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MUCORMYCOSIS (Black Fungus) – An Encyclopedic Review

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Abstract

Mucormycosis also acknowledged as black fungus is a deadly fungal disease with devastating mortality statistics as per recent reports. It is manifested clinically as rhinocerebral (the most common) followed by five more types on the basis of anatomical position namely disseminated, gastrointestinal, pulmonary, cutaneous and miscellaneous. The disease progresses on the basis of a variety of etiological factors/ pathologies, one of which is disorders caused by autoimmunity. There must be proper knowledge regarding its mechanism and pathogenesis of all the six clinical types for relatable diagnosis and treatment planning.

Key Words: Disease, Fungus, Rhinocerebral, Prevalence

Introduction

Mucormycosis is still considered as a tedious infection with distressing adverse impact on the population regardless of latest technological advances in early detection. The causative agent of black fungus belongs to the family mucorales. In approximately 70% of the cases of the infection, microorganism named *Rhizopus oryzae* is most frequently discovered and isolated on examining patients [1].

Incidence & Prevalence:

Hyphae vigorously invade in the vasculature after having an interface particularly with endothelium and as a consequence, tissue necrosis and infarction of the host begins. Rhino-orbito-cerebral and pulmonary form of Mucormycosis are considered as most prevalent in terms of occurance. The incidence of cases are greater than before as reported lately perhaps because of augmented population at threat and superior diagnostic advances. For an instance, a study conducted in France reported an increase of black fungus occurrence by 7.3% annually [2].

A variety of pathogens cause human mucormycosis but its site is associated with *Rhizopus arrhizus* (mucorales). According to a retrospective French study, mucorales were spotted in 85% of clinical form rhino-orbital cerebral while only 17% of all other five types constitute this species in totality. This extensive difference in the percentage is because of the virulent dissimilarities amid mucorales [3].

Transmission :

The mucorale mechanism and routes of doorway into the host can be in the course of skin abrasion, ingestion of infected foodstuff, or abraded skin or inhaling gulp of air. Necrosis of tissues and thrombosis of blood vessels are the ultimate outcomes of mucormycosis due to its angioinvasion trait. Mucorale entry manifests into respiratory, digestive, cerebral, orbital and skin diseases. The severity of mucorales can result in increase in iron content, high sugar levels or diabetes and acidification of ketone bodies. Therefore, the virulence of mucormycosis makes the host susceptible to diabetic acidosis and chelating agent deferoxamine. GRP78 or glucose regulator protein present on the endothelial cells combines with protein named CotH/ spore-coating protein on *Rhizopus* surface resulting in angioinvasion. This interface ensues injury to the host and successive dissemination of fungi by hematogenous route [4]. The progression of *Rhizopus* is stimulated by increased iron content, glucose and ketone bodies which in turn provoke the binding capacity of the protein present on endothelial cells and on *Rhizopus* simultaneously. In result to these mechanisms, the capacity of mucorales to gain entry into the host is also amplified [5].

Risk factors:

Many factors are accountable for increased dominance and risk of mucormycosis. These include metabolic acidosis, unrestrained diabetes due to increased ketone bodies, trauma, organ transplantation, decreased neutrophil count, malignancies, and aided Desferal injections in patients with multiple blood transfusions and hemochromatosis [1, 6, 7]. In the developed countries like United states of America, prevalence of malignancies, ketoacidosis and kidney transplantation are spectacularly shooting especially in old age population due to which they are at a higher risk to develop mucormycosis at a later stage [8]. In patients with cyclic neutropenia or any other radiating disease , death rate proceed towards 50% or a total of 100% in some extreme cases, inspite of prescribing anti-fungal drugs and surgical debridement procedures [1]. There should be an urgent intervention of innovative and up to the minute procedures in order to avoid and treat mucormycosis with better remedies and regimens.

Clinical Presentation, Symptoms & Diagnosis

The aggressive occurance of rhino and non- rhino cerebral forms namely disseminated, gastrointestinal, pulmonary, cutaneous and miscellaneous are mainly due to deteriorated immunity or host defence mechanisms predominantly occurs in rhino-orbital-cerebral mucormycosis and rarely in non-rhino forms [10-13].

Rhinocerebral Mucormycosis:

In the most common and widespread form i.e. Rhinocerebral mucormycosis, in the initial stages, there is commencement of cellulitis/sinusitis [14, 15] facial palsy, pain in the eyes, succeeded by the beginning of redness of conjunctiva, decreased clarity and sharpness in vision, and swelling in the soft tissues [16, 17]. Fever may or may not occur [15], leucocytosis occurs if the person has efficiently working bone marrow [17]. The utility of extraocular muscle becomes disabled followed by exophthalmos and striking chemosis because of the pulling out of infection to the eyes from the ethmoidal air sinus if left untreated. There is a prominent and vigorous extension of infection into the adjoining tissues. During the initial stages of spread of *Rhizopus*, tissues may come out as healthy and normal on inspecting optically. After the incubation or latent period, the heterolateral eye start showing many signs and symptoms with consequential exophthalmos bilaterally, Conjuctival edema, blindness and occulomotor paralysis. There is a succession of grimy tissues in the course into the inflammatory stage along with edema, previous to developing violaceous. At the end, there is a progression of a mortified black colored slough/eschar infarction and blood vessel thrombosis [18, 19]. Hard palates becomes ulcerated and necrotic due to the spread of Infection into the oral cavity from the sinuses [19].

