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Review Article

MUCORMYCOSIS – A RECENT OUTLOOK

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ABSTRACT
Mucormycosis is an infectious disease caused by fungi of order Mucorales. It is an infection common in immunocompromised individuals and uncontrolled diabetes mellitus. It is clinically presented as vascular invasion resulting in thrombosis and tissue infarction or necrosis. This article discusses the etiopathogenesis, clinical features, diagnosis, investigatory procedures and management of Mucormycosis.

Key words:- Mucormycosis, COVID – 19, Diabetes Mellitus, SARS CoV-2, Mucormycetes.

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INTRODUCTION

Mucormycosis is a life threatening, angio invasive infection caused by saprophytic fungi of Order Mucorales. Mucorales fungi are ubiquitous fungi. Rhizopus oryzae is the most common organism isolated from patients with mucormycosis.

It usually occurs in patients with uncontrolled diabetes mellitus with or without ketoacidosis, corticosteroids treatment, organ or bone marrow transplantation, neutropenia, malignant hematologic disorders, trauma and burns, deferoxamine therapy in patients receiving haemodialysis. A new underlying factor experienced in recent months is COVID-19.

Etiopathogenesis:

1. Diabetes Mellitus:

Diabetes Mellitus is known to be the underlying disease for occurrence of Mucormycosis in most cases.

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Diabetes prevalence has risen faster in low- and middle-income countries than in high income countries. Uncontrolled Type II Diabetes mellitus is the most common type in diabetes patients with mucormycosis. [1]

Patients with Diabetic Ketoacidosis are more prone to develop mucormycosis due to inoculation of organism due to trauma like unhygienic dental procedures during tooth extraction, accidents, injury. Impaired healing also plays a vital role in inoculation of organism.

2. Solid Organ Transplantation:

Solid Organ Malignancy and associated solid organ transplantation is also an important risk factors factor of Mucormycosis. In a review by Almyroudis et al incidence in renal transplant recipients was 0.4–0.5, in liver recipients 4–16, in heart recipients 8 and in lung recipients 13.7–14, all per 1000 patients.[3]

3. Malignant Haematologic Disorders:

Haematologic Malignancy and associated haematopoietic stem cell transplantation is the underlying cause in countries with high income population. Acute Myeloid Leukemia, Acute Lymphoid Leukemia, Non – Hodgkin's Lymphoma, Myelodysplastic Syndrome are some of the related haematological malignant disorders. Risk of Mucormycosis increases with prolonged Neutropenia.[1,4]

4. Treatment with Corticosteroids and Other Immunosuppressants:

Chronic Administration of immunosuppressive drugs like corticosteroids in treatment of malignancy, transplantation, autoimmune disorders is the major risk factor associated with mucormycosis. Minor Trauma and Impaired healing worsens situation by exposing patients to fungal infection.[1]

5. Increased Iron Levels in Plasma & Deferoxamine Therapy in Haemodialysis:

In normal physiological states iron is attached to ferritin in mucosal cells of gastrointestinal tract and transferring it to plasma and deposits Iron in liver or bone marrow. In patients suffering from Diabetes mellitus with acidosis the affinity of protein to bind with iron is decreased causing increased levels of iron in plasma. This causes availability of iron to Mucorales fungi.[1,5]

Serum Iron may be increased in patients undergoing multiple transfusion or dialysis due to decrease of proteins in plasma. Deferoxamine an iron chelator used in the past for treating increased serum iron levels. It is a bacterial siderophore. However, Mucorale Fungi utilizes Deferoxamine to acquire iron from host causing Mucormycosis in host.[5]

6. COVID -19:

Corona Virus disease (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Virus (SARS CoV-2) along with associated emergence of Mucormycosis is increased in recent days. Poorly controlled Diabetes Mellitus and other comorbidities are major risk factors. Also use of Corticosteroids critical COVID-19 patients causes well known risk factor for Mucormycosis.

Infections such as SARS CoV-2 produces drastic impact on human immune system by inducing an inflammatory storm.

