuria

Predisposing Factors:

Diabetes mellitus with or without diabetic ketoacidosis
Malignancies (haematological and solid organ tumor)
Transplant recipients (haemopoietic stem cell and solid organ transplants)
Corticosteroid therapy
Neutropenia
HIV infection
Intravenous drug use
Low birth weight infants

Malnutrition
Liver diseases
Chronic alcoholism
Chemotherapy
Use of calcineurin inhinitors
Chronic kidney disease

Pathogenesis

Host Defenses

Both mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and cationic peptides defenses [Fig1]. Clinical evidence demonstrates that these phagocytes are the major host defense mechanism against mucormycosis. For example, neutropenic patients are at increased risk of developing mucormycosis. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the organisms by both oxidative and nonoxidative mechanisms.

The exact mechanisms by which phagocytes are impaired by ketoacidosis, diabetes mellitus, and corticosteroid are yet to be determined. Furthermore, phagocyte dysfunction alone cannot explain the high incidence of mucormycosis among patients with DKA, because the incidence of mucormycosis among these patients is increased more than the incidence of infections caused by other pathogens.

The skin barrier represents a host defense against cutaneous mucormycosis, as evidenced by the increased risk for developing mucormycosis in persons with disruption of this barrier. The agents of mucormycosis are typically incapable of penetrating intact skin. However, burns, traumatic disruption of the skin, and persistent maceration of skin enables the organism to penetrate into deeper tissues.

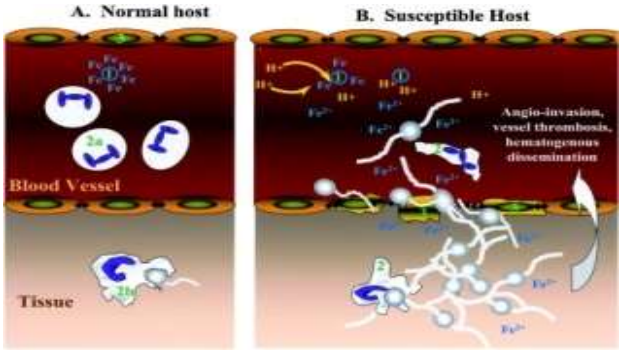

Fig.3. Pathogenetic mechanisms of and host defense mechanisms against mucormycosis. To cause disease, the agents of mucormycosis must scavenge from the host sufficient iron for growth, must evade host phagocytic defense mechanisms, and must access vasculature and disseminate. A) In a normal host, primary defense mechanisms against mucormycosis include sequestration of iron in serum by specialized iron-binding proteins (1), phagocytes including circulating neutrophils (2a) and tissue macrophages (2b), and endothelial cells (3), which regulate vascular tone and permeability. Acting in concert, these mechanisms prevent establishment of infection in tissue and subsequent endovascular invasion. B) In susceptible hosts, normal defense mechanisms breakdown. For example, in diabetic ketoacidosis (DKA), the acidic pH of the serum causes dissociation of free iron from sequestering proteins (1). This release of free iron allows rapid fungal growth. Defects in phagocytic defense mechanism (2), for example, deficiency in cell number (neutropenia) or functional defects caused by corticosteroids or the hyperglycemia and acidosis of diabetic ketoacidosis, allow proliferation of the fungus. Finally, adherence to and damage of endothelial cells by the

fungus (3) allows fungal angioinvasion and vessel thrombosis and subsequent tissue necrosis and dissemination of the fungal infection.

Role of iron in pathogenesis:

A recently identified important clinical feature is the increased susceptibility to mucormycosis of patients with elevated available serum iron. In addition to host factors that predispose patients to mucormycosis, Mucorales possess virulence factors that enable the organism to cause disease. One such trait is the ability to acquire iron from the host. Iron is an essential element for cell growth and development, contributing to many vital processes of the cell. Therefore, successful pathogens use multiple processes for obtaining iron from the host.

The clinical observation that patients with DKA are uniquely susceptible to mucormycosis lends support to the role of iron uptake in the pathogenesis of the disease. Patients with DKA have elevated levels of free iron in their serum, and such serum supports growth of R.oryzae at acidic pH(7.3-6.88) but not at alkaline pH(7.78-8.38). Furthermore, adding exogenous iron to serum allowed R.oryzae to grow profusely at acidic conditions but not at pH≥7.4.

