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Case Report

A case study of rhino orbito cerebral Mucormycosis (ROCM) in a diabetic patient reported from a multispeciality hospital in Tamil Nadu

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ABSTRACT

ROCM is the most common type of Mucormycosis and it can rapidly spread from the paranasal sinuses to orbit and brain which can be fatal in most patients. Diabetes mellitus is the most common risk factor in India. As invasive fungal diseases present with nonspecific clinical features, increasing awareness and education among clinicians about this deadly enemy is very crucial for early diagnosis and prompt initiation of appropriate therapy. We are reporting a case study on ROCM in a Diabetic patient caused by *Rhizopus* species along with a short review on the taxonomy, risk factors, pathogenesis, clinical forms, diagnosis and management of mucormycosis. We hope that this will help in expanding awareness among medical community about mucormycosis which is a lethal opponent of patients with Diabetes Mellitus.

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1. Introduction

The fungi which are placed under the order Mucorales and subphylum Mucormycotina are the causative agents for mucormycosis.¹ This disease causes opportunistic, deadly infection in immunocompromised hosts such as patients with uncontrolled Diabetes mellitus, patients with hematological malignancies and transplant recipients who are on immunosuppressive drugs.² Diabetes mellitus is the most common risk factor in India.³ ROCM is the most common type of this disease and it can rapidly spread from the paranasal sinuses to orbit and brain which can be fatal in most patients.⁴ The mortality ranges from 25% to 80% which is very significant.⁵ Early diagnosis and treatment are the foundation to decrease morbidity and mortality. Mucormycosis outbreak happened in India during the second COVID-19 wave. It was mainly ROCM type

and it affected diabetic patients with uncontrolled Glucose levels and who were on treatment with corticosteroids.⁶ We are reporting a case of ROCM successfully treated with antifungal drug and surgery along with a review on the taxonomy, risk factors, pathogenesis, clinical forms, diagnosis and management of mucormycosis.

2. Case Study

64-year-old male patient who was a known case of type 2 Diabetes mellitus for 5 years on irregular treatment presented at the emergency department of Annai arul Hospital, Chennai, Tamil Nadu with complaints of left eye and facial swelling and tooth ache for 10 days. On admission patient was afebrile and blood sugar level was >200 mg/dl. CT facial bone revealed left sinusitis with orbital cellulitis. Fungal sinusitis was suspected and patient was treated with surgical debridement and started on Amphotericin B. The samples collected during surgery were sent for fungal

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culture and Histopathological examination (HPE).

HPE showed large areas of necrotic tissue fragments with degenerated inflammatory cells. Within the necrotic tissue are seen fungal elements with broad aseptate hyphae showing occasional right-angled branching and morphologically resembling Mucorales. Special stains for fungal elements, PAS (periodic acid-Schiff) and Grocott methenamine-silver (GMS) stains were also positive.

KOH mount was done and it was negative for fungal elements. But in fungal culture there was growth in SDA on the second day of inoculation. The colonies were initially white in colour and then turned to grey. The colonies developed small black dots on the surface which are matured sporangia. Lacto Phenol Cotton blue (LPCB) mount was done and it showed broad, hyaline, irregularly branched, ribbon like sparsely septate hyphae. Sporangioophores were seen arising singly as well as in groups and bear sporangia with sporangiospores. The rhizoids are nodal and present at the junction between the stolon and sporangioophore. The organism was identified as *Rhizopus* species. The patient responded well to medical treatment with Amphotericin B for 14 days and also recovered uneventfully from surgical debridement. Thus, the patient was discharged after successful treatment at our hospital.