1. An increase in Neutrophil count.
2. Decrease in Lymphocyte count , specifically CD4+ and CD8+ T cells.

SARS CoV – 2 Infection may affect CD4+ and CD8+ T cells which are involved in COVID-19 infection. There is a marked reduction of absolute number of lymphocytes and T cells in COVID-19 Patients. Mucorale specific T cells (CD4+ and CD8+ T cells) produces cytokines such as IL-4, IL-10, IL-17 and Interferon γ that damage fungal hyphae. Such specific T cells are seen only in patients affected with invasive mucormycosis.[7]

Also COVID-19 diseases causes increase in pro inflammatory markers such as IL-1, IL-6, TNF-alpha and fewer CD4 and CD8 cells. Hence CD4+ and CD8+ T cells serve a prominent role against infection with mucormycosis via recruiting cytokine such as IL-4, IL-10, IL-17 and Interferon γ.[8]

7. Other Predisposing Factors:

Other causes may include IV drug use, Renal failure, AIDS, Liver diseases, alcoholism. Health Care associated issues like use of non-sterile products is most commonly suspected cause of infection. Bandages, adhesives, nitro glycerine patches, contaminated linen, osteotomy bags and Various medical devices, such as catheters, insulin pumps and finger sticks , and insertion of tubes, tooth extractions and surgery may be a carrier factor. Minor Trauma like animal bite or major trauma like surgery, motor vehicle accidents may also be a cause for mucormycosis.[1]

Clinical features – Diagnosis:

The clinical hallmark of Mucormycosis is tissue necrosis resulting from vascular invasion causing thrombosis and tissue infarction. Diplopia in a neutropenic patients affected with diabetes mellitus or COVID-19 is an alarming sign for Mucormycosis. However necrotic eschar does not preclude the diagnosis. The Warning signs presented in patients with Mucormycosis are:

1. Pain
2. Proptosis
3. Periorbital Swelling
4. Orbital apex Syndrome
5. Palatine Ulcers
6. Blackish or Brownish discharge from nose

Prolonged fever, not responding to broad-spectrum antibiotics, is usually present. Non-productive cough is a common symptom, whereas haemoptysis, pleuritic chest pain and dyspnoea are less common.[1]

Clinically the various types of mucormycosis seen are:

1. Rhinocerebral Mucormycosis
2. Pulmonary Mucormycosis
3. Cutaneous Mucormycosis
4. Gastrointestinal Mucormycosis
5. Disseminated Mucormycosis
6. Palatal Mucormycosis
7. Miscellaneous

Rhinocerebral mucormycosis is the most common form of the disease. The initial onset of rhinocerebral mucormycosis begins with sinusitis or periorbital cellulitis with eye or facial pain and facial numbness, succeeded conjunctival inflammation, blurry vision and soft tissue swelling. Fever may or may not be present. If left untreated, infection usually spreads from

the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function and proptosis in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia.

Pulmonary Mucormycosis of occurs most commonly in leukemic patients who are receiving chemotherapy or patients undergoing hematopoietic stem cell transplants. Symptoms of pulmonary mucormycosis include dyspnoea, cough, and chest pain. Radiographically, a variety of findings may be present, including, in descending order of frequency: lobar consolidation, isolated masses, nodular disease, and cavitation.

Cutaneous Mucormycosis occurs in patient with disruption of the normal protective cutaneous barrier. The agents of mucormycosis are typically incapable of penetrating intact skin. However, burns, traumatic disruption of skin like laceration and persistent maceration of skin enables the organisms to penetrate into deeper tissues. For example, traumatic implantation of soil, due to a motor vehicle accident or penetrating injury with plant material like a thorn or piece of stick.

Gastrointestinal mucormycosis is rare. It mainly occurs in patients who are extremely malnourished (especially infants or children).

Palatal Mucormycosis may be presented with bilateral maxillary sinus tenderness and an ulcerative hard palate lesion with necrosis. Palatal ulceration, necrosis, and perforation can also be seen.

Mucorale Infection can occur in any body site. Miscellaneous expressions of Mucormycosis includes Endocarditis, Osteomyelitis, Peritonitis, Renal Mucormycosis.[4]

Tissue Necrosis is hallmark of mucormycosis but presentation and syndrome-oriented approach lacks sensitivity and specificity. Early Diagnosis of Mucormycosis is of utmost importance as it has influence on its management.

Investigations:

Lab Investigation involves Microscopic Examination and Visual Examination of Histopathologic culture, Serology and Molecular Assays.

A confirmatory diagnosis of Mucormycosis is made from biopsies of affected tissues or Bronchoalveolar Lavage. A definitive diagnosis is based on the demonstration of fungal hyphae typical for mucormycetes species in biopsies of affected tissues, or bronchoalveolar lavage in patients with pulmonary mucormycosis. Selection of tissue site for biopsy is of utmost importance because it can be used to distinguish the presence of species as a pathogen or as a culture contaminant.