Pulmonary Mucormycosis:

Another form of mucormycosis is pulmonary type or zygomycosis. This type is comparatively uncommon occurring usually patients with very low immunity and is considered [20]. Higher blood glucose levels, neoplasm and organ grafting predisposes to pulmonary mucormycosis [21]. Pneumonia due to spore gulping came out to be the major etiology resulting in consequent necrosis and lung tissue infarction [22]. It also extend to heart and other tissues surrounding the mediastinum through hematogenous or direct route [23]. Detection of pulmonary type can be best done radiographically by high resolution chest Computed Tomography as it directs the extent and also gives an confirmation of infection before emanating on the chest X-ray. Fungi invade into the blood vessels, resulting in thrombosis which can be seen as wedge shaped infarcts on the radiographs. Many other acquisitions such as cavitation defects, consolidation of lobes and nodular diseases were also discovered when viewed radiographically [24-27].

Another promising finding is mass expansion/ consolidation in the direction of mediastinum [28-30]. Diagnosis of zygomycosis can be best done by histopathological examination or tissue biopsy as cultures of sputum proves to be defective. For example, in many case reports, bronchiolar and sputum cultures came out to be negative as compared to biopsy procedures [26]. In serious cases of untreated infection, complications such as respiratory failure can occur due to its spread to the opposite side of the lung by haematogenous route resulting in death. The mortality / death rate varies from 70 to 95% depending upon the extent or spread [26, 31].

Cutaneous Mucormycosis:

Cutaneous mucormycosis is a further clinical form affecting patients with decreased immunity elicited by mucorales. The predisposing factors include diabetes mellitus, blood disorders with patients being immunocompromised. The fungi gain entry into the skin in case of any serious burns, trauma and maceration and reach out deeply into tissues as they are naturally incompetent to pierce undamaged skin [19, 32]. The transmission of ubiquitous mucorales into the skin is commonly as a result of many types of trauma by the process of inoculation such as road traffic accidents, natural calamities, animal bites, stings etc. Specifically, cutaneous type appears as a necrotic eschar but subsequently some other signs can also be seen. The spread and extent of the infection may be insidious or disseminated as they can go deep down to dermis reaching to muscles, fat etc. For diagnosis, the findings are usually non-specific but biopsy must be performed as gold standard along with sputum culture. Treatment options are transdisciplinary and comprises of, antifungal drugs, debridement surgically and curing of the underlying causative factors. Death rates in this type are significantly lower (4-10%) as compared to other forms.

Disseminated Form:

The origin of disseminated form of mucormycosis can be from infection located in the primary spot. On the other hand, pulmonary type shows the upsurged incidence of dissemination especially in patients suffering from severe neutropenia followed by GI tract infections, skin lesions, and severe burn patients. Location of this form is majorly brain, while other organs such as heart, spleen and skin can also be a less common site for metastatic lesions. Infection of the cerebrum also occurs in this type due to dissemination but it is different from rhino-orbito-cerebral type due to formation of abscess and infarction [6]. A hazardous expression of this form is that it approaches to the brain and thus the mortality rate nearly approaches to 100% [31].

Molecular Pathogenesis of Mucorales [1]

A very few and restricted methods are available to deeply study molecular pathways and signalling genetic manipulation of fungi mucorales. Due to the process of gene duplication and multiplication, the whole genome is replicated. In this way, there is expansion of the afferent and signaling routes. This class of fungi contains a single set of chromosomes and reproduces sexually by the process of meiosis occurring in a zygote. Genetic manipulation can only be willingly seen in bread mould and dimorphic fungi circinelloides. Factors such as uncommon unification of chromosomes, decreased transformation potency and absence of overriding markers for selection makes genetic manipulation difficult in these two fungi. To combat these disadvantages, RNA interference or RNAi comes to the rescue as the most efficient method for genetic knockdown [1].

A variety of factors has been linked to the succession of mucormycosis including Acquired immune deficiency Syndrome (AIDS), lower levels of neutrophils, rheumatoid arthritis, and haematopoitic Stem cell transplantation (HSCT 48), glucose intolerance in myotonic dystrophy, decreased immunity, haemochromatosis, and peritoneal dialysis in case of kidney failure, undernourishment, distress, and serious burns. The normal immune response protects many forms of mucormycosis, even though if soft tissues are affected or injured then infection can happen. Mucormycosis mostly predisposes if any underlying invasive condition such as low immunity, burns, trauma is present [3, 18, 35-44].

Whenever due to any enervating disease, the blood vessels becomes narrow and the blood is imperiled is considered as most devastating risk factor for mucormycosis like in case of diabetes and open sores. Patients affected in any natural calamity, wounds grimed with soil or polluted water, tumors and serious burns are also likely at elevated threat to get this infection [45].

Treatment

First line of treatment is always aimed at removal of underlying disease/ condition such as increased blood glucose, diabetic ketoacidosis, iron overload, autoimmunity etc. Antifungal drugs and debridement surgically go hand in hand as an approach to treatment [2,28]. Framing of an ultimate diagnosis is usually complicated due to enormous risk factors and syndromes associated. The preferred

drug of choice is amphotericin B intravenously. The patients who have responded to anti-fungal drug amphotericin B are then given Posaconazole. Also, Isavuconazole is also prescribed if amphotericin B is ineffective or intolerable to the patients as salvage therapy. Its use is based on condition of the patient i.e. state in which the digestion and administered course of amphotericin B.

Conclusion

Mucormycosis is a fatal disease with lot of complications. One Should Be Aware To How To Diagnose And Treat This Disease Properly With Right Treatment Approach.

Conflict of Interests: The authors declare that there are no conflicts of interest.

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