

REVIEW ARTICLE

Mucormycosis: A Brief Review

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Abstract

Mucormycosis is an angio invasive infection 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 though the aggressive treatment is given. The main aim and purpose of this review related to overview and Etiopathogenesis of Mucormycosis, fatality of rhinocerebral Mucormycosis, recent advances in diagnostic and treatment methods.

Keywords: *Diabetes mellitus* (DM), Rhinocerebral Mucormycosis, Fungal invasion.

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INTRODUCTION

American pathologist R.D. Baker coined the term Mucormycosis. It is also known as Zygomycosis. It can be defined as an insidious fungal infection caused by members of Mucorales and zygomycotic species¹. Mucormycotina are the common saprobes originating from the rotten matter or soils. Infections with Mucorales are categorized by rapid progression¹.

History

In 1885, the German pathologist Paltauf, reported the first case of Mucormycosis and described it as Mycosis Mucorina². During 1980s and 1990s Mucormycosis was increasingly seen among immuno compromised individuals³. Based on the prevalence rate, a study carried out in France reported amplification by 7.4% per year⁴. Worldwide occurrence along with the possibility of seasonal variation of mucorales infection has been reported⁵.

Etiopathogenesis

Mucorales attack deep tissues by means of ingestion or inhalation of spores, and percutaneous injection of spores. As soon as the spores penetrate into lung or cutaneous tissues, the first line of defence in the healthy host is capable of destroying the spores via oxidative metabolites and cationic peptides⁶. Risk factors include uncontrolled diabetes mellitus, especially ketoacidosis, steroid use, extremes of age, neutropenia; especially with haematological malignancy, AIDS, renal insufficiency, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition⁷.

In diabetic patients, mucormycosis occurs as a destructive and potentially critical condition due to augmented availability of micronutrients and diminished defence mechanism of the body⁷. Various hypotheses include (i) Low serum inhibitory activity against Rhizopus species, (ii) Improved availability of iron for the pathogen at decreased PH level and (iii) Pulmonary macrophages of persons with diabetes mellitus show diminished facility to inhibit germination of Rhizopus species^{8,9,10}. Ketone reductase in Rhizopus allows the organism to increase the glucose and acidic environment.

In DM particularly with ketoacidosis

all types of mucormycosis will occur^{11,12,13,14}. Neutrophils play a major role in host defence against mucorales. Its function is impaired at different level in DM^{10,11,15}. Ketoacidosis in diabetes accelerate the fungal invasion¹⁶. The acidic milieu produces more free iron by reducing its binding to transferrin and low level of dialyzable inhibitory factor in diabetics present suitable conditions for fungal duplication¹⁷. Mortality rate was reported 90% or even more with Mucormycosis, before the administration of amphotericin B and radical surgery¹⁸.

Severely neutropenic patients and those who lack phagocytic function are more prone for mucormycosis. But it's not same in the case of AIDS patients¹⁹. It implies that the T lymphocytes are not significant for inhibiting fungal proliferation but only the neutrophils. Prolonged administration of voriconazole, principally among the patients with haematological malignancies and hematopoietic stem cell transplants are more prone for mucormycosis^{20,21,22,23,24}. Moreover mucormycosis is also seen in patients without any obvious immune-deficiency²⁵. In such conditions, it may be related with burns, trauma and or allied with iatrogenic factors^{26,27}.

Clinical Presentations and Manifestations

Infection of Mucormycosis in human beings occurs in two types. 1 Superficial and Visceral and 2. Localized and Disseminated. Superficial form occurs in external ear, fingernails, skin. Visceral forms are manifested as pulmonary, gastrointestinal and rhino cerebral types. Entry of these spores may takes place either through cutaneous or respiratory route. (E.g. spread of spores during intake of soiled food or by tainted needles)²⁸.

Rhinocerebral Mucormycosis

Incidence of Rhinocerebral Mucormycosis is 33 - 50%. *Apophy-somyces elegans* is considered as the presumptive aetiological agent²⁹. An infection that begins from paranasal sinuses, subsequent inhalation of spores, and probable extension to the brain and successively, sinuses, nose and eyes are affected. Its clinical manifestation starts with palatal and sinuses necrosis, further enters to the orbit prior to getting intra-cranial structures. Symptoms include fever, blindness, exophthalmos, nose-bleed, facial paralysis and signs of invasion of the trigeminal

nerve. Cavernous sinus thrombosis will be the effect of unsettled rhino-sinus mucormycosis. Appearance of reddish - black nasal turbinate and septum along with a nasal discharge is also seen. Progression of disease into cranial vault leads to blindness, lethargy and seizures followed by death²⁸. According to Lanternier et al., this infection shows varying clinical appearance with increased incidence of primary skin infection and a significant prognosis predisposed by localization³⁰. In USA, the prevalence of mucor infection is around 500 individuals a year³¹. It is 10 to 50 times fewer than candidiasis or aspergillosis³². Occurrence of mucormycosis may possibly be around 2 - 3% among allogenic bone marrow transplant patients^{33,34}.