Direct microscopy:

For a rapid diagnosis of mucormycosis, direct microscopy of Potassium Hydroxide wet mounts can be used usually accompanied with fluorescent brighteners like Blankophor and Calcofluor White for accurate diagnosis. When fluorescent brighteners are used Fluorescent Microscope are used. Routine Haematoxylin and Eosin stains can be used for demonstrating only the cell wall with no structures inside.[1]

Mucorales genera produce typically non-pigmented, wide (5–25 μm), thin-walled, ribbon-like hyphae with no or few septations (pauciseptate) show an irregular, ribbon-like appearance and right-angle branching. Routine Haematoxylin and Eosin stains can be used for demonstrating only the cell wall with no structures inside.[1,12] .

Culture:

Culture on Sabouraud Agar with an antibacterial agent but without cycloheximide, on which fungi grow easily. After incubation for 3 – 4 days on Sabouraud agar at 30-37C, the colonies are grey – white with a thick, cottony, fluffy surface. However culture, has low sensitivity, as it can be falsely negative. This can be attributed to a number of reasons, such as grinding or homogenization of tissue specimens, which may destroy the delicate hyphae of mucormycetes, or even a lack of expertise.[1]

Proper sampling and handling of the specimens before examination are a prerequisite for an optimal yield. Therefore, upon suspicion of a case, good communication and close collaboration between clinicians and the microbiology laboratory is essential to ensure that all steps of the diagnostic procedure will be taken properly.

Serology:

Presently, there are no commercially available antigen markers to detect Mucorales. Mucorale specific Antigen or any other surrogate diagnostic markers will be of the subject of further studies. There is a specific antigen marker named galactomannan for Aspergillus. However, Galactomannan testing in blood and bronchoalveolar lavage in haematology patients or patients with compatible chest CT imaging results may be used to decrease the likelihood of mucormycosis.

Molecular methods:

Serum Mucorales PCR has been shown to be a highly reliable tool for the diagnosis of invasive mucormycosis in immunocompromised patients. Several Studies are going in this field of Molecular assays.

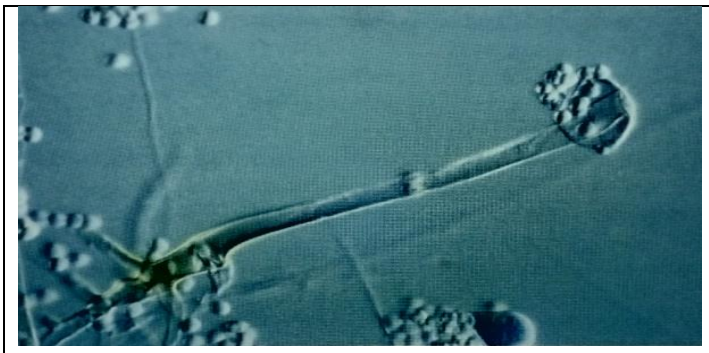
According to Millon et al. in a study using three qPCR [for Absidia corymbifera (Lichtheimia), Mucor/Rhizopus and Rhizomucor 18S ribosomal RNA genes] on sera of mucormycosis patients showed that this method was highly sensitive, had a low detection level and could detect infection 3–68 days earlier than the conventional methods.[11]

Metabolomics-Breath Test

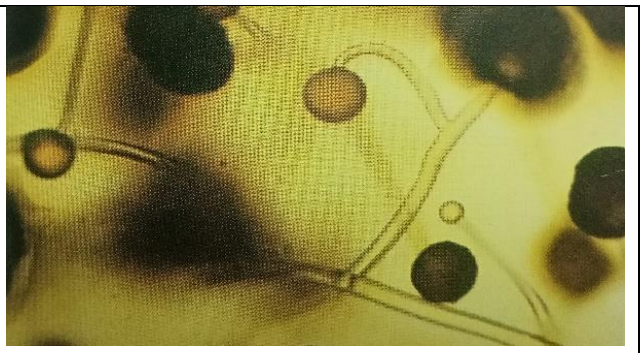
Koshy et al. examined breath volatile metabolite profiles, using the three Mucorales species, by thermal desorption gas chromatography/tandem mass metabolites from five patients. The findings showed that the three Mucorales species had distinct breath profiles.

