European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 07, Issue 03, 2020

MUCORMYCOSIS - A REVIEW

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Abstract: Mucormycosis is a rare angio invasive infection mainly recognized in immunocompromised patients which occurs due to the fungi mucorales. This rare fungal infection can be classified into rhino-orbitocerebral, cutaneous, disseminated, gastrointestinal, and pulmonary types. Inspiote of aggressive treatment once detected or diagnosed overall increased mortality rate is reported. This review aims in providing with brief details regarding the Etiopathogenesis of Mucormycosis, fatality of rhinocerebral Mucormycosis along with recent advances in diagnostic and treatment methods.

Keywords: Mucormycosis, Diabetic ketoacidosis, PAS stain, Antifungal Theraphy.

1. INTRODUCTION

The term Mucormycosis was given by the American pathologist R.D.Baker and it can also be called as Zygomycosis. Mucormycosis is defined as an insidious fungal infection caused by members of Mucorales and zygomycotic species[1].Mucormycotina falls under the common saprobes which are found in rotten matter or soils. Infections due to Mucorales are categorized by rapid progression[1]

2. HISTORY

The first reported case of Mucomycosis dates back to 1885 when the German pathologist Paltauf described the first case as Mycosis Mucorina [2]. Rate of mucormycosis increased rapidly mostly in immunocompromised individuals consequently in 1980s and 1990s [3]. Thus a study was carried out depending upon the prevalence rate in France which showed amplification by 7.4% per year [4]. The supposed possibility of seasonal variation of mucorales and its occurrence all over the world was also reported [5] **.**

ISSN 2515-8260 Volume 07, Issue 03, 2020

ETIOPATHOGENESIS

Deep tissues most effectively get affected by mucorales by the means of ingestion or inhalation of spores, and percutaneous injection of spores. But even if it enters the lung or cutaneous tissues the first line of defense action in a healthy body eliminates the spores with the help of oxidative metabolites and cationic peptides [6] but this becomes a topic of concern in the presence of debilitating diseases like diabetes, especially ketoacidosis, when body under steroids, old age, neutropenia or any other hematological malignancies, AIDS, condition like renal insufficiency, underwent any organ or stem cell transplantation iron overload, any types of trauma to skin, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole mainly given for aspergillosis and malnutrition [7] . Mucormycosis appears as a destructive and potentially critical condition in diabetic patients due to increased availability of micronutrients and reduced defence mechanism of the body [7]. Various hypotheses include-

(i) Serum inhibitory activity appears to be low against Rhizopus species,

(ii)With the reduction in PH level iron availability for pathogen improve drastically.

(iii)Capability of pulmonary macrophages of diabetes mellitus patients to inhibit germination of Rhizopus species appear to be reduced [8,9,10].

The glucose and acidic environment is effectively raised in presence of Ketone reductase produced by Rhizopus species. There is a chance of occurrence of every types of mucormycosis in patients with DM especially with Ketoacidosis [11,12,13,14]. An important role in host defence mechanism is played by Neutrophil against mucorales so in case of host affected with DM function of it gets impaired at each level of DM [10,11,15]. Moreover ketoacidosis in diabetes helps to further accelerate the fungal invasion [16]. The acidic background results in more free iron production by reducing its binding to transferrin and low level of dialyzable inhibitory factor in diabetics provide suitable conditions for fungal duplication [17] 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 [18]. Severely neutropenic patients and those who lack phagocytic function thus come under the highly risk category of developing mucormycosis. But it's not same in the case of AIDS patients [19] thus implying that the T lymphocytes are not that important for hampering the fungal proliferation but only the neutrophils. Patients undergoing long term administration of voriconazole especially those with haematological malignancies and hematopoietic stem cell transplants are considered to be more prone for mucormycosis[20, 21, 22 ,23 ,24]. Apart from that mucormycosis infection also can occur in patients without notable immune-deficiency condition [25]. Most of the time such conditions are related with burns, trauma and or allied with iatrogenic factors [26,27]

CLINICAL PRESENTATIONS AND MANIFESTATIONS

Infection of Mucormycosis in humans occur mainly in two forms [1] Superficial and Visceral and [2]. Localized and Disseminated. The characteristic superficial form are seen in external ear, fingernails 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) [28].