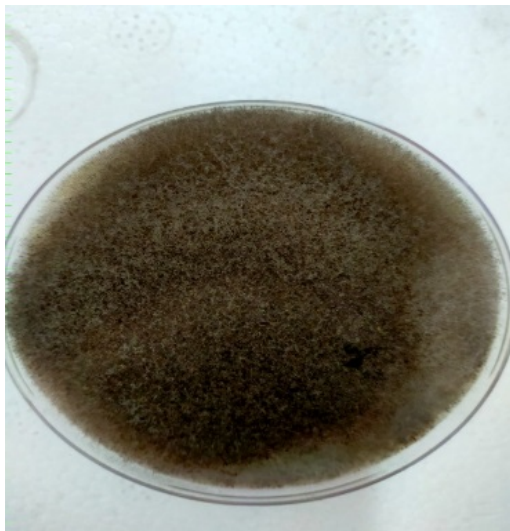


Fig. 1: Growth of *Rhizopus* in SDA plate

3. Discussion

3.1. Taxonomy of mucorales

Initially the Mucorales and Entomophthorales were placed under the phylum Zygomycota. Using molecular methods, reanalysis of kingdom fungi was done and different taxa were placed into phylum Glomeromycota which is further subdivided into four subphyla named as Mucormycotina, Entomophthoromycotina,

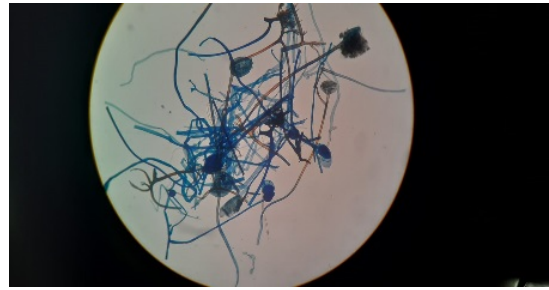


Fig. 2: LPCB mount of *Rhizopus* species

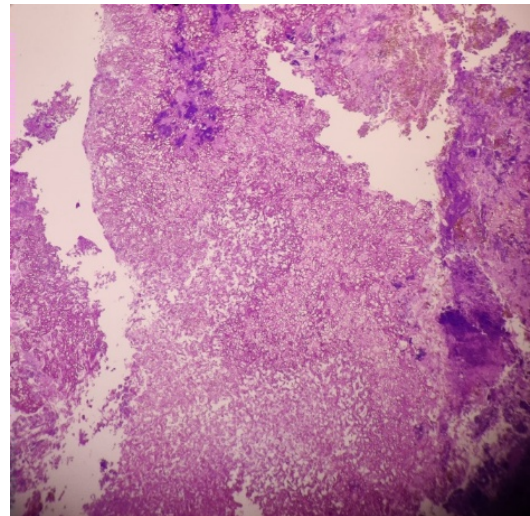


Fig. 3: H&E - 40X.

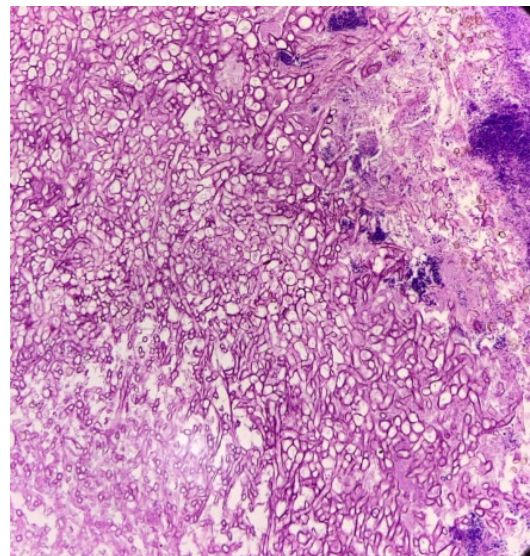


Fig. 4: GMS Stain: Broad aseptate hyphae 40x

Zoopagomycotina and Kickxellales.^{1,7} The Mucormycetes which were previously named as Zygomycetes belong to the order called Mucorales and includes six families. This change in Taxonomy led to renaming the disease as well. Earlier the term Zygomycosis was used to name invasive fungal infection caused by the fungi belonging to phylum Zygomycota. This was replaced by Mucormycosis or Entomophthoromycosis.^{8,9} *Rhizopus* and *Mucor* species belonging to family Mucoraceae and *Lichtheimia* species belonging to family Lichtheimiaceae were responsible for 70% to 80 % cases of Mucormycosis.

3.2. Characteristics of mucormycotina

These fungi are found commonly in the environment containing dead and decaying organic matter. Mucormycotina have the potential to grow at 37°C and are thermotolerant. For the growth of fungi iron is essential and therefore acquisition of Iron is an important virulence factor which determines the survival of the organism. Research has identified three methods of iron uptake in fungi which include reductive uptake of iron, using an enzyme siderophore permease and uptake of iron from haem.¹⁰

3.3. Risk factors and underlying conditions

In India, Diabetes mellitus with or without Diabetic ketoacidosis (DKA) is the number one underlying condition which is followed by hematological malignancy and solid organ transplantation. This is in contrast with the data from western countries where hematological malignancy and transplantation [both Hematopoietic stem cell transplants (HSCT) and Solid Organ transplants (SOT)] are the most common risk factors.¹¹ The other causes include neutropenia, prolonged use of corticosteroids, trauma, iron overload, intravenous drug use, prematurity and malnutrition. Due to inappropriate and over usage of steroids during the second COVID-19 outbreak, ROCM cases increased to unprecedented numbers.¹²

3.4. Pathogenesis and clinical forms

3.4.1. Pathogenesis

Although ubiquitous in nature, the fungi are not a part of normal flora in humans. The mode of spread is by asexual spores and spores enter susceptible population via respiratory tract or skin. They are encountered by immune cells like Neutrophils and Macrophages. Along with Natural killer cells they are able to destroy the fungi. If the host is immunocompetent, they are able to fight the infection with immune cells.

Patients with DKA are more prone for infection with Mucorales. The main host defense against this fungal invasion in humans are macrophages and neutrophils whereas in DKA, because of low serum pH, the phagocytic

activity of Macrophages and the chemotactic and oxidative burst which occur in Neutrophils are decreased. Also at acidic pH, transferrin is less active and will not bind Iron efficiently leading to increase in unbound Iron which is used by the fungi^{13–15} Angioinvasion is the most important mechanism in the pathogenesis of Mucormycosis. This causes thrombosis of blood vessels which results in subsequent ischemia and necrosis of tissue. The occlusion of vasculature by the fungus leads to lack of blood supply in that area which further protects the organism from antifungal drugs and host inflammatory cells.

3.4.2. Clinical forms

1. Rhino-orbital-cerebral mucormycosis — This is the most common clinical presentation of mucormycosis. Diabetes mellitus is the reported underlying condition in most of the cases. The infection presents as acute sinusitis and then spread to nearby structures such as palate, orbit, and brain. The disease usually progresses rapidly over the course of a few days. *Rhizopus oryzae* is the fungus responsible for this type in majority of cases.¹⁶
2. Pulmonary mucormycosis — Pulmonary involvement occurs after inhalation of spores into the bronchioles and alveoli. This causes Pneumonia with infarction and necrosis and there is chances of involving contiguous organs like the mediastinum and heart or the fungi can spread hematogenously to other organs¹⁷ Most patients present with symptoms of fever and hemoptysis. This is common in patients with hematologic malignancies, those who are treated with glucocorticoids or deferoxamine, and solid organ transplant recipients, and less commonly reported in Diabetic patients.
3. Gastrointestinal mucormycosis — Rarely, Gastrointestinal tract may be involved due to ingestion of spores. The underlying diseases include diabetes mellitus, transplantation, glucocorticoids administration and prematurity and malnutrition in children.¹⁸ Pain in the abdomen and hematemesis are the presenting complaints. The lesions usually present as necrotic ulcers which may lead to perforation and peritonitis. The prognosis is very poor in this type.
4. Cutaneous mucormycosis — When the spores are inoculated into dermis, infection of the skin and soft tissues occurs. Thus, cutaneous involvement is mostly associated with trauma or some wounds. In Immunocompromised host even minor breaks in the skin can cause infection. Major trauma is the reason in immunocompetent individuals. Cases of Cutaneous Mucormycosis have been reported after natural disasters and in injuries during wars. The clinical presentation is often with a single,

indurated area of cellulitis which later develops into an ecthyma-like lesion.¹⁹ Rarely complications like systemic dissemination and deep tissue involvement have been reported.

5. Renal mucormycosis — Isolated kidney involvement with mucormycosis has been reported and is believed to occur through seeding of the kidneys when an episode of fungemia happens. The risk factors include intravenous drug use and intravenous catheters.²⁰ The clinical presentation of renal mucormycosis is with flank pain and fever.
6. Isolated CNS involvement — Central nervous system