



Welcome

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THE HIDDEN ENEMY OF HUMAN LIFE : MUCORMYCOSIS (BLACK FUNGUS)

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LEADING
INTERNATIONAL
FUNGAL
EDUCATION



Mucormycosis

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Intended Learning outcomes

To be aware of the epidemiology of mucormycosis

To understand the pathophysiology of mucormycosis

To be familiar with different clinical manifestations of mucormycosis

To be aware of the available management options for mucormycosis

To be aware of the complications and prognosis of mucormycosis

Introduction: Mucormycosis

- Mucormycosis (previously Zygomycosis) is an uncommon life-threatening fungal infection that occurs mostly in immunocompromised or trauma patients
- It is an aggressive (acute), granulomatous, and opportunistic infection that is caused by several members of fungi in the subphylum Mucoromycotina
- Agents of mucormycosis (Mucorales) have an intrinsic ability to invade blood vessels and can affect different parts of the body
- Cerebro-rhino-orbital mucormycosis is the most common, and the most aggressive, form of mucormycosis
- Uncontrolled metabolic conditions (especially diabetes mellitus in ketoacidosis) is the main risk factor and the core determinant of the world-wide incidence of mucormycosis

Epidemiology

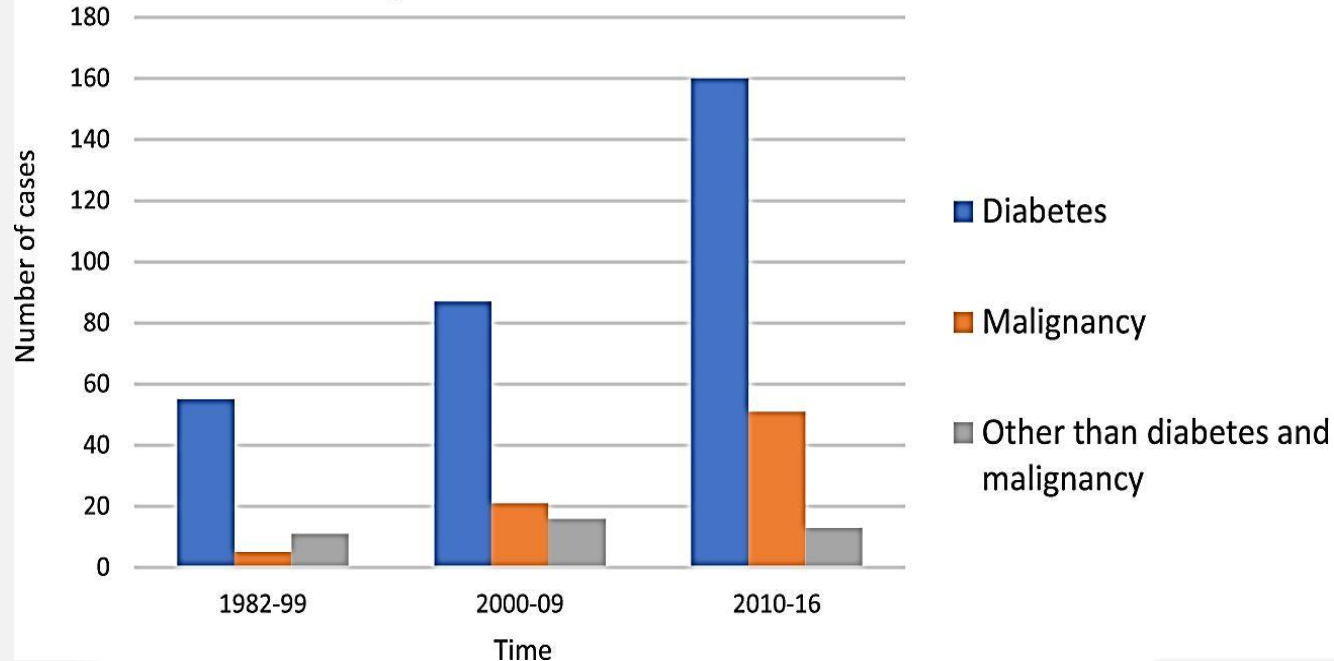
- Mucormycosis is a rare fungal infection, estimated to affect ~10,000 individuals globally, although the incidence in India is much higher
- Most affected individuals have poorly controlled diabetes and may have metabolic acidosis, or are immunocompromised
- Rare cases occur in immunocompetent individuals following traumatic inoculation of fungal spores, including tornadoes and bomb blasts
- Outbreaks and clusters of mucormycosis, though rare, have been reported in hospitals and among organ transplant recipient populations
- Mortality remains high (30-70%) despite advances in diagnosis and treatment