These profiles distinguished the infections from each other and from aspergillosis, therefore this method can be employed to diagnose fungal infection non-invasively. This could be used in a high-risk population such as patients with neutropenia due to treatment for leukemia or those undergoing hematopoietic cell transplantation. This method seems to be convincing, but needs further research.[12]

spectrometry. Mice infected with Aspergillus fumigatus were used as controls. They also analyzed breath volatile



Rhizopus Species (Normarski Optics, x450)



Mucor Species (Unstained, x450)

Courtesy : Textbook of Diagnostic Microbiology, Fifth Edition by Connie R. Mahon, Donald C. Lehman, George Manuselis.

COVID – 19 patients Severely ill patients (admitted in ICU, required mechanical ventilation, long hospital stay)
Risk Factors Trauma, Diabetes mellitus, Corticosteroids use, Solid organ transplantation, Prolonged Neutropenia, Haematological Malignancy
Direct Microscopy Using fluorescent brightener and histopathology with special stains (eg.: PAS & GMS) Findings: Non – Septate/ Pauci-Septate; Ribbon like hyphae at least 6-16microns wide
CULTURE Routine Media at 30C and 37C Findings: Cottony white or Greyish black colony
Molecular identification PCR based assays
Primary Prophylaxis with Posconazole First Line of Treatment Am B Lipid Complex, Liposomal Am B, Posconazole Oral Suspension Surgical Treatment Adjunctive Therapy (if needed)

Treatment:

Management of Mucormycosis includes

1. Rapidity of Diagnosis
2. Reversal of Underlying Conditions
3. Appropriate Antifungal Therapy
4. Appropriate Surgical Debridement

Antifungal Therapy:

Amphotericin B is the first-line drug of choice, posaconazole and isavuconazole are also a part of effective treatment. The drawbacks in treating mucormycosis in India are a gap in treatment protocol and the financial constraints of patients that they cannot afford liposomal Amphotericin B. In addition to it, systemic antifungals should be added to first-line management. There is a strong recommendation of high dose liposomal amphotericin B along with the adequate dosage of intravenous isavuconazole and posaconazole. Both triazoles can be given as salvage treatment as well.[1,13]

Surgical Treatment:

Diagnosis of mucormycosis states an immediate and complete surgical intervention. Early diagnosis in clinical examination is helpful because small, focal lesions can be easily excised before they progress into critical structures. The classical sign of angioinvasion prevents the entry of antifungal drug to the infection site.

Surgical Debridement becomes necessary because of the massive amount of tissue necrosis during the progression of infection which may not be prevented by the killing the organism using antifungal therapy alone. In most cases the infection is progressive in nature until management with antifungal therapy and surgical debridement is done at right time.

Iron Chelators:

Iron Overload plays an important role in developing Mucormycosis. Iron Chelators can be used as an adjunctive therapy for Mucormycosis. Unlike Deferoxamine which supports the growth of Mucorales in presence of Iron, other Iron Chelators like Deferiprone and Deferasirox did not allow organisms to take up iron.[13]

Other Adjunctive Therapy:

Hyperbaric Therapy can be used as adjunct along with surgical and antifungal therapy. Adjunctive Cytokine Therapy is another treatment area need to be researched for treating Mucormycosis.[13]

The mortality rate is low in patients treated with a combination of Amphotericin B and surgical debridement of the infected tissue than patients treated with Amphotericin B alone.[9]

Conclusion:

Mucormycosis is rare and destructive fungal disease which can affect any organ in the human body. Clinical Hallmark signs are angioinvasion resulting in tissue necrosis or infarction. Patients with poorly controlled diabetes mellitus with or without acidosis, corticosteroid treatment, organ or bone marrow transplantation, neutropenia, malignant hematologic disorders, trauma and burns, deferoxamine therapy in patients receiving haemodialysis are majorly affected by Mucormycosis.

In recent months, incidence of mucormycosis has steeply increased in COVID affected patients with comorbidities and also patients who had rigorous corticosteroid therapy. Rhinocerebral Mucormycosis is the most common type of Mucormycosis. Present Investigatory Procedures lacks sensitivity and specificity. Early diagnosis and management reduce risk in most cases. Management includes antifungal therapy, surgical debridement and adjunctive therapy. A combination of antifungal therapy and surgical debridement is known to result in good prognosis.

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