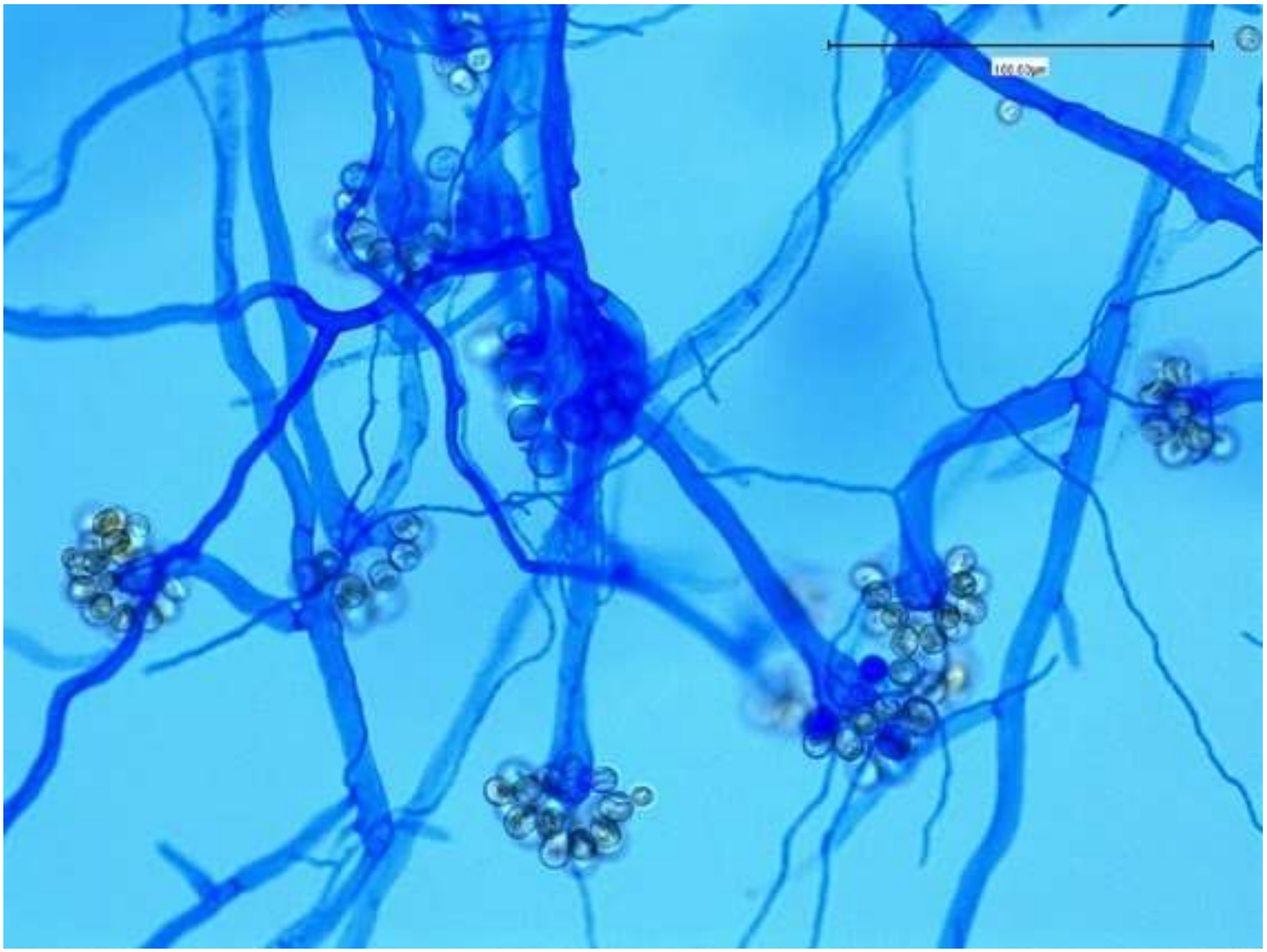
THE NORTHERN HOSPITAL

MUCORMYCOSIS - RHINOCEREBRAL

"Human Parodie" c. 1878-1881, Felicien Rops.

MUCORMYCOSIS - RHINOCEREBRAL



Cunninghamella bertholletiae - sporangiophores with vesicles and attached sporangioles, X 400 magnification.

