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MUCORMYCOSIS-A DEADLY DISEASE

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ABSTRACT

Mucormycosis is caused by the fungi of the order mucorales. It is also known as black fungus or zygomycosis. It usually affects the immunocompromised host. The major forms of mucormycosis include rhino-orbito -cerebral, gastrointestinal, disseminated, cutaneous and pulmonary mucormycosis. The signs and symptoms of mucormycosis are nonsspecific and a definitive diagnosis requires the identification of causative organism. A successful treatment requires early diagnosis, reversal of underlying conditions and initiation of antifungal therapy. Amphotericin B is the first line agent for the management of mucormycosis. The aim of the review is to provide a brief insight into the aetiology, pathogenesis, diagnosis and management of mucormycosis.

KEYWORDS: Mucormycosis, Mucorales, Liposomal Amphotericin B, posaconazole, Rhizopus arrhizus.

INTRODUCTION

Mucormycosis is a life threatening infection caused by the fungi of the order mucorales. Mucorales enter the body through inhalation, ingestion or implantation of spores.[1] 11 genera and 27 species from the order Mucorales are associated with mucormycosis among which *Rhizopus arrhizus* is the most common agent. The other agents known to cause mucormycosis include *Lichtheimia, Aphophysomyces, Rhizomucor, Mucor and Cunninghamella.*[2] An American pathologist R. D. Baker coined the term mucormycosis.[3]

According to Brown, mucormycosis is ranked third among opportunistic fungal infection after Aspergillosis and Candidiasis. Mucorales are found in soil, residue plants, spoiled food and upper respiratory tract of healthy individuals. Depending upon the anatomic site of

infection mucormycosis can be exist-rhino-orbito cerebral, pulmonary, disseminated, cutaneous, gastrointestinal and miscellaneous (bones, joint, heart, kidney).[4]

Management of mucormycosis is difficult due to several reasons. Firstly it is difficult to isolate and maintain the organism under laboratory conditions. Secondly treatment options are limited due to resistance to several antifungal agents.[5]

EPIDEMOLOGY

Of all the types rhino-orbito-cerebral mucormycosis is the most common form (34%) of mucormycosis followed by cutaneous (22%), pulmonary (20%), disseminated (13%) and gastrointestinal (11%).[6]

Genera of Mucorales varies from country to country, the most common agents being Rhizopus spp and Mucor spp. In Europe Mucorspp, Licthmiaspp and Rhizopusspp (34%, 19% and 19%) are the most common. In India Rhizopus is the most common species.

Another species Apophysomyces was reported in Mexico.[7]

According to Ana Daniela Castrejon a variation in causative organism exists between developed and developing countries. In developed countries the disease is uncommon and is commonly seen in patients with haematological malignancies whereas in developing countries like India it is common in patients with uncontrolled diabetes or trauma.[8]

CLINICAL PRESENTATION AND MANIFESTATIONS

Mucormycosis occurs in two forms: superficial and visceral and localised and disseminated. Superficial forms affect the external ear, fingernails and skin whereas visceral forms affect the gastrointestinal, pulmonary and rhino cerebral.[9]

Rhino-orbito-cerebral mucormycosis

It occurs following inspiration of spores. It affects the nose, eyes, sinuses and the brain. Symptoms include sinus pain, nasal congestion, fever, headache, soft tissue swelling and redness of skin overlying sinuses. If left untreated the disease can progress and can affect the eye causing blurred vision and even blindness.

Cutaneous mucormycosis

It results from direct inoculation of wounds or burns. It is characterised by formation of

abscess, skin swelling and necrosis.

