

# Mucormycosis (Zygomycosis)

# Case presentation

- 59-year-old non-diabetic female patient without any underlying disease with clinical symptoms of cough, shortness of breath, & O<sub>2</sub> sat = 76% on room air was admitted to Hospital.
- His vital signs: T = 37.9 °C, BP = 140/85 (mm Hg), RR = 30 HR = 90
- Positive results of CT scan of lungs and RT-PCR showed a definite diagnosis of COVID-19



# Case presentation

- She was treated with remdesivir injection at a dose of 200 mg stat and then 100 mg daily.
- The patient was under supportive care for six days, and thereafter methylprednisolone was administered at a dose of 250 mg stat and then 125 mg for 3 days.
- After 10 days, the patient was discharged while she was relatively in good general condition.



# Case presentation

- Eight days after her discharge, the patient was readmitted to hospital because of nasal obstruction and left side facial and orbital swelling



# Case presentation

- In sinus endoscopic surgery, by Rhinologist, severe involvement and **necrosis of the left side lateral nasal wall, floor, and septum as well as left ethmoid and sphenoid sinuses were observed and also destruction of the left orbital floor and medial wall were observed**

H

Spin: -0  
Tilt: -13

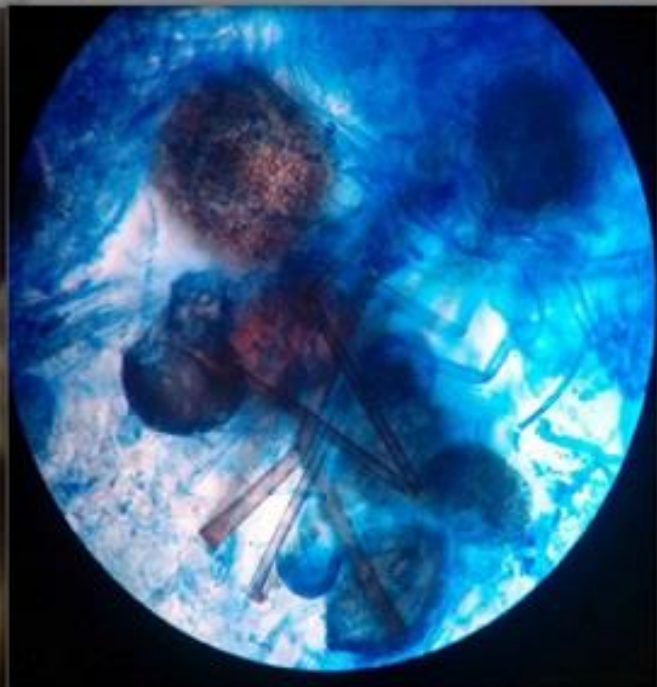
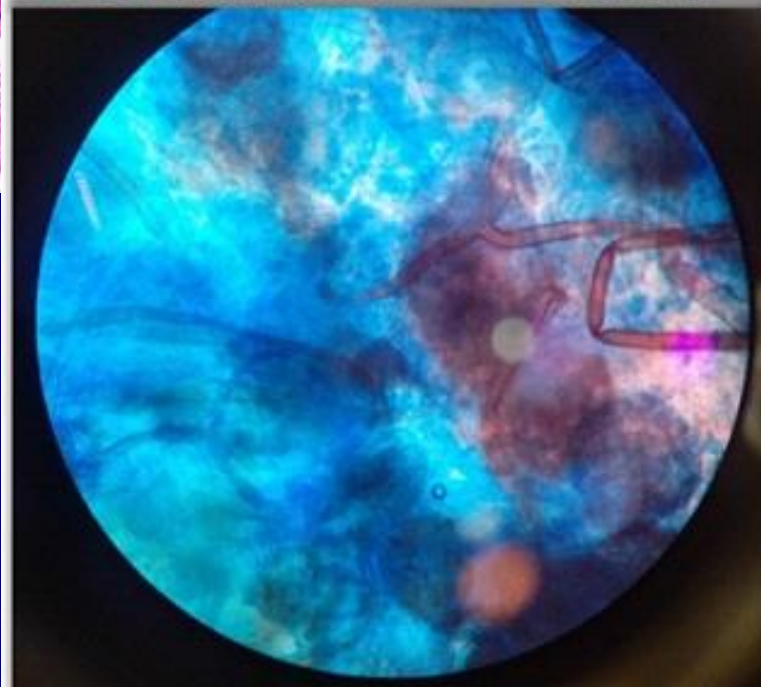
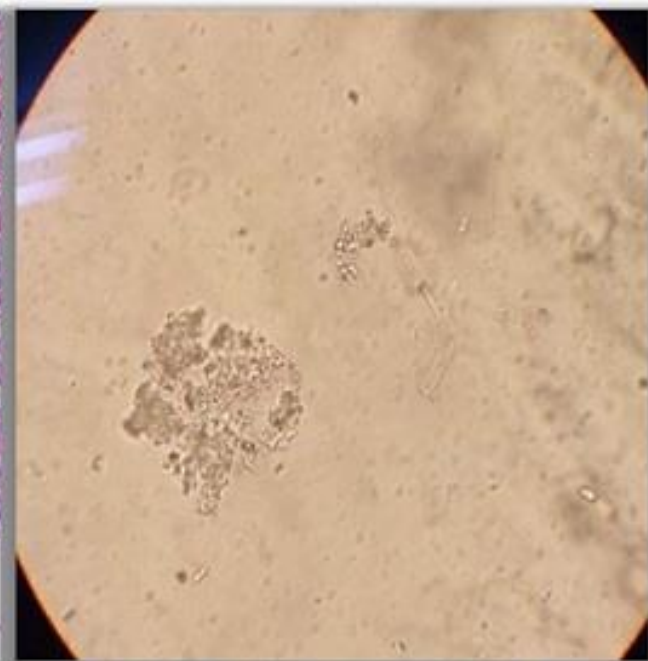
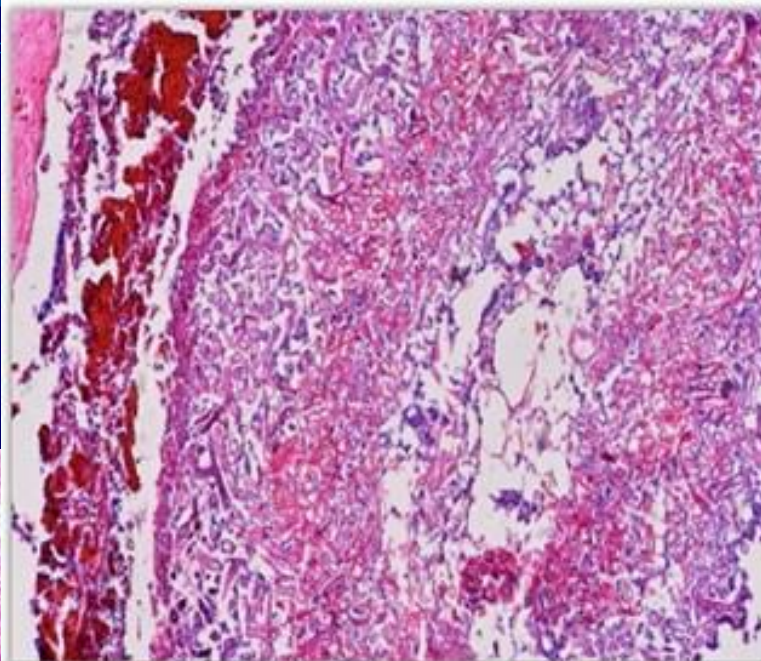
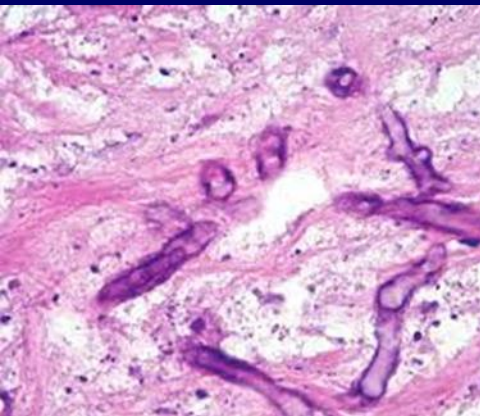


10cm  
F

# Case presentation

- Since clinical results confirmed the possibility of mucormycosis in the patient, treatment with IV liposomal amphotericin B (5 mg/kg/day)
- In addition, the patient underwent daily paranasal sinuses debridement & IV amphotericin B.
- The results with H&E staining & direct smear with 10% KOH showed irregular hyphae, wide and aseptate





# Case presentation

- A 65-year-old woman presented with a 3-day history of dry cough, shortness of breath, myalgia, and fatigue.
- Her medical history included type 2 diabetes mellitus and hypertension, which had been diagnosed 5 years previously
- The patient did not use any medications for her diabetes
- She used two antihypertensive drugs (diltiazem and losartan) on a daily basis
- The patient was admitted with a presumptive diagnosis of COVID-19

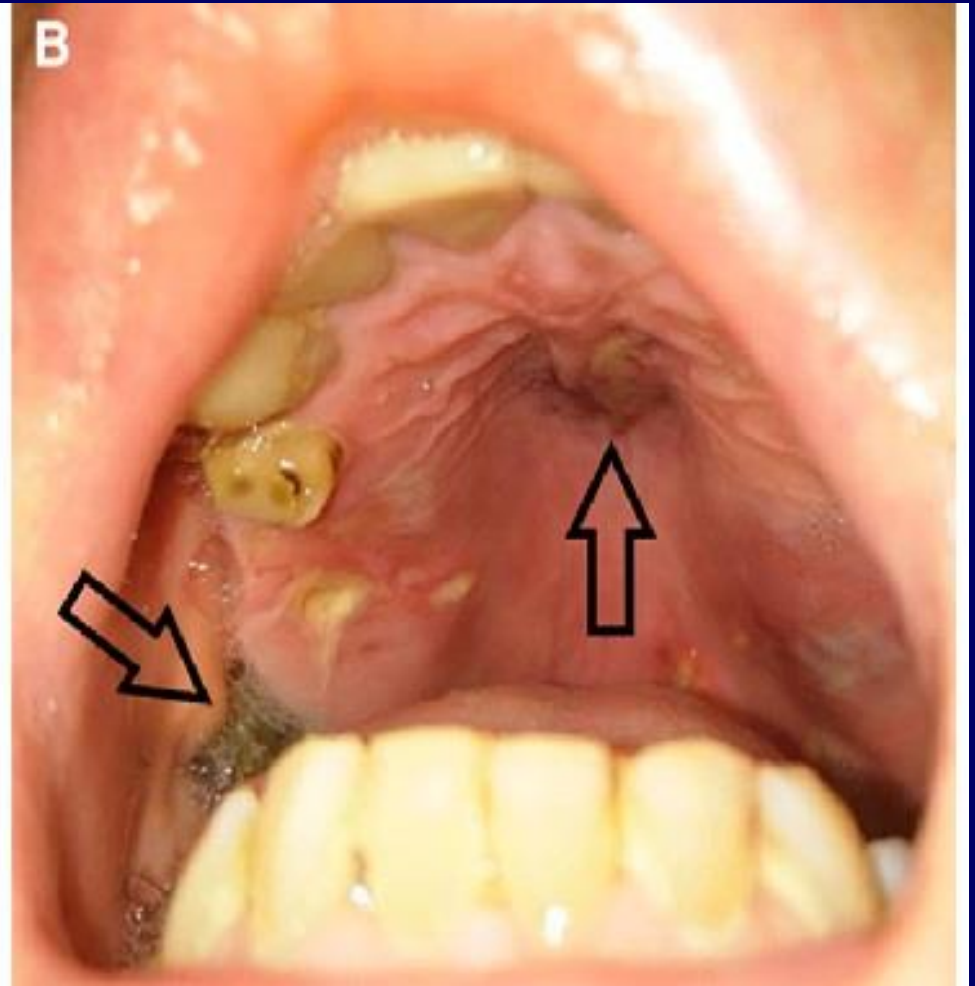
# Case presentation

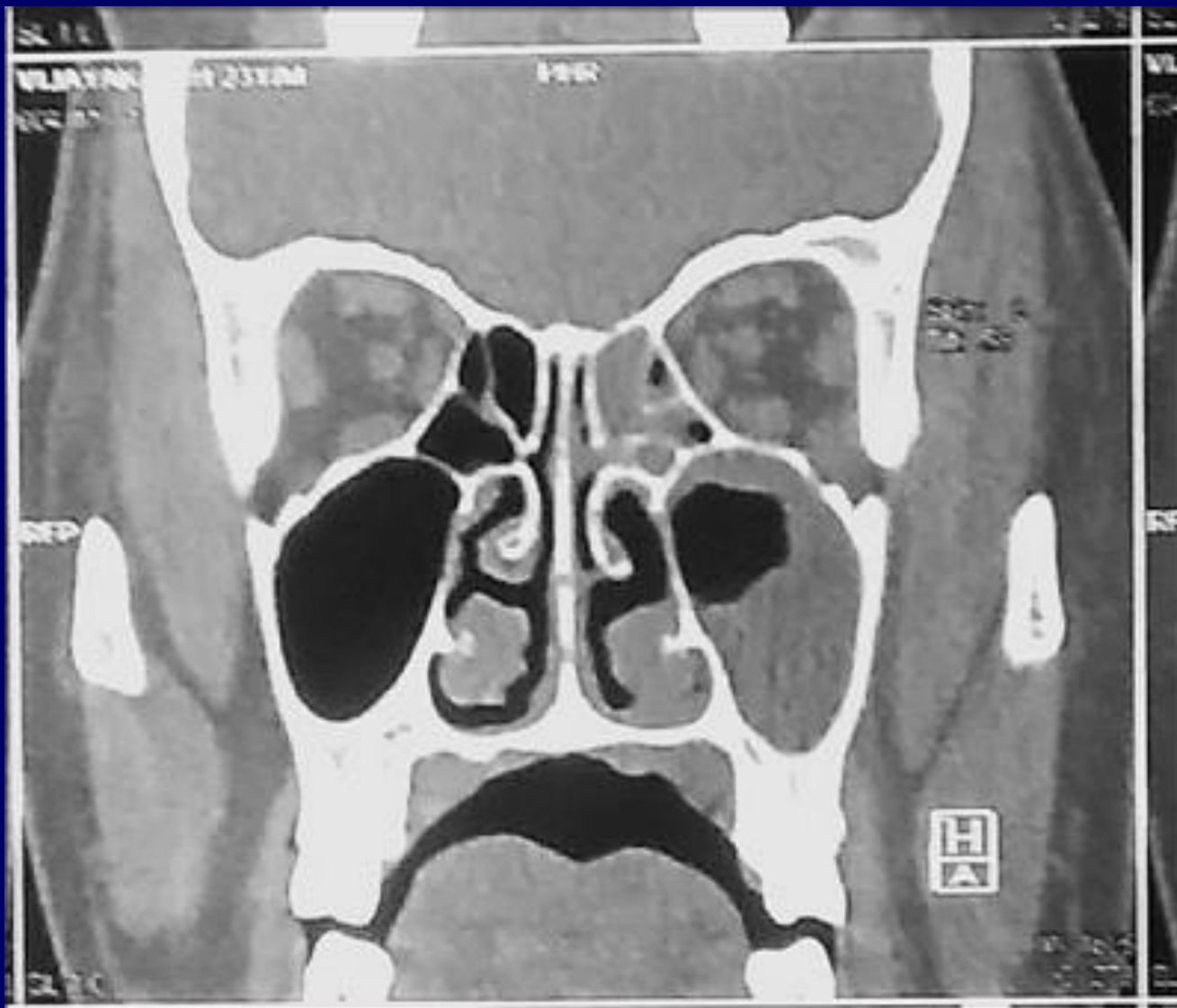
- On admission, she was hemodynamically stable,:
- BP = 160/100 mmHg, PR = 78 /min
- T(oral ) = 37.2C , RR = 32 breaths/min,
- Oxygen saturation of 88% on room air.
- Blood tests revealed normal results
- Her blood glucose level was = 224 mg/dL.
- RT-PCR → indicated SARS-CoV-2 → diagnosis of COVID-19 pneumonia was confirmed.



# Case presentation

- During hospitalization:
  - Remdesivir (200 mg on day 1 and 100 mg on days 2–5)
  - Dexamethasone (6 mg once daily for 10 days).
- After 21 days, the patient was discharged with significant clinical improvement and an oxygen saturation of 95% on room air.
- Ten days later, the patient was readmitted because of facial swelling, facial numbness, periorbital edema, and erythema, which were more prominent on the left side of the face, and headache.





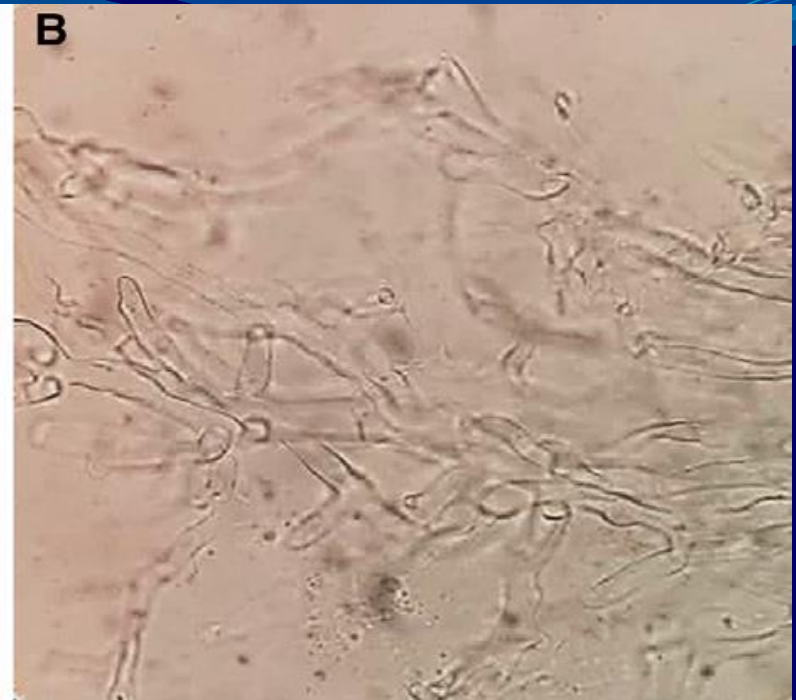
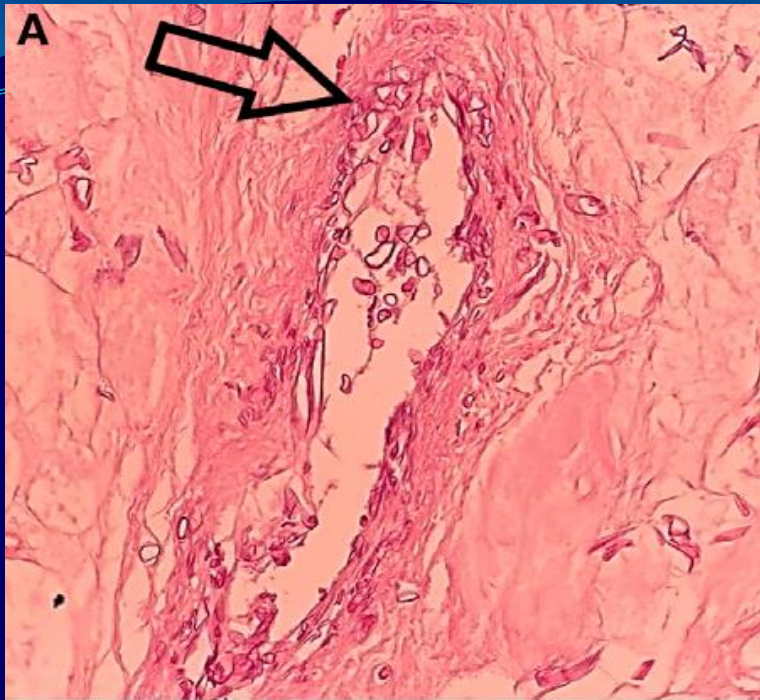
# Case presentation

- A careful and thorough physical examination revealed necrotic eschars on the palate and nasal turbinates.
- Subsequently, the patient underwent nasal endoscopy
- Surgical evaluation was immediately performed for debridement of the necrotic tissues, and multiple biopsies were performed for diagnostic purposes.

# Case presentation

- Histopathological examination of tissue biopsy  
→ broad, pauciseptate hyphae with right-angle branching that were visible within the wall and lumen of blood vessels.
- A direct smear with 10% KOH → hyaline mycelium with hyphae typical of mucorales.
- Culture of the tissue → positive results and showed growth of grayish-white (and later grayish dark brown) colonies





# Case presentation

- Several time debridement was performed
- The patient received intravenous liposomal amphotericin B during her stay at the hospital. She was finally discharged after 28 days.

# Background

- Mucormycosis, previously called zygomycosis, refers to several different diseases caused by infection with fungi belonging to the order Mucorales.
- Most mucormycosis infections are life-threatening.



# Background

- Risk factors such as diabetic ketoacidosis & neutropenia are present in most cases.
- Successful mucormycosis treatment requires correction of the underlying risk factor(s), antifungal therapy (traditionally with a polyene), and aggressive surgery.

# Etiology and Pathophysiology

- Risk factors:
  - Diabetes mellitus → especially ketoacidosis
  - Patients with cancer, especially → neutropenic & receiving broad-spectrum antibiotics
  - Patients with immunosuppressive agents → steroids & TNF-alpha blockers
  - Patients with hematologic cancer → CMV inf. & GVHD

# Etiology and Pathophysiology

- Prior receipt of voriconazole
- Extreme malnutrition → GI
- Deferoxamine use (older iron chelators)
- Trauma & contaminated medical supplies over wounds → cutaneous mucormycosis.

# Etiology and Pathophysiology

- Nonsterile tape & contaminated wooden splints with trauma/surgery
- Presence of a preexisting wound or IV line.
- Patients with burns
- No identifiable risk factors.

# Pathophysiology

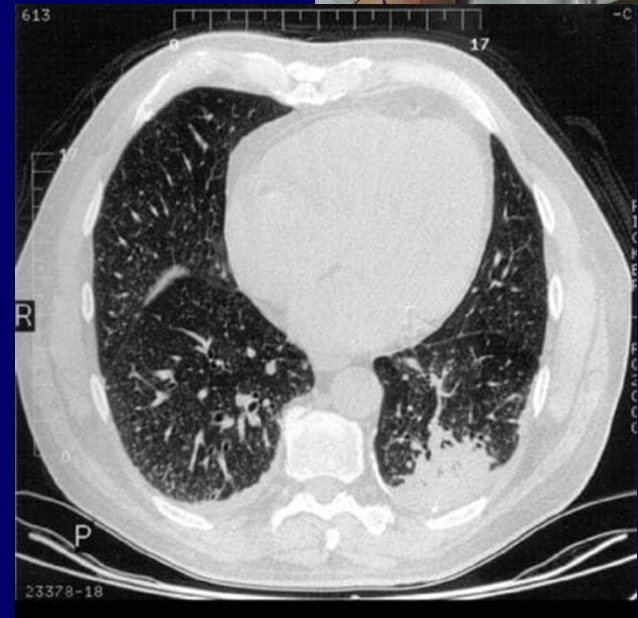
- Mucorales are ubiquitous fungi that are commonly found in soil and in decaying matter.
- Rhizopus can be found in moldy bread.
- The major route of infection → inhalation of conidia
- Other routes:
  - Ingestion
  - Traumatic inoculation

# Pathophysiology

- **fungal hyphae invade blood vessels, producing tissue infarction, necrosis, and thrombosis.**
- When spores are deposited in:
  - Nasal turbinates → rhinocerebral disease
  - Lungs → pulmonary
  - Ingested → GI disease
  - Interrupted skin → cutaneous disease

# History and Physical Examination

- Rhinocerebral disease
- Pulmonary disease
- Cutaneous disease
- Gastrointestinal
- Disseminated disease
- Central nervous system



# Prognosis

- Prognosis and survival depend on early diagnosis and timely initiation of treatment.
- Mortality varies between 40%-80%, despite advances in treatment
- Mortality depends on the site of infection.



# Prognosis

- Higher mortality of 80% → disseminated disease to CNS
- Rhino-orbital-cerebral → mortality rate of 25% to 62%
- Rapid diagnosis, and early surgical debridement, lead to lower mortality

# Rhino-orbital-cerebral mucormycosis

- The most common clinical presentation of mucormycosis
- Inhalation of spores into the paranasal sinuses of a susceptible host
- Acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and sinus pain.
- All of the sinuses become involved, and spread to contiguous structures, such as the palate, orbit, and brain, usually progresses rapidly over the course of a few days.

# Rhino-orbital-cerebral mucormycosis

- Acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and sinus pain.
- All of the sinuses become involved, and spread to contiguous structures, such as the palate, orbit, and brain, usually progresses rapidly over the course of a few days.

# Rhino-orbital-cerebral mucormycosis

- There have been some reports of rhino-orbital-cerebral mucormycosis with an indolent course that progresses over the course of weeks.
- The hallmarks of spread:
  - Tissue necrosis of the palate resulting in palatal eschars
  - Destruction of the turbinates
  - Perinasal swelling
  - Erythema and cyanosis of the facial skin overlying the involved sinuses and/or orbit

# Rhino-orbital-cerebral mucormycosis

- Orbital involvement → periorbital edema, proptosis, & blindness.
- Facial numbness → results from infarction of sensory branches of the 5<sup>th</sup> cranial nerve.
- Obtundation → Spread of the infection from the ethmoid sinus to the frontal lobe.

# Rhino-orbital-cerebral mucormycosis

- Cranial nerve palsies → Spread from the sphenoid sinuses to cavernous sinus can result in cranial nerve palsies, thrombosis of the sinus, & involvement of the carotid artery.
- Hematogenous spread to other organs is rare → underlying hematologic malignancy with neutropenia

# Rhino-orbital-cerebral mucormycosis

- Fever → 44 %
- Nasal ulceration or necrosis → 38 %
- Periorbital or facial swelling → 34 %
- Decreased vision → 30 %
- Ophthalmoplegia → 29 %
- Sinusitis → 26 %
- Headache → 25 %

# Diagnostic Considerations

- Bacterial orbital cellulitis
- Cavernous sinus thrombosis
- Rapidly growing orbital tumor
- Aspergillosis
- *Pseudallescheria boydii*
- *Fusarium* infection (fusariosis)

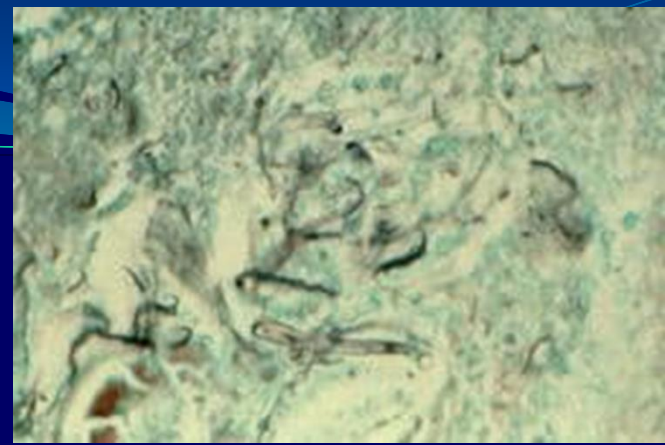


# Laboratory Tests

- Complete blood cell
- Chemistry panel
- Molecular based testing

# Diagnosis

- Imaging
- Non-pigmented hyphae showing tissue invasion must be shown in tissue sections stained with haematoxylin-eosin, periodic acid-Schiff stain or Grocott-Gomori's methenamine-silver stain or both.
- Histopathologically, Mucorales hyphae have a variable width of 6–16  $\mu\text{m}$ , but may be up to 25  $\mu\text{m}$ , and are non-septate or pauci-septate



# Treatment & Management

- Urgent surgical and medical intervention is lifesaving
- Approach Considerations
  - Diabetic control
  - Neutropenia
  - Wean off glucocorticosteroids & other immunosuppressive.

# Antifungal Therapy

- Liposomal & lipid complex amphotericin B
  - Amphotericin B deoxycholate
  - Isavuconazole
  - Posaconazole
- 
- Duration of Therapy & Long-Term Monitoring

# Consultations

- Otolaryngology consultation
- Neurosurgery consultation
- Thoracic surgery consultation
- Gastroenterology surgery consultation
- Plastic surgery consultation

# COVID-19 and Mucormycosis

- COVID-19 disease can be complicated by:
  - Secondary bacterial infection
  - Invasive fungal infection (COVID-19-associated pulmonary aspergillosis, Pneumocystosis, and mucormycosis)



Criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include:

- Black, necrotic turbinate's easily mistaken for dried, crusted Blood
- Blood-tinged nasal discharge and facial pain, both on the same side

Criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include:

- Soft peri-orbital or peri-nasal swelling with discoloration and induration
- Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia & Multiple cranial nerve palsies unrelated to documented lesions

## A number of triggers that may precipitate mucormycosis in people with COVID-19 in relation to corticosteroids:

- Presence of DM with or without DKA increases the risk of contracting mucormycosis and DM is often associated with an increased severity of COVID-19,
- Uncontrolled hyperglycemia and precipitation of DKA is often observed due to corticosteroid intake.
- Low pH due to acidosis is a fertile media for mucor spores to germinate.

## A number of triggers that may precipitate mucormycosis in people with COVID-19 in relation to corticosteroids:

- Low pH due to acidosis is a fertile media for mucor spores to germinate.
- Steroid use reduces the phagocytic activity of WBC (both first line and second line defense mechanism), causes impairment of bronchoalveolar macrophages migration, ingestion, and phagolysosome fusion, making a diabetic patient exceptionally vulnerable to mucormycosis.

## A number of triggers that may precipitate mucormycosis in people with COVID-19 in relation to corticosteroids:

- COVID-19 often causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in CD4 and CD8 T-cell level and thus predisposes to secondary or opportunistic fungal infection,
- Free available iron is an ideal resource for mucormycosis.

A number of triggers that may precipitate mucormycosis in people with COVID-19 in relation to corticosteroids:

- Hyperglycemia causes glycosylation of transferrin & ferritin, & reduces iron binding allowing increased free iron.



## A number of triggers that may precipitate mucormycosis in people with COVID-19 in relation to corticosteroids:

- Increase in cytokines in patients with COVID-19 especially interleukin-6, increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transport.
- Concomitant acidosis increases free iron by the same mechanism and additionally by reducing the ability of transferrin to chelate iron,

# COVID-19 and Mucormycosis

- The most common clinical manifestation was rhino-orbital form.
- Case fatality at 12 weeks was 45.7% with no difference in mortality among COVID-19 and non-COVID-19 patients.
- Case reports describe patients who were diagnosed with rhinocerebral mucormycosis and COVID-19 simultaneously
- Patient who was diagnosed with GI mucormycosis five days after admission for COVID-19 treated with both steroids and tocilizumab

# COVID-19 and Mucormycosis

- COVID-19 has a predisposition to cause extensive lung damage, which promotes colonization and infection of invasive fungi of airway, sinuses, and lung.
- Alteration in T cell immunity, use of steroids, and broad-spectrum antibiotics are additional risk factors for acquiring invasive fungal infection.

# COVID-19 and Mucormycosis

- COVID-19 disrupts iron metabolism, resulting in high ferritin state and increasing intracellular iron, which causes tissue damage.
- This causes more iron to be released into the circulation, and it is this increase in free iron that is a risk factor for mucormycosis.

# COVID-19 and Mucormycosis

- Patients with diabetes and infected with SARS-CoV2 are at increased risk for mucormycosis
- A retrospective study conducted in India from Sep -Dec 2020, reported a 2.0 fold rise in 2020 compared to 2019 of COVID-19 mucormycosis

# COVID-19 and Mucormycosis

- One review of case reports of mucormycosis in patients with COVID-19 included 101 cases:
  - 80 % had pre-existing diabetes mellitus
  - 76 % received glucocorticoids
- The majority of cases were from India
  - 90 % of cases involved the nose and sinuses
- Overall mortality was 31 %
- Clinicians should be aware of the potential for rhinocerebral mucormycosis as a complication of COVID-19, especially in patients with underlying diabetes mellitus.



