CHAPTER

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Mucormycosis: A Challenge Not Limited to Diabetics

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Mucormycosis is a devastating life threatening fungal infection caused by fungi of the order Mucorale and class of mucormycets; and is associated with high mortality of 40 -70%. It's ubiquitous in nature and abundant in our environment. It is highly concentrated near construction activities, decaying vegetables and organic material, soils etc. Mucorale's growth is favored in tropical countries as temperature and humidity supports sporulation. Inhalations of spores infect humans. Seasonal variation in infection rates has been described in various parts of the worlds. India has more cases of mucormycosis in peri-monsoon period and in autumn.[1]

Thus generally speaking this is a community-acquired infection in susceptible population. In the last decade cases of mucormycosis are also being increasingly recognized in hospital settings and nosocomial mucormycosis outbreaks been described. Recent outbreak involving 5 cases were described in Queens Marry hospital at Hong Kong in June-July 2015 due to contaminated linen.[2] Adhesive tapes, wooden spatula are important source of nosocomial mucormycosis apart from contaminated air filters in the hospitals.

Risk factors

Mucorale spores germinate with available free iron, glucose and with acidic pH. Diabetic ketoacidosis creates an appropriate environment for spores lodged in patient's paranasal sinuses and lung parenchyma during inhalation to germinate and produce clinical infection. Acidosis makes excess free iron available to fungus. Patients with qualitative neutrophil dysfunction &/or macrophage dysfunction (uncontrolled diabetes, steroids therapy) helps in tissue & vascular invasion by mucorale to produce devastating distant lesion with area of infarct. Patient can get cutaneous mucormycosis following subcutaneous inoculation of spores, minor trauma, penetrative injuries following road traffic accidents and even insect bite, tattooing can lead to infection. Intravenous drug users are also included in vulnerable populations and get brain abscess due to mucormycosis.

In India, diabetic patient outnumbers other risk factors for getting mucormycosis. Many of these diabetic patients were unaware about diabetic status and presented with mucormycosis. Other risk factors are hematological malignancy, solid organ transplant recipients, receiving immunosuppressants, victims of natural disaster like tsunami, tornado, Road traffic accident victims, iron over load states and desferioxamine therapy. Cases related to iron overload and chelation therapy is going down significantly in last decade. In recent years, many mucormycosis patients have been described as a breakthrough infection in patients receiving voriconazole or ecchinocandins. Exact association between voricanazole exposure and susceptibility for mucormycosis is not well understood. Animal model suggest that voriconazole may increase virulence of certain mucorale species by uncertain mechanism.

Sites of mucormycosis lesion are used to describe cases of mucormycosis. E.g. rhino-orbital-cerebral mucormycosis (ROC) involving paranasal sinuses, orbit with intracranial extension, pulmonary, cutaneous, gastrointestinal, disseminated and others like isolated renal in immunocompetent host, brain abscess, endocarditis in IV drug users etc.

High index of suspicion is required for the diagnosis of mucormycosis, mainly due to non-specific clinical features and culture can be sterile in up to 50% of cases due to aseptate fungus being damaged during tissue handling in laboratory.

Clinical manifestations depend upon site of infection.

In a diabetic or organ transplant recipient patient with ROC, acute onset of facial pain, orbital pain with proptosis, fixed eye ball, black eschar over palate, black necrotic discharge from nose and rapid progression are sufficient clinical findings supporting clinical diagnosis of mucormycosis.

Organ involvement preference in mucormycosis is different in different vulnerable host, is described in Table 1.

Treatment principles include

1. Reversal or control of precipitating cause like correction of diabetic ketoacidosis, minimization of immunosuppressions if possible etc
2. Antifungal therapy: Amphotericin B, Posaconazole, Isavuconazole
3. Surgical debridement/ excision of lesion
4. Adjuvant therapy: Hyperbaric oxygen, Deferasirox, Caspofungin, statins

Early diagnosis and prompt treatment is critical in improving outcome in patients with mucormycosis. Delay in institution of amphotericin B therapy by 1 week is associated with doubling mortality.[3] Standard dose of Liposomal Amphotericin B (L AmB) 5mg/kg is drug of

Table 1

Host/Site	ROC	Lungs	GI	Cutaneous	Disseminated	Other
Diabetes	++	+	+	-	-	-
Organ Tx/ steroids	++	++	+	+	+	+
HSCT	++	++	+	+	++	+
IV drug	-	-	-	+	+	Brain abscess, Endocarditis
Malnutrition	-	-	++	-	+	+
Trauma	-	-	-	++	+	+

choice for management of mucormycosis. Higher dosage up to 10mg/kg didn't improve outcome but was associated with higher rate of renal toxicity (40%).[4]

Newer azole, Posaconazole and Isavuconazole has antimucor activity in vitro and vivo and are well tolerated.[5] Recent introduction of extended release tablet formulation of posaconazole has better pharmacokinetics. US FDA approves Isavuconazole for treatment of invasive mold infections and mucormycosis. Clinically relevant important benefit of isavuconazole over other newer azole is that it is not an inhibitor of hepatic cytochromal enzyme system, though it is a substrate and metabolized by CYP 450 enzyme system. Thus it has fewer drug-drug interactions.

Combination antifungal therapy for mucormycosis is generally not recommended, though in vitro studies and animal experiments showed evidence of synergism between polyenes and echinocandins, and also few clinical studies & experts also supports combination of L AmB + ecchinocandins in treatment of mucormycosis.[6] One recent presentation at ICAAC conference failed to show any benefit from combination therapy compared to amphotericin B monotherapy in hematological malignancy patient.[7] In summary of antifungal treatment for mucormycosis: Standard dosage of L AmB 5mg/kg is firstline therapy. Oral posaconazole & Isavuconazole are acceptable salvage option for intolerant patients and can be use for longer duration if required.

Surgical debridement or resection of necrotic lesion improves outcome of patients with mucormycosis and should be performed in ROC, cutaneous, renal mucormycosis and selected cases of pulmonary mucormycosis.

Adjuvant treatment with hyperbaric oxygen (HBO) inhibits fungal growth and improves the rate of wound healing. HBO therapy may be beneficial in patients with diabetes who have sinusitis, or in cutaneous mucormycosis.

Iron chelator, deferasirox showed promising results in animal model but didn't showed usefulness in a small human study.[8] Case series from India showed acceptable response with deferasirox in diabetic patients with mucormycosis.[9]

Mortality with mucormycosis varies and it depends upon host factor and site of infection apart from species of mucorale causing infection. Patients with disseminated infections, pulmonary, CNS and deep-seated infections where surgical debridement or resection is not possible have higher mortality. Similarly patients with HSCT, hematological malignancies have higher mortality.[10] Certain mucorale species like Cunninghamella is associated with a 2.78 fold-increase in the risk of death compared with more common Rhizopus species.[11] Breakthrough mucormycosis in cancer patients receiving voriconazole has highest mortality of > 70%.[12]

Despite advancement in diagnosis of fungal infections and availability of newer antifungal agents, mortality of mucormycosis is still high. Clinicians shall be ready to face challenges of treating mucormycosis due to rising numbers of at risk population and cost of therapy.

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