Duffy *et al. Pediatr Infect Dis J.* 2014;33:472-6.
Neblett *et al. N Engl J Med.* 2012;367:2214-25.

Epidemiology: Recent study from Mexico

- 72% of 418 cases of mucormycosis were diabetic patients
- Sinusitis accounted for 75% of the reported cases
- Mortality rate was 51%

Cases of mucormycosis and entomophthoromycosis reported since 1982



Corzo-León *et al.* *Med Mycol.* 2018; 56

Clinical spectrum of mucormycosis

- Rhino-cerebral mucormycosis Brain and nasal sinuses
 - Most common
- Pulmonary mucormycosis
- Cutaneous mucormycosis
- Gastrointestinal mucormycosis
- Disseminated mucormycosis
- Isolated renal mucormycosis



Kauffman CA. *Clin Infect Dis* 2004;39:588-90.
Roden et al. *Clin Infect Dis* 2005;41:634-53

Risk factors - major risk factors

- Uncontrolled diabetes mellitus in ketoacidosis
 - 80-90% of rhinocerebral mucormycosis
- Deferoxamine therapy
- Iron and aluminium overload
- Burns (major)
- Severe trauma (tornados, tsunamis, war)
- Protein energy malnutrition

Risk factors - other risk factors

- Other forms of metabolic acidosis
- Treatment with immunosuppressive drugs (corticosteroids, anti-neoplastics)
- Organ or bone marrow transplantation
- Neutropenia
- Malignancies
- IV drug abuse
- Prematurity and low birthweight (gastro-intestinal mucormycosis)
- HIV/AIDS
- Chronic kidney disease
- Liver cirrhosis and hepatic failure
- ~15-20% of patients have no evidence of underlying conditions

Aetiology: Several genera of Phycomycetes

- Common

- *Rhizopus* spp.
 - ~70% of rhinocerebral mucormycosis cases
- *Mucor* spp.
- *Rhizomucor* spp.

- Rare

- *Apophysomyces* spp.
- *Cunninghamella* spp.
- *Lichtheimia* (*Absidia*) spp.
- *Saksenaea* spp.

Kauffman CA. *Clin Infect Dis* 2004;39:588-90.

Roden *et al.* *Clin Infect Dis* 2005;41:634-53.

Binders *et al.* *Clin Microbial Infect.* 2014;6:60-6

Pathogenesis

- Agents of mucormycosis are ubiquitous and frequently airborne.
- Infections mainly involves the lungs, sinuses and the brain
- Pathogenesis involves invasion of major blood vessels, with consequent ischemia, necrosis, and infarction of contiguous tissues
- Neutrophils play a central role in the defence of the host against mucormycosis
- Ketoacidosis, hyperglycaemia, and hypoxia are excellent growth conditions for these fungi
- Ketoacidosis decreases inflammatory responses and delays local aggregation of granulocytes and fibroblasts

Binders *et al.* *Clin Microbial Infect.* 2014;6:60-6

Wali *et al.* *J Infect Public Health.* 2012;5:116-26

Clinical manifestation: Rhinocerebral mucormycosis

- Unilateral headache - behind the eye
- Facial pain
- Eye swelling (Proptosis) + visual disturbance
- Necrotic lesions on the hard palate or nasal mucosa
- ENT symptoms
 - Nasal congestion
 - Black discharge
 - Acute sinusitis
 - Epistaxis
- Systemic symptoms: fevers