Introduction

Mucormycosis (previously called zygomycosis) is a **serious life threatening** but fortunately rare infection caused by a group of **aggressively invasive fungi** called the **mucormycetes.**

The mucormycetes are a common class of fungi typically found in soil or decaying organic matter.

Mucormycosis fungal infection is usually only seen in patients with significant immunocompromise or trauma.

Mucormycosis can affect nearly any part of the body, but it most commonly affects the **sinuses** of people who have weakened immune systems. This entity is termed **Rhinocerebral mucormycosis** - as in severe cases the infection can spread from the **sinus cavities** into the **anterior and middle cranial fossae.**

This document predominantly relates to the most common variant, Rhinocerebral mucormycosis

Clues in early presentation can include black necrotic lesions within the mouth or nasal cavity, with **severe pain seemingly out of proportion to the rest of the clinical picture**, especially in an **immunocompromised** patient.

Left undetected and untreated catastrophic and lethal invasion of the orbit and cranial cavity can occur.

Overall mortality from rhino-orbital-cerebral mucormycosis ranges from 25 - 62 %, with the best prognosis in patients with infection **confined** to the sinuses.

The prognosis is especially poor for patients with brain, cavernous sinus, or carotid involvement, although some patients with these complications have been cured of the infection. The outcome in patients with pulmonary mucormycosis is worse than for patients with rhino-orbital-cerebral involvement, with mortality rates as high as 87 percent.

Physical deformity can be devastating.

Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment is critical for improving outcomes for patients with mucormycosis

The clinician must retain a high clinical suspicion for mucormycosis in patients at who are risk, as a delay in diagnosis can be fatal.

Treatment is urgent and involves:

- Systemic antifungal agents
- Surgical debridement of necrotic tissue
- Treatment of any underlying predisposing immunosuppressive pathology

History

No survivors of mucormycosis were reported before 1955.

Survival rates began to increase following the introduction of **amphotericin** in the late 1950s.

Epidemiology [1]

Although most cases are sporadic, healthcare associated outbreaks have been linked to adhesive bandages, wooden tongue depressors, hospital linens, and building construction.

Community onset outbreaks have been associated with trauma sustained during natural disasters (such as during a tornado in Joplin, Missouri in 2011).

Pathology

Fungal hyphae enter the nasal cavity and paranasal sinuses via inhaled dust particles.

Infection aggressively spreads along **vascular** and **neuronal** structures and infiltrates the walls of blood vessels resulting in thrombosis and infarction of bone and soft tissues.

Penetration through the cribriform plate into the anterior cranial fossa or orbital penetration into the middle cranial fossa can occur via blood vessels and nerves, (hence "rhinocerebral").

Organisms:

Colonies of the fungus, Cunninghamella bertholletiae (http://atlasmicologia)

The **mucormycete** fungi are ubiquitous molds in the environment, particularly in soil and in association with decaying organic matter, such as leaves, compost piles, or rotting wood.

The hyphae of the Mucorales are distinct and allow for a presumptive identification from clinical specimens.

The hyphae are broad (5 to 15 micron diameter), irregularly branched, and have rare septations. This is in contrast to the hyphae of ascomycetous moulds, such as Aspergillus, which are narrower (2 to 5 micron diameter), exhibit regular branching, and have many septations.

Moulds grow best in warm, damp, and humid conditions, and spread and reproduce by making spores. Mould spores can survive harsh environmental conditions, such as dry conditions, that do not support normal mould growth

The mucormycete fungi belong to the **order** of **Mucorales.**

Fungal genera that can cause mucormycosis include:

1. Rhizopus:
    - Rhino-orbital-cerebral mucormycosis is most commonly caused by **Rhizopus oryzae**.
2. Mucor
3. Cunninghamella
4. Apophysomyces
5. Lichtheimia (formerly Absidia) species

Types of mucormycosis:

Mucormycosis can affect nearly any part of the body, but it most commonly affects the sinuses or the lungs in people who have weakened immune systems.

Recognized clinical manifestations include: [1]

1. **Rhinocerebral (sinus and brain) mucormycosis**:
    - This is an infection in the sinuses that can spread to the brain. This form of mucormycosis is most common in people with uncontrolled diabetes.