ISSN 2515-8260 Volume 07, Issue 03, 2020

RHINOCEREBRAL MUCORMYCOSIS

The prevalence of Rhinocerebral Mucormycosis is about 33 - 50%. Presumably Apophysomyces elegans is regarded as the aetiological agent [29]. This type of Mucormycosis infects that paranasal sinuses with subsequent inhalation of spores, and later can extend to the brain resulting in successive infection of sinuses, nose and eyes appropriately giving the term Rhinocerebral Mucormycosis. Its clinical manifestation characterized by palatal and sinuses necrosis which further extends to the orbit before affecting the intra-cranial structures. Symptoms often manifested are fever, often accompanied by blindness, exophthalmos, bleeding from nose, facial paralysis and signs of invasion of the trigeminal nerve. Cavernous sinus thrombosis marks the effect of unsettled rhino-sinus mucormycosis. Sometimes reddish - black nasal turbinate and septum along with a nasal discharge can be seen. As the disease progresses into cranial vault it results in blindness, lethargy and seizures often followed by followed by death if still left untreated [28]. Lanternier et al., pointed out the diversity in clinical manifestation of this infection with increased degree of primary skin infections and a significant prognosis predisposed by localization [30].The incidence of mucor infection in USA is roughly 500 individuals per year [31]. So in comparison to that of candidiasis or aspergillosis it is 10 to 50 times fewer [32]. Percentage of occurrence of mucormycosis may be only 2 - 3% among the patients with allogenic bone marrow transplant [33, 34]

HISTOPATHOLOGICAL FEATURES

On histological examination, extensive necrosis is manifested in the affected tissue along with numerous large branching pale-staining, wide, flat non-septal hyphae with branching at right or obtuse angles. The culture often presents with typical round or ovoid shaped sporangia. Hyphae which have thin wall (infrequently septae) and 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 [35] 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 mucor [36]. Maxillary sinus neoplasia, maxillary sinus aspergillosis, soft tissue infarction, soft tissue radio necrosis, other deep fungal infections are the differential diagnosis [37].

TREATMENT

Treatment success for mucormycosis lies in impromptu and accurate diagnosis, followed by surgical debridement and administration of drugs, with additional application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte and prosthetic obturator. According to Spellberg et al., high mortality rate especially with hematology patients can be noticed with recent availability of monotherapy and hence proposed the choice of "Combination therapy" for Mucormycosis [38]. Coventional antifungal therapies mainl;y consisting of AmB Dexycholate, Liposomal AmB (5-10mg/kg), AmB lipid complex, AmB colloidal dispersion, Posaconazole (400mg bid) and with subsequent management of core conditions. Second-line of treatment goes with mixture of caspofungin and lipid AmB, a combination of lipid AmB and Posaconazole, not

grouping with Deferasirox is suggested. In case of soft tissues, cerebral disseminated, localized pulmonary lesion and rhino-orbito- types surgical treatment should be considered [39].

PROGNOSIS AND MORBIDITY RATE

The prognosis largely depends on the disease extension and subsequent effective treatment given in response to the diseases. 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% 40. 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 infection [37]

3. CONCLUSION

Though the etiopathogenesis of this disease differ in all over the world its manifestation can be very aggressive and having an alarming mortality rate if not treated in proper time. Thus it serves as a challenge to many clinicians. So by keeping its high mortality rate in mind, success to treat this infestion efficiently lies within early and prompt diagnosis, attempt for recovery from the predisposing factors. With early intervention with surgical debridement and therapeutic drugs condition of this deadly disease can also be improved.

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