Clinical progression of rhinocerebral mucormycosis

- Stage I: Infection of the **nasal** mucosa and **sinuses**.
- Stage II: **Orbital** involvement (orbital apex syndrome, superior orbital fissure syndrome).
- Stage III: **Cerebral** involvement in which intracranial spread occurs via one of the following routes:
 - ❖ Ophthalmic artery
 - ❖ Superior orbital fissure
 - ❖ Cribriform plate

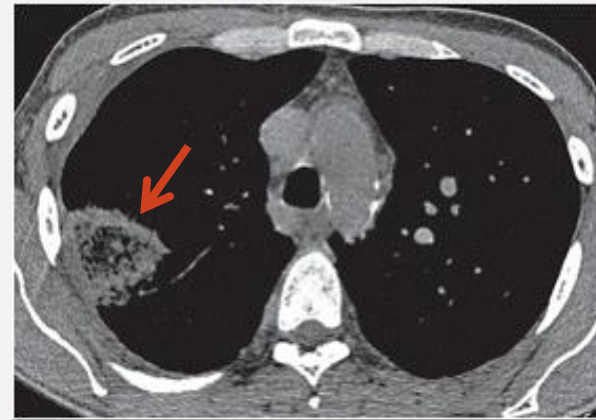
Onerci *et al.* *Rhinology*. 1991;29:321-4

Wali *et al.* *J Infect Public Health*. 2012;5:116-26

Clinical manifestation - Pulmonary

- 2nd most common presentation after Cerebro-Rhino-Orbital mucormycosis
- Mainly in non-diabetic immunocompromised patients
- **Clinical presentation**
 - Fever,
 - Cough +/- haemoptysis
 - Chest pain
 - Increasing shortness or breath
 - Pleuritic rub or rhonchi
- Chronic pulmonary mucormycosis is a rare recognised syndrome

Radiologically. *Acute pulmonary mucormycosis* is usually indistinguishable from **invasive pulmonary aspergillosis – the halo and reverse halo signs may be seen**



Reverse halo sign in mucormycosis

Clinical manifestation – Cutaneous

- ~20% of mucormycosis
- Pathophysiology
 - **Primary** - direct inoculation of organism into disrupted integument; trauma or burns
 - **Secondary** - haematogenous seeding from disseminated diseases
- **Clinical presentation**
 - Skin induration and erythema
 - Necrotic ulcers with dark central area
 - The margins of the ulcers are sharply demarcated



Primary cutaneous mucormycosis

Clinical manifestation –Gastrointestinal

- The **least common** clinical form
- ~10% of mucormycosis
- **At risk:**
 - Protein energy malnutrition,
 - low-birth weight and premature infants,
 - Ambulatory peritoneal dialysis
- **Presentation**
 - Abdominal pain or distension
 - Nausea, vomiting, diarrhoea
 - Haematochezia
- Pathology: GI necrosis and perforation



Isolated Renal Mucormycosis

- The kidney is involved in up to 20% of disseminated mucormycosis
- Isolated renal mucormycosis is very rare
- **>70%** of patients are **immunocompetent** with no identifiable classic risk factors
- Renal transplant recipient with concomitant diabetes mellitus are highest risk group
- Other risk factors
 - AIDS
 - Diabetes
 - Drug abuse
 - Organ transplantation
 - Male > Female
- Pathogenesis is not clear; **haematogenous dissemination** to the kidneys and **retrograde spread** from lower urinary tract have been suggested
- **Pathology**
 - Extensive hyphal angioinvasion
 - Renal vessels thromboses
 - Parenchymal necrosis
 - Cortical and medullary

Gupta *et al.* *Nephrol Dial Transplant* 1999;14:2720-5

Pahwa *et al.* *Korean J Urol.* 2013;54:641-643.

Chakrabarti *et al.* *J Infect.* 2001;42:261-6.

Goel *et al.* *Am J Med Sci.* 2009;338:330-3.

Isolated Renal Mucormycosis

- Clinical manifestation
 - Flank pain
 - Flank mass
 - Renal angle tenderness
 - Gross haematuria
 - Pyuria
 - Fever
 - Renal failure due to occlusion of renal arteries

Gupta *et al. Nephrol Dial Transplant* 1999;14:2720-5.