Radiographic Features

Opacification of the sinuses may be observed in conjunction with patchy effacement of bony walls of sinuses. In cavernous sinus thrombophlebitis mucor infection can interpret with "Black turbinate sign" which refers to an area of non-enhancing mucosa on MRI³⁵. A radiographic or CT scan of the head may show thickened mucosa or cloudy sinuses, densely crowded extra ocular muscles, enlarged compactness of the orbital apex, proptosis and inflammation of the optic nerve³⁶. The development of micro nodules along with additional ten nodules were found out in the visualization of lung in pulmonary Mucormycosis, which is in accordance with the findings of Chamilos et al.^{37,38}.

Histopathological Features

On examination, the affected tissue with lesions show extensive necrosis with numerous large branching pale-staining, wide, flat non-septal hyphae with branching at right or obtuse angles. Round or ovoid sporangia are also frequently seen in culture. Thin - walled hyphae (infrequently septae) with non - parallel sides ranging from 3 to 25µm in diameter, branching irregularly and often with bulbous hyphal swelling. Necrotic tissue containing hyphae might be seen with signs of angio - invasion and infarction are seen; in non granulocytopenic conditions, infiltration of the neutrophils and with chronic infection granuloma formation will also be observed.³⁹ Gomori Methamine Silver (Grocott) or Periodic - acid Schiff are the staining of choice.

Diagnostic Method

Diagnosis of mucormycosis includes cautious evaluation of clinical manifestations, magnetic resonance imaging modalities, utilization of computed tomography (CT) in the early stages, specialist assessment of cytological and histological provision, finest application of clinical microbiological technique and execution of molecular detection⁴⁰. Detection of host factors contribute extensively to the estimation of a patient's possibility for invasive mucormycosis. PAS stains, direct examination, calcofluor, histopathological examination, Gomori methenamine silver stain, culture, molecular methods and fluorescent in situ hybridization are the various laboratory techniques for detecting mucor⁴⁰. According to Kontoyiannis et al., a major problem in the identification of mucormycosis includes its indefinable clinical appearance and recurrent occult distribution, and hence a need for a sensitive nonculture-based investigative method is required. Gold standard analytic technique for confirmation is the tissue based analysis²⁰.

Differential Diagnosis

Differential finding of mucormycosis include maxillary sinus neoplasia, maxillary sinus aspergillosis, soft tissue infarction, soft tissue radio necrosis, other deep fungal infections⁴¹.

Treatment

Successful treatment for mucormycosis includes rapid accurate diagnosis, surgical debridement, and administration of drugs, adjunctive application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte and prosthetic obturator^{42,46}. According to Spellberg et al., currently available monotherapy shows high mortality rate especially with haematology patients and hence proposed the choice of "Combination therapy" for Mucormycosis⁴².

Antifungal therapies include AmB Dexycholate, Liposomal AmB (5-10mg/kg), AmB lipid complex, AmB colloidal dispersion, Posaconazole (400mg bid) and manage of core conditions. Second-line treatment includes combination of caspofungin and lipid AmB, mixture of lipid AmB and Posaconazole, not grouping with Deferasirox is suggested⁴³.

In case of soft tissues, cerebral disseminated, localized pulmonary lesion and rhino-orbito- types surgical treatment should be considered⁴³.

Prognosis and Morbidity Rate

The prognosis generally depends on the extent of manifestation of the disease and effective treatment initiated in response to the diseases. The survival rate for rhino-cerebral disease in patients without systemic diseases is about 75%; with other diseases is about 20%; and in pulmonary disease is considered to be fatal.

Survival rate varies with foci of the infection: rhino cerebral mucormycosis – 45%, focal cerebral mucormycosis – 33%, pulmonary forms – 36%, sinusitis without cerebral involvement – 87%, cutaneous isolated – 90%, disseminated disease – 16%, and involvement of gastro intestinal form – 10%^{44, 45}.

Better survival rate can be achieved in patients with low baseline serum concentration of iron / ferritin, neutropenia and malignant cases which is not associated with infection⁴¹.

CONCLUSION

To conclude, mucormycosis is a disease which usually shows aggressive and an alarming mortality rate. However the actual etiopathogenesis remains varied throughout the world, diagnosis of this disease remains a challenge for the clinicians. But still in the view of its high mortality rate, (i) early and prompt diagnosis, (ii) recovery from the predisposing factors, (iii) early intervention with surgical debridement and therapeutic drugs are the only hopes to improve the condition from this devastating disease.

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CONFLICT OF INTERESTS

The authors declares that there is no conflict of interest.

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