Disseminated mucormycosis

It originates from the primary sites of infection. In most cases the organ from which dissemination occurs is the lungs.it may show a great variety of symptoms but a metastatic skin lesion is a unique sign of disseminated mucromycosis.[10]

Pulmonary mucormycosis

In general fever and cough are the symptoms seen in most patients, together with pleuritic pain and dyspnoea. If the organism invades the blood vessels severe haemoptysis can occur.[11]

Gastrointestinal mucormycosis

It is a less frequent form of mucormycosis. It occurs through ingestion of contaminated food and beverages. Stomach is the most common sight of infection. Abdominal pain, GI bleeding and changes in the bowel habits are the most frequent symptoms. Fever occurs to a lesser extent.[11]

RISK FACTOR

Predisposing factors for mucormycosis include malignancies like lymphoma and leukemia, neutropenia, poorly controlled diabetes mellitus with or without ketoacidosis, prolonged use of corticosteroids, renal failure, organ transplant, long term immunosuppressant therapy, cirrhosis, trauma, burns, protein energy malnutrition and acquired immunodeficiency syndrome.[12,13]

Nosocomial mucormycosis occurs as a result of fungal exposure from contaminated air filters or health care associated procedures such as contaminated wound dressing, intravenous catheters, tongue depressors and even allopurinol pill.[14]

ETIOPATHOGENESIS

Mucorales attack deep tissues by means of ingestion or inhalation or percutaneous injection of spores. As soon as the spores penetrate into lung or cutaneous tissues they are encountered by the first line of defence mononuclear and polynuclear phagocytes which are capable of destroying the spores via oxidative metabolites and cationic peptides. Risk factors for mucormycosis include uncontrolled diabetes mellitus with or without ketoacidosis, steroid use, elderly, neutropenia, AIDS, renal failure, organ or stem cell transplantation, iron

overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse. Patients with diabetes are at an increased risk of developing all types of mucormycosis. The possible reasons could be: (i) reduction in serum inhibitory activity (ii) reduction in PH level and increase in serum iron concentration (iiiI) Incapability of pulmonary macrophages of diabetes mellitus patients to inhibit Rhizopus species. Another risk-factor for mucormycosis is the presence of iron overload in serum. Patients treated with deferoxamine are at an increased risk of mucormycosis because this iron chelants transports iron to mucorales. If the spores escape phagocytosis they invade the blood vessels by adherence to endothelial cells.[15,16]

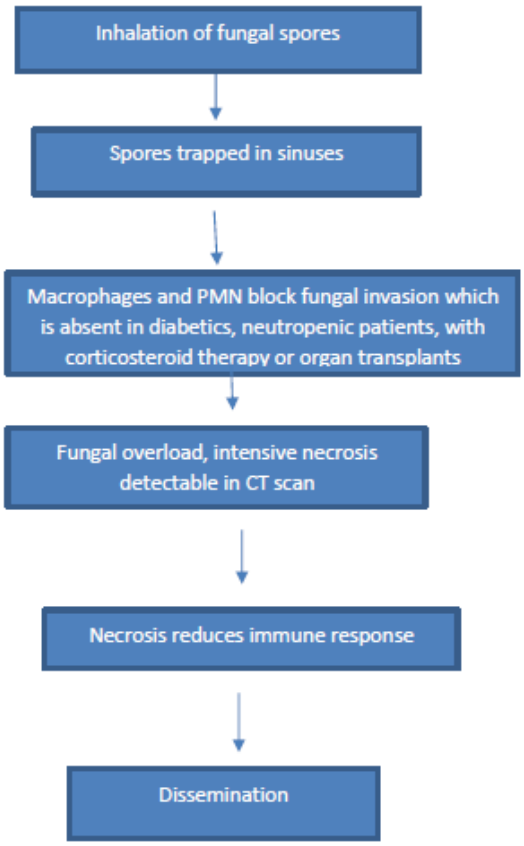

Fig 1. Pathogenesis of Mucormycosis.[17]

DIAGNOSIS

Success of antifungal therapy depends on the early diagnosis of mucormycosis. The signs and symptoms and radiographic features are nonspecific so definitive diagnosis requires identification of causative organism.

Cytopathology: Hyphal elements can be observed on a potassium hydroxide wet mount with the help of chitin binding stains such as Calcofluor, Fungi flour or Blancoflour.

Histopathology: Periodic acid schiff and Gomori methenamine silver stains gives a full characteristic appearance of the organism. Microscopic characterization of hyphae, columellae, sporangiospores and sporangia helps to identify genus and species of mucorales.

Culture: Specimens are inoculated into appropriate media and incubated to 37^0C. Colonies appear 24-48hours unless antifungal agents are given which suppress growth. Mucorales can be distinguished from colonial appearance and growth pattern.