Verma *et al. Basic Appl Pathol.* 2011;4:66-70.

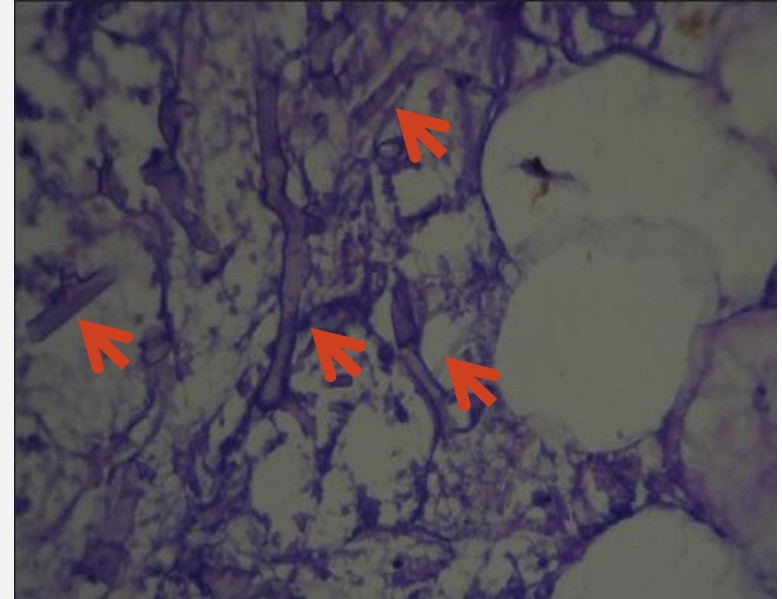
Thomas *et al. Indian J Med Microbiol* 2008;26:269-71.

Management

- Renal mucormycosis **WITH** systemic dissemination
 - Early nephrectomy +
 - Parenteral antifungal
- Renal mucormycosis **WITHOUT** systemic dissemination
 - Early nephrectomy +/- parenteral antifungal
 - Antifungals alone (2 of the 4 reported cases died)

Clinical manifestation – Disseminated

- Disseminated disease stems from pulmonary focus
- Spread is haematogenous
- Deferoxamine therapy is the most significant risk factor for disseminated disease
- Manifestation:
 - Headache
 - Fever
 - Visual disturbance
 - Altered mentation



Sarrami *et al.* *Int J Prev Med.* 2013; 4: 1468–1471

Diagnosis: Laboratory

- **Sample collection**

- Tissue biopsy - **GOLD STANDARD**
- Tissue swabs – unreliable

- **Direct microscopy**

- 10-20% KOH + routine fungal stains
- Fluorescent brighteners (Calcofluor)

- **Culture**

- Blood cultures are rarely positive
- Positive tissue cultures alone are not sufficient to make a diagnosis