Less commonly:

2. Pulmonary (lung) mucormycosis:

   - This is the most common type of mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant.

3. Gastrointestinal mucormycosis:

   - This can result from ingestion of the fungal spores. This type of mucormycosis is less common among adults and is more common among young children, especially infants < 1 month of age.

4. Cutaneous (skin) mucormycosis:

   - This occurs after the fungi enter the body through a break in the skin (for example, after surgery, a burn, or other type of skin trauma).

     This is the most common form of mucormycosis among people who do not have weakened immune systems.

5. Disseminated mucormycosis (rare):

   - This occurs when the infection spreads through the bloodstream to affect another part of the body.

   - The brain is the most commonly affected part of the body, but other organs such as the spleen, heart, and skin can also be affected

   - The mortality rate in patients with disseminated mucormycosis is extremely high (up to 96 %).

Transmission

Mucormycosis cannot be directly transmitted between immunocompetent people or animals, so only those predisposed patients who have been exposed to mucormycetes in their environment can be infected.

The sinus or lung forms of the infection can occur after **inhalation of spores** from the air.

Mucormycosis of the skin can occur after the fungus enters the skin through a cut, scrape, burn, or other type of skin trauma.

Reservoir

Mucormycetes are thermotolerant moulds that are ubiquitous in the environment.

Susceptibility and Resistance

Risk factors:

Recognized risk factors include:

1. The immunosuppressed:
    - Diabetics (the most common predisposing factor).
    - Patients on immunosuppressive drugs
    - Patients with haematological or other malignancies
    - Neutropenic patients
    - Organ transplantation patients
    - Prolonged corticosteroid therapy
    - HIV infection
    - Malnutrition
2. Local trauma/ burns.
3 Intravenous drug use
4. Patients with excess total body iron:
    - Iron enhances fungal growth and may increase susceptibility.
5. **Voriconazole** prophylaxis (in immunocompromised individuals) has been shown to be an independent risk factor for mucormycosis; (selects for mucormycosis species which are resistant to Voriconazole). [3]

Clinical Features

The clinician must retain a high clinical suspicion for mucormycosis in patients at who are risk, as a delay in diagnosis can be fatal.

Clues in early presentation can include **black necrotic lesions** within the mouth or nasal cavity, with severe pain *seemingly out of proportion to the rest of the clinical picture*, especially in an immunocompromised patient.

Left undetected and untreated disastrous and lethal invasion of the orbit and cranial cavity can occur.

Physical deformity can be devastating.

Mucormycosis is characterized by **infarction and necrosis** of host tissues that results from aggressive invasion of the vasculature by hyphae. Disease progression is usually rapid, but there are rare descriptions of infections with a more indolent course. [3]

Symptoms of rhinocerebral (sinus and brain) mucormycosis include:

Early symptoms:

1. Fever

2. Severe headache

3. **Nasal** or **sinus** pain:

    - This is **severe** and typically appears **out of proportion** to the rest of the clinical picture.

4. Sero-sanguinous nasal discharge.

5. Unilateral facial swelling

6. Necrotic lesions:

    The **hallmark** of spread beyond the sinuses are patches of tissue necrosis.

    The disease by this stage can be far *more extensive* than is visibly apparent.

    A black eschar, which results from necrosis of tissues after vascular invasion by the fungus, may be visible in the:

    - **Nasal mucosa**
    - **Hard palate**
    - **Skin overlying the orbit**

    (See Appendix 1 below)

Late Symptoms:

With **late** presentations there can be **extensive local invasion** into the **orbit** and the **anterior cranial fossa:**

8. Orbit involvement:

    - Ptosis
    - Proptosis

- Loss of extraocular muscle function
- Vision disturbance/ blindness
- Palsies of cranial nerves II, III, IV, V and VI.

9. Invasion into the cranial fossa

- Meningitis
- Signs of cavernous sinus thrombosis
- Altered conscious state/ coma/ seizures/ death

10, Skin and bone tissue loss:

- Loss of skin and bone tissue can result in devastating cosmetic deformity, **(see Appendix 1 below).**

Prognosis:

Mucormycosis is a life-threatening infection.