Radiographic/Imaging techniques: Computed tomography (CT scan) is useful in determining the extent of the disease. Magnetic resonance imaging (MRI) is useful in determining intradural and intracranial extent of disease.[18]

Molecular methods: Molecular methods include polymerase chain reaction (PCR), PCR combined with mass spectroscopy. These methods helps in the identification of strains.

Serology: These include IgG test, Enzyme-linked immunosorbent assay (ELISA).[19]

A CT scan can be used in the diagnosis of pulmonary mucormycosis. The following changes are observed in a CT scan of a pulmonary mucormycosis patient:

a) Reversed halo sign
b) Consolidation or module or mass with halo sign
c) Central necrosis.[20]

How to prevent Mucormycosis?

1) Use masks when going outdoors
2) Use gloves while handling soil (gardening).
3) Maintain personal hygiene.
4) Controlling underlying conditions like diabetes, discontinuing immunomodulating drugs, using steroids judiously.[21,22]

TREATMENT

Four steps in the successful treatment of mucormycosis are:

a. Early diagnosis
b. Reversal of underlying predisposing factor if possible
c. If needed surgical debridement
d. Prompt antifungal therapy

Corticosteroids and other immunosuppressive drugs should be tapered as early as possible or to the lowest effective dose.[23]

1. Surgical management

Tissue necrosis may result in poor penetration of antifungal agent at the site of infection. Therefore surgical removal of necrotic tissues is essential for complete eradication of mucormycosis. In multiple case series the mortality rate in patients who did not undergo surgical debridement was found to be higher.[24]

2. Antifungal therapies for mucormycosis

Amphotericin B (AmB) and its lipid formulation and recently isavuconazole has been considered as the first line agent for mucormycosis. Posaconazole and deferasirox are considered as salvage therapy.

2.1. Amphotericin B

The 2016 recommendations from the European conference on infections in leukaemia suggests Amphotericin B as the first line agent in the treatment of mucormycosis. Currently lipid formulation of Amphotericin B is preferred (LAmB). Liposomal amphotericin B (LAmB) is less nephrotoxic and can be administered at larger doses for a long time. The recommended dose for liposomal Amphotericin B is 5 mg/kg/day and 10 mg/kg/day for CNS infections.[25]

2.2. Triazoles

Triazoles act by inhibiting ergosterol from the fungal cell membrane. Among triazoles fluconazole and itraconazole have little or no activity against mucorales. Newer triazoles posaconazole and isavuconazole show high activity against mucorales.[26]

2.2.1. Isavuconazole

Isavuconazole is formed by the hydrolysis of isavuconazonium sulfate. It has high oral bioavailability and broad antifungal spectrum when compared to posaconazole.

Isavuconazole has less toxic effects.A cost effectiveness study demonstrated a positive impact on the use of isavuconazole compared to AmB in the treatment of mucromycosis.[26]

2.2.2. Posaconazole

Posaconazole has been shown to have in vitro and in vivo activity against Mucorales. Some

patients developed mucormycosis while on prophylactic treatment with posaconazole. Posaconazole was ineffective in the treatment of mucormycosis in preclinical animal model. For these reasons it is not used as first line agent for the treatment of mucormycosis.

Posaconazole is used for prophylaxis or as a maintenance therapy for mucormycosis.[26,27]

Table 1: Dose of antifungal therapy for Mucromycosis.[28,29,30]

Antifungal agent	Dose
Liposomal amphotericin B	5-10 mg/kg CNS infections:10mg/kg/day
Posaconazole	Oral suspension:200 mg po three times daily Tablets:300mg po q12 h for first 24 hours, followed by 300mg po once daily IV:300mg IV q12h for first 24 hours, followed by 300mg IV daily
Isavuconazole	IV:372 mg q8h×6doses followed by 372 mg once daily Oral:186 mg(2 capsules) q8h ×6 doses followed by 2 capsules once daily

3. Salvage therapy of mucormycosis

Deferasirox, granulocyte colony stimulating factor and posaconazole are used as salvage therapy of mucormycosis. Deferasirox treatment can be continued upto4weeks beyond which toxicity increases whereas posaconazole are less toxic and can be used for months to years.[31]

4. Combination antifungal therapy for mucormycosis

4.1. Echinocandins

A combination of LAmB plus either micafungin or anidulafungin and a combination of LFAB-capsofungin therapy showed improved outcomes in disseminated and rhino-orbital-cerebral mucormycosis respectively when compared with polyene monotherapy.