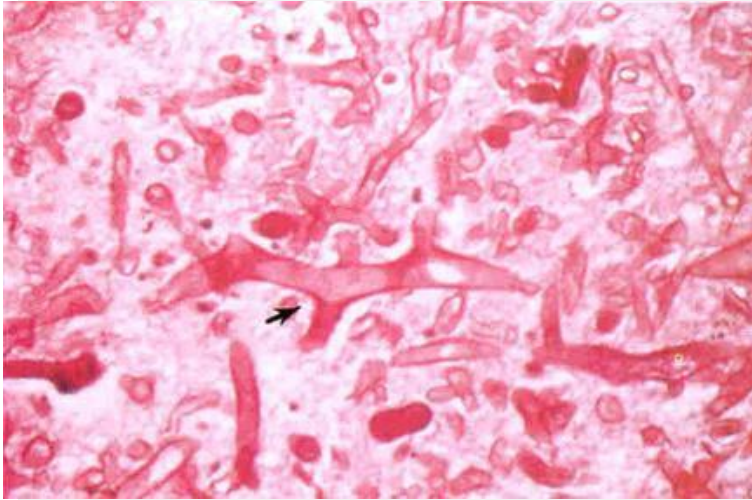
- **Molecular analysis**

Biomarkers

- Beta- D-glucan
 - Negative
- Galactomannan
 - Negative

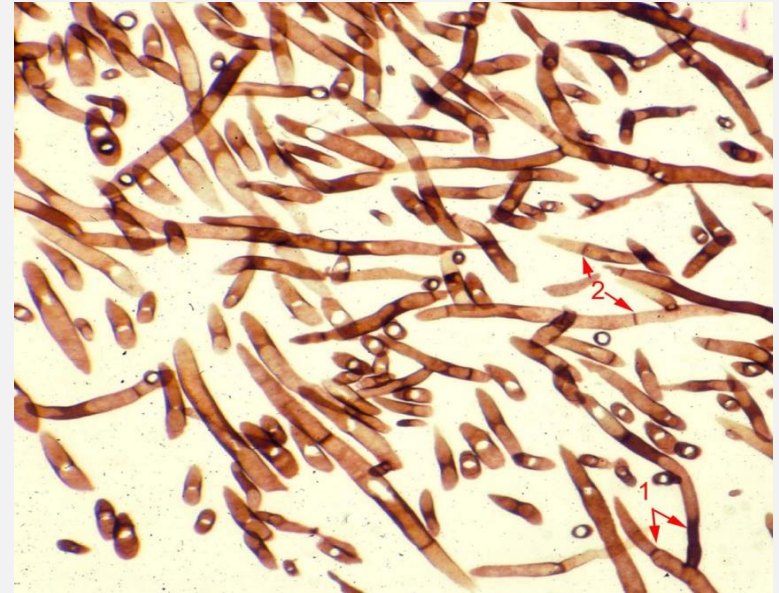
Diagnosis: Histopathology

Agents of mucormycosis



Non-septate hyphae with right-angle branching

Aspergillus spp.



Septate hyphae with acute-angle branching

Diagnosis: Imaging studies

Both CT and MRI can be used

- Roles

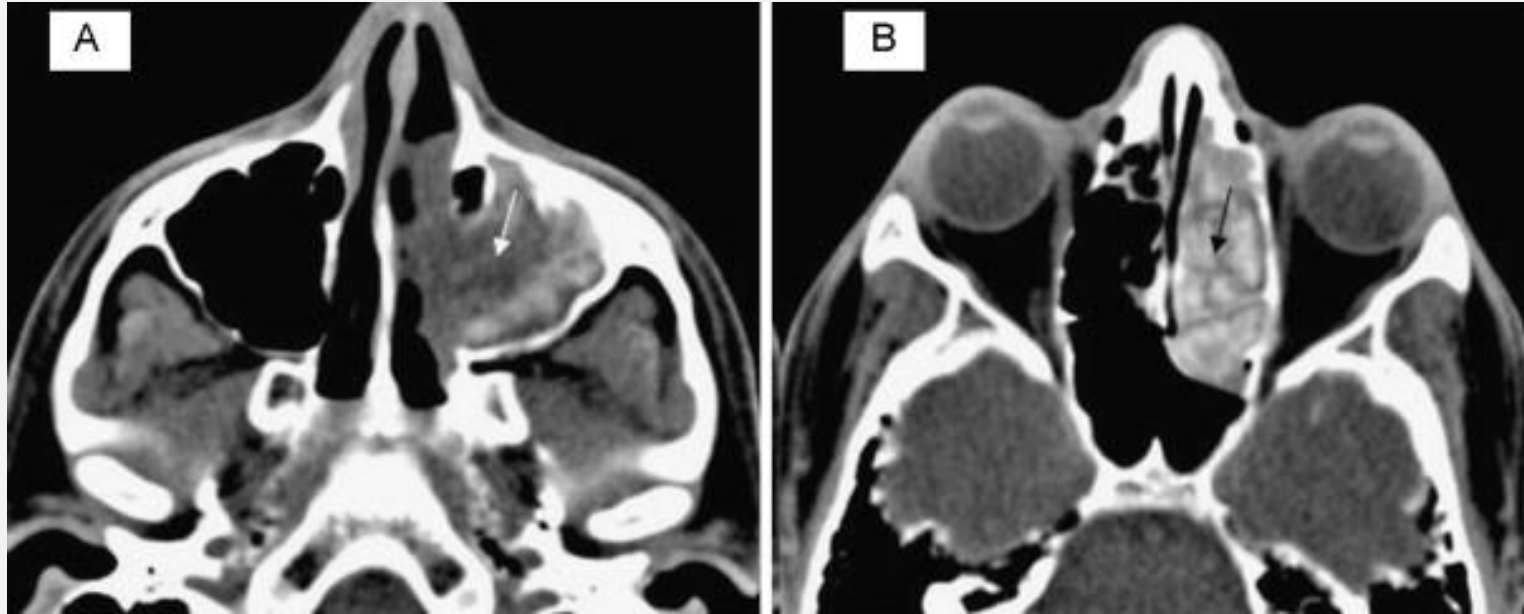
- Detect fungal angioinvasion
- Bone destruction and necrosis
- Soft tissue involvement
- Intracranial involvement

- Sinus imaging

- Mucosal thickening
- Changes in air-fluid level
- Cavernous sinus involvement

MRI provides better delineation of the blood vessels and intracranial extension

Paranasal sinus mucormycosis



Opacification of the left maxillary (white arrow) and ethmoidal (black arrow) sinuses with scattered high-density areas in a patient with mucormycosis.

Management of mucormycosis

- Antifungal therapy
 - Amphotericin B
 - Posaconazole
 - Isavuconazole
- Surgery (**early surgical intervention is associated with improved survival**)
 - Removal of pulmonary lesions
 - Aggressive-all necrotic tissues (palate, nasal cavity or eye structures)
 - Excision of infected brain tissue may be required
 - Revision surgeries may be required
- Hyperbaric oxygen therapy
 - High oxygen pressure increases the ability of neutrophils to phagocytose agents of mucormycosis
- Diabetic control

Early surgical debridement + antifungal therapy + control of underlying risk factor (if possible) is recommended

Monitor carefully for any signs of recurrence, with repeated local inspection

Complications

- **Cerebro-Rhino-Orbital mucormycosis**

- Neurological deficits
- Blindness
- Cerebral thrombosis / infarction and stroke
- Anosmia - loss of sense of smell
- Cavernous sinus thrombosis
- Internal carotid artery thrombosis

- **Pulmonary**

- Pulmonary thrombosis/infarction

- **Cutaneous**

- Soft tissue loss
- Amputations

- **Gastrointestinal**

- Malnutrition
- Short gut syndrome (following resection)

Prognosis

- Prognosis is generally poor but variable (late diagnosis, extensive spread)
- All-cause mortality rate ~54%
- **Mortality rates depends on:-**
 - Clinical form (body site affected),
 - Type of fungus
 - Severity
 - Underlying risk factors
 - Use of surgical intervention

Clinical form	Mortality
Mucormycosis in HIV/AIDS	~100%
Disseminated mucormycosis	~90%
Rhino-cerebral mucormycosis	~30-85%
Sinus mucormycosis	~46%
Pulmonary mucormycosis	~76%
Cutaneous mucormycosis	~4-10%
Isolated renal mucormycosis	~35%

Roden *et al. Clin Infect Dis* 2005;41:634-53.
 Skiada *et al. Skinmed.* 2013; 11:155-9

Summary

- Mucormycosis is an uncommon, aggressive and necrotizing infection, estimated to affect some ~10,000 individuals globally each year
- Cerebro-rhino-orbital mucormycosis is the most common, and the most aggressive form of mucormycosis
- Radical surgical debridement, antifungal therapy, correction of the underlying metabolic or impaired immunological status, and control of other concomitant infections are necessary for improved survival
- Mortality is relatively low for cutaneous forms, higher (30-90%) in disseminated disease and cerebro-rhino-orbital mucormycosis, and is almost always fatal in HIV/AIDS