A review of published mucormycosis cases found an overall all-cause mortality rate of 54%. [1]

The mortality rate varied depending on underlying patient condition, type of fungus, and body site affected, for example the mortality rate was:

- 46 % among people with sinus infections
- 76 % for pulmonary infections
- 96 % for disseminated mucormycosis

Differential diagnoses:

There are many potential differential diagnoses, depending on the stage at which the patient presents, but for practical purposes the principal ones will include:

1. May initially resemble bacterial sinusitis

2. May mimic local malignant disease.

3. May initially be confused with allergic fungal sinusitis, which is caused by phaeohyphomycoses in individuals with histories of allergic rhinitis, elevated immunoglobulin E levels, nasal polyps, and recurrent or chronic sinusitis.

4. Allergic fungal sinusitis slowly progresses over months to years, and although it causes proptosis and a large rhinocerebral mass, it does **not** invade tissue or meninges.

5. **Aspergillosis** can cause a similar disease, with CNS invasion, and also carries a poor prognosis if left untreated. This infection however is much less aggressive than that seen with the mucormycete fungi.

   An important difference is that itraconazole may play a role in treatment.

   Histologic stains can differentiate between the fungi.

Investigations

Blood tests:

1. FBE
2. CRP
3. U&Es/ glucose
4. LFTs
5. Coagulation profile

Others as clinically indicated:

6. Blood cultures

Microscopy and culture:

A definitive diagnosis of mucormycosis typically requires histopathological evidence or positive culture from a specimen from the site of infection

Mucormycetes may be difficult to differentiate from other filamentous fungi in tissue; and so experienced pathological and microbiological assistance is often required.

Biopsy:

A biopsy of involve tissue may be required in order to make a histological diagnosis, as well as to obtain tissue from which to culture the causative organism.

Endoscopic evaluation of the sinuses may be performed to look for tissue necrosis and to obtain specimens

PCR testing:

This may be available in some specialist centres.

CXR:

The diagnosis of pulmonary mucormycosis is difficult since the presentation does not differ from pneumonia due to other angioinvasive moulds.

Chest radiographs findings are non-specific and may show focal consolidation, masses, pleural effusions, or multiple nodules.

Endoscopy:

The diagnosis of gastrointestinal mucormycosis can be made with endoscopic biopsy of the lesions that demonstrate characteristic hyphae.

CT Scan:

CT imaging studies help to support the diagnosis of rhinocerebral mucormycosis and to determine the extent of disease.

It can demonstrate soft tissue extent, mucosal thickening, opacification of sinuses, and bony destruction of the sinuses and orbit. In general, bone erosion is a late finding.

A CT scan may also demonstrate cavernous sinus thrombosis, enhancement of vessels, and CNS lesions

MRI Scan:

MRI scanning is the imaging modality of choice to help to support the diagnosis of rhinocerebral mucormycosis and to determine the extent of disease.

MRI may also help to define early vascular intracranial invasion and infection along peripheral nerves before clinical signs develop.

Management

There is no vaccine to prevent mucormycosis.

Mucormycosis is a rapidly life threatening infection and needs to be treated urgently.

1. Analgesia
    - Pain is usually severe and so opioids will be required in most cases.
2. Supportive as required:

- IV fluids for patients unable to take fluid orally and/ or have become dehydrated.

3. Antifungal medications:

- **Amphotericin B** (lipid formulation) is currently considered the first line antifungal agent.
  Consider also local irrigation and packing of the areas to aid delivery of amphotericin to necrotic and poorly perfused tissues. Because poor vascular supply may prevent systemic therapy from reaching the fungus, local irrigation of infected tissue has been reported as an important adjunct to treatment and may even prevent disfiguring surgery.

  A favourable clinical response usually takes several weeks.

Second line antifungal agents include:

- Posaconazole (IV or as oral "step down" therapy).

- Isavuconazole (IV or as oral "step down" therapy).

Other antifungal agents, including **voriconazole** (which is effective for aspergillosis), **fluconazole,** and **flucytosine**, are **not** effective against the **Mucorales fungi**.

Therapy should continue until there is clinical resolution of the signs and symptoms of infection, as well as resolution of radiographic signs of active disease. Therapy should also continue until reversal of underlying immunosuppression has been achieved, where feasible. Antifungal therapy may extend for many months.