Fungal-Endothelial Interactions

A hallmark of mucormycosis infections is the virtually uniform presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. This angioinvasion is associated with ability of the organism to hematogenously disseminate from the original site of infection to other target organs. Hence damage of and penetration through endothelial cells lining blood vessels is likely a critical step in the organism's pathogenetic strategy. R.oryzae spores but not germlings (i.e., pregerminated spores) have the ability to adhere to subendothelial matrix proteins including laminin and type IV collagen invitro. The disparity of spore and germ tube adherence to subendothelial matrix proteins but equivalent adherence to endothelial cells indicates that R.oryzaeadhesins to endothelial cells are likely distinct from the adhesins used to bind to subendothelial matrix proteins. In a subsequent pilot study, intravenous administration of four doses of heat-killed R.oryzaeblastospores resulted in a 40% mortality in diabetic mice (unpublished observations). The precise mechanisms by which dead R.oryzae mediates tissue injury remain unclear. Nevertheless, the clinical implication is that simply killing R.oryzae once it has already established a presence in tissue may not prevent subsequent tissue injury, perhaps in part explaining the lack of efficacy of cidal antifungal agents during clinical disease.

Diagnosis:

Mucormycosis is difficult to diagnose. Diagnosis is often delayed, and disease tends to progress rapidly.

No antigen detection tests and standardised blood polymerase chain reactions are available for diagnosis of mucrormycosis so analysis of biological specimens, tissue biopsies for histopathology and culture from clinically involved sites are mandatory for diagnosis.

Imaging- MRI may demonstrate variable T1 & T2 intensity with focal lack of enhancement in areas of devitalized sinus mucosa.

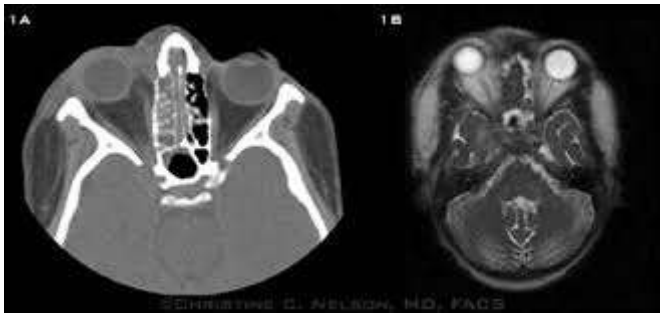

Fig.1.(1A). CT of orbits showing opacification of right paranasal sinus. (1B). MRI demonstrates correlating nonenhancement of right nasal sinus mucosa

With involvement of cavernous sinus, CT scans may show lack of enhancement in this region, which is consistent with thrombosis from the invasive fungus

Other radiographic findings of mucormycosis include a rim of soft tissue thickness along with paranasal sinuses, opacification of sinuses, fluid levels in sinuses, bone destruction. Because these are often nonspecific findings, it is difficult to differentiate mucormycosis from other sinoorbital conditions. Therefore, once the diagnosis of mucormycosis has been made, CT and MRI can help to delineate the extent of infection and can guide surgical debridement.

Biopsy- The fungal invasion may be patchy, so multiple biopsies nay be required for diagnosis. Biopsy may need to be repeated if initial biopsies are negative, yet the patients has signs of progressive orbital involvement and imaging reveals affected sinuses.

Histopathology with special stains-such as Grocott-Gomori methenamine-silver nitrate, periodic acid-Schiff, or calcofluor white- demonstrates the pathognomonic broad, irregular, nonseptate, and right-angle branching hypae. Evidence of angioinvasion and tissue infarction may also observed.

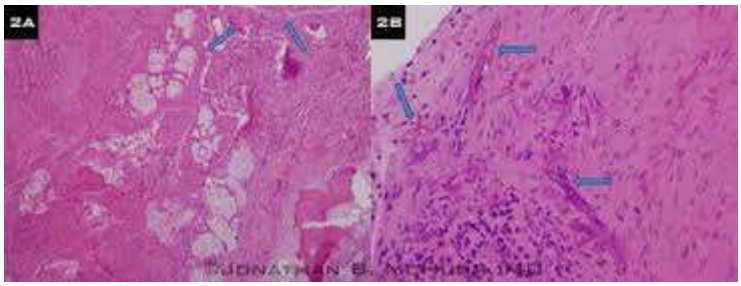

Fig.2.(2A). Low-power view of fungal sinusitis with extensive tissue necrosis in the absence of strong inflammatory response. Rare Mucor organisms(arrows) can be seen invading adjacent tissue to the areas of necrosis. (2B). Mucorales organisms can be seen invading connective tissue(arrows). Typical hyphae forms are broad with irregular, thin, non-parallel cell walls lacking septae.

Treatment for Mucormycosis

Successful treatment of Mucormycosis requires four steps:-

Early diagnosis
Reversal of underlying predisposing risk factors, if
Surgical Debridement where applicable
Prompt Antifungal Therapy

Early diagnosis- A recent study from chamilos et al quantified the benefit of early initiation of polyene antifunal therapy. They reported that it treatment labs initiated within 5 days of diagnosis of Mucormycosis, so survival was Markedly improved compared to initiation of polyene therapy at $\geq$ 6 days. After diagnosis

(83% VS49% survival0 Mucormycosis in patients with cancer could be distinguished from aspergillosis on the basis of sinusits, presence of Multiple nodules by CT Scan, and Pleural Effusion.

Reversal of underlying disease-

Immunosuppresive Medications, particularly corticosteroids, shouldbe dose reduced or stopped if at all possible. Aggresive management to rapidly restore euglycemia and normal acid-base status is critical in diabetic patients in ketoacidosis. Administration of iron should be avoided because it exacerbates the severity of infection in animal model of Mucormycosis so it may be advisable to minimize blood transfusions, if feasible.

Surgical management-Blood vessel thrombosis and resulting tissue necrosis during Mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be eritical for complete eradiation of Mucormyco sis. Furthermore, in mutltiple case series, patients who not undergo surgical debridement of Mucormycosis had a far higher mortality rate than patients who undergowent surgery.

Anti-fungal Therapy:- First time monotherapy options:- In general, primary antifungal therapy for mucormycosis should be based on a polyene, if possible although amphotericin B deoxy cholate (AMB) was the conerstone of Mucormycosis therapy for decades, lipid formulations of AMB arc significantly less Nephrotonic and can be safely administered at higher doses for a longer period of time than AMB furthermore, treatment of Mucormycosis with liposomal amphotericin B (LAMB) was associated with a 67% survival rate, compared to 39% survival rate, compared to 39% survival when patients were treated with AMB = 0.02

Fluconazole, voriconazole, and itraconazole do not have reliable activity against Mucormycosis and the posaconazole is relatively in effective for the treatment of Mucormycosis. In pre-clinical animal models. The efficacy of posaconazole as a treatment option is further called into question by reports of Mucormycosis developing as a breakthrough infection.

Combination antifungal therapy for mucormycosis:- It is now known that R oryzae exprebbes the target enzyme for echinocandins. In DKA Mice infected with R. Oryzae, Combination caspofungin plus. ABLC therapy markedly improved survival compared to either monotherapy.

Reference:

1. Hernández JL, Buckley CJ. Mucormycosis. [Updated 2020 Jun 26]. In: Statpearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. https://www.ncbi.nlm.nih.gov/books/NBK544364/
2. Ashraf S. Ibrahim, Brad Spellberg, Thomas J. Walsh, and Dimitrios P. Kontoyiannis. Pathogenesis of Mucormycosis. Clin Infect Dis. 2012 Feb 1; 54(Suppl 1): S16-22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3286196/
3. Anna Skiada, Fanny Lanternier, Andreas H. Groll, et al., Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 2013 Apr; 98(4): 492-504. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659979/
4. Gary M Cox, MD. Mucormycosis(zygomycosis) [Updated Jan 04, 2021]. https://www.uptodate.com/contents/mucormycosis-zygomycosis/print
5. Centers for Disease Control and Prevention. Fungal Diseases. [Online Updated Jan 14,2021]. https://www.cdc.gov/fungal/diseases/mucormycosis/definition.html
6. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. J Fungi (Basel). 2019 Mar 21;5(1):26. https://pubmed.ncbi.nlm.nih.gov/30901907/

7. Ana Daniela Castrejón-Pérez, Esperanza C. Welsh et al., Cutaneous Mucormycosis. Ana Bras Dermatol. 2017 May-Jun; 92(3): 304-311. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5514567/#__sec4title
8. Brad Spellberg, John Edwards, Jr., and Ashraf Ibrahim. Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management. Clin Microbiol Rev. 2005 Jul; 18(3): 556-569. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1195964/
9. Oliver A Cornely, et al., Global guidelines for the diagnosis and management of mucormycosis; an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. November 04, 2019. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30312-3/fulltext
10. Courtney Y. Kauh, MD, MS, et al., Diagnosis and Management of Orbital Mucormycosis. [online June 2014]. https://www.aao.org/eyenet/article/diagnosis-management-of-orbital-mucormycosis#Fig.%201