Echinocandins should be administered at the doses approved by the US FDA. The increase in survival rates with combination therapy may be due to improved polyene delivery after disruption of cell wall which may lead to immunostimulation.

4.2. Iron chelation therapy

Deferoxamine an iron chelant increases the risk of mucormycosis as it increases the delivery

of iron to mucorales. However another iron chelator deferasirox was approved by the US FDA to treat iron overload among patients with transfusion dependant anaemia. A combination of deferasirox-LAmB was found to increase the survival rate when compared to monotherapy (80% survival in combination versus 40% in monotherapy) in DKA mice with disseminated mucromycosis.[32]

4.3. Posaconazole combination therapy

A combination of posaconazole with AmB was found to increase the survival rate neutropenic mice infected with Rhizopus oryzae when compared to AmB monotherapy. Recent studies suggest that posaconazole combination therapy does not cause an increase in survival rate when compared to AmB monotherapy. No clinical studies have evaluated posaconazole-polyene therapy for mucromycosis.[32]

Table 2: Combination therapy of mucormycosis.[33]

Combination therapy	Dose
Caspofungin plus Liposomal Amphotericin B	70 mg iv load, then 50 mg/day for ≥2 weeks
Micafungin OR anidulafungin plus Liposomal Amphotericin B	100 mg/day for ≥2 weeks
Deferasirox plus Liposomal Amphotericin B	20 mg/kg po qd for 2–4 weeks

Duration of antifungal therapy

There is no standard duration in the treatment of mucormycosis. Antifungal therapy should be continued till there is resolution of signs and symptoms of infection reversal of immunosuppression resolution of clinical, laboratory, radiological and imaging tests.[33]

5. Adjunctive therapies

5.1. Immunostimulating drugs

A case report has recently reported the benefit of treatment with nivolumab and interferon gamma for an immunocompetent patient with extensive abdominal mucormycosis unresponsive to conventional therapies.

5.2. Iron chelators

Iron chelators reduce the transport of iron to mucorales and thereby inhibit their growth. Deferasirox is the preferred iron chelator for the management of mucormycosis.

5.3. Hyperbaric oxygen (HBO)

The increased oxygen pressure achieved with hyperbaric oxygen treatment improves the

functionality of neutrophils. The high oxygen pressure promotes the healing of wounds by inhibiting fungal growth. It also promotes the AMB action by reversing acidosis. HBO is recommended as adjunct to surgical and antifungal therapy for mucormycosis.

5.4. Granulocyte colony stimulating factor or interferon gamma

They have been proposed as adjunctive based on limited data from case reports. They are used for life threatening infections as it can restore monocyte functions.[34]

5.5. Statins

Statins have shown to have fungicidal activity against Glomeromycota. It acts similar to the antifungal agent voriconazole. Statins cause apostolic cell death of mucorales through inhibition of protein prenylation.

5.6. Colistin

Colistin has been shown to be valuable in treating infection caused by R oryzae. Colitis cause disruption of cytoplasmic membrane which leads to leakage of intracellular contents. The usefulness of colistin in mucormycosis may require further investigation.[35]

6. New investigational antifungal agents

The investigational agent VT-1161 a fungal CYP51 inhibitor has shown to inhibit various Mucorales. It was shown to prolong the survival mice infected with Rhizopus oryzae when given therapeutically or prophylactically.[36]

APX001A an antifungal agent in phase 1 trials protected immunocompromised mice from Rhizopus delemar infection.[37]

Haemofungin another antifungal agent inhibits the growth of several fungi including Rhizopus.[38]

Prognosis

Mortality rate of mucormycosis ranges from 30-70 percentage. An early diagnosis increases the survival rate. Permanent deformities like blindness, cranial nerve defects and surgical disfigurement have been reported in most of the survivors. Survival rate was found to increase in patients with low serum concentration of iron or hematological malignancies without infection.[39,40]

Complications of mucormycosis

Complications of mucormycosis can be from the disease itself or are from the antifungal therapy. Complications that result from the disease include periorbital destruction, palatine ulcers, disseminated infection, cavernous sinus thrombosis, osteomyelitis and death and those that result from antifungal therapy include nephrotoxicity, hypokalemia and prolonged hospitalization. Cutaneous mucormycosis can result in necrotizing fascists and gastrointestinal mucormycosis can result in GI disturbances.[41,1]

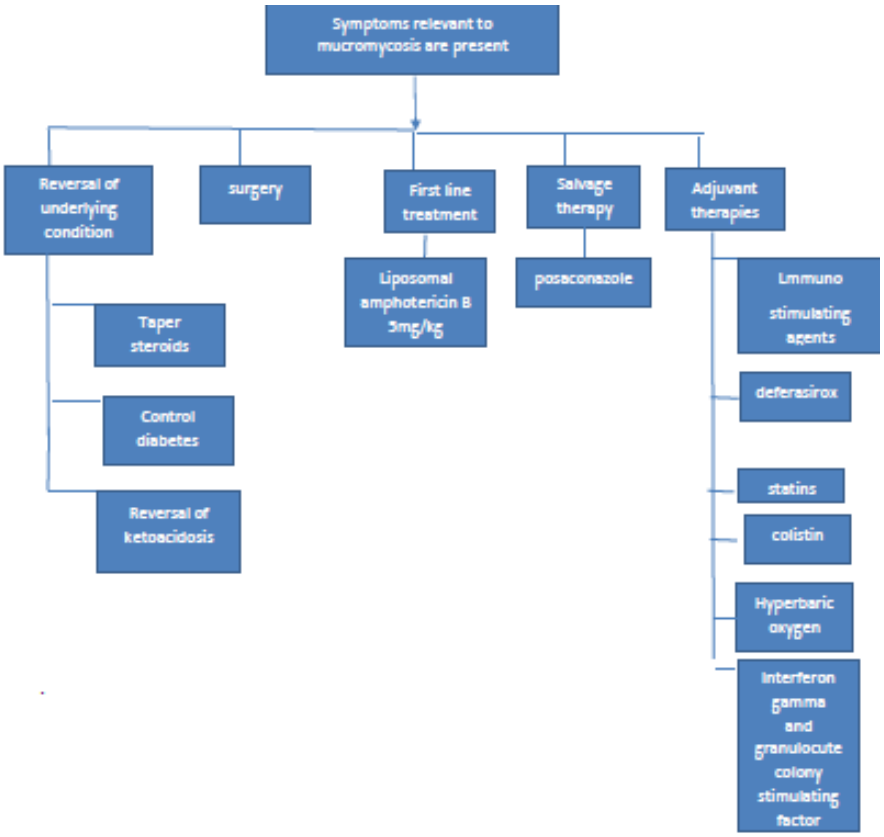

Fig 2: Therapy of mucromycosis.[42]

Mucormycosis in Covid 19 patients

The increasing incidence of mucormycosis in covid19 patients may be related to Covid 19 itself. Covid 19 cause damage in blood vessels and airway mucosa, increase in serum iron concentration which facilitates fungal growth. Severely ill patients are prescribed steroids which may increase in blood sugar levels and facilitates fungal growth. Critically ill patients requires humidifiers through which fungus may enter the body along with oxygen.[43,44]

Dos and don'ts in Covid 19 patients Do's

- Control high blood sugar.

- Frequent monitoring of blood glucose in post-COVID-19 discharge and also in diabetics
- Proper use of steroids
- Use clean humidifiers during oxygen therapy

Don'ts

- Do not neglect any small symptoms especially in immunocompromised or covid 19 patients.[45]

CONCLUSION

Mucormycosis is a life threatening fungal infection. Mucormycosis has poor prognosis and can have high mortality rates if not treated at the right time. In developing countries like India diabetes is a major risk factor for developing mucormycosis. Rhino-orbito cerebral and pulmonary mucormycosis are the most common. Liposomal amphotericin B is the first line agent for the management of mucormycosis. A suspicion of mucormycosis based on symptoms, risk factors and improved lab diagnosis can increase survival rates.

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