4. Surgery:

- **An essential aspect of treatment is the surgical drainage of all sinus and abscess fluid collections and debridement of necrotic tissue.**

  Aggressive surgical debridement of involved tissues should be undertaken as soon as the diagnosis of any form of mucormycosis is suspected.

- Surgery is often is significantly disfiguring. Reconstructive surgery should only be considered after **complete resolution** of the infection.

5. Hyperbaric therapy:

- This may be a useful *adjunctive* therapy.

HBO may show fungi-static activity by reducing tissue hypoxia and acidosis. However, no studies have addressed its efficacy.

6. Treatment of the **underlying predisposing pathology.**

- **Optimizing blood glucose levels in diabetics**.
- Discontinuation or at least maximally reduce any chemotherapy and immunosuppressive therapy if clinically possible.

  Any steroid medication, antimetabolites, or immunosuppressants that the patient is on should also be addressed and discontinued if appropriate.
- Granulocyte colony-stimulating factor (GCSF) can be administered to assist host defences.

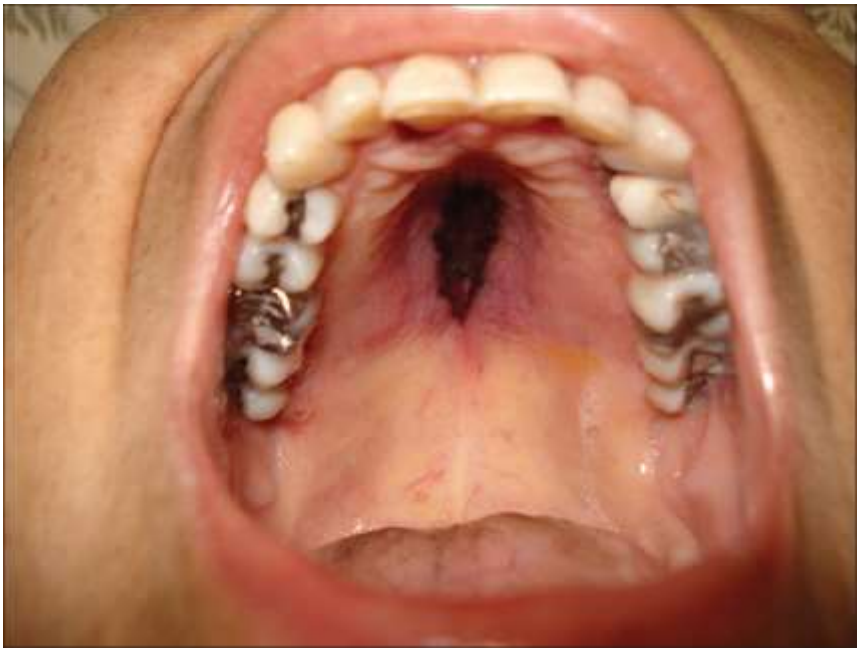
Disposition

Depending on the stage of presentation, a wide range of specialties will need to be involved including:

1. Infectious Diseases Unit
2. Microbiology
3. Radiologists
4. Surgical specialities
   - ENT
   - Neurosurgical
   - Ophthalmology

Treatment may require 7 months or more or therapy. Chronic presentations and late sequelae after successful therapy can occur and so therefore, patients will require long term monitoring to detect recurrence or low grade residual infection.

Appendix 1



Necrotic hard palate lesion in an immunocompromised patient, suggestive of a fungal infection, (in this case aspergillosis) (from Indian Journal of Dental Research, vol 23, Issue 5, 2012).

Rhinocerebral mucormycosis can cause devastating facial deformity. (Clinical photograph from C. Alfano et al. Combined Mucormycosis and Aspergillosis of the Rhinocerebral Region, Department of Plastic and Reconstructive Surgery, University La Sapienza, 00161 Rome, Italy. In Vivo 20: 311-316, 2006).

References

1. Mucormycosis in CDC Website; Accessed June 2016.

2. Michael T Yen, Rhinocerebral Mucormycosis in eMedicine Website, 3 April 2015.

3. Gary M Cox et al. Mucormycosis (zygomycosis) in Up to Date Website, August 2017.

Dr J. Hayes
Reviewed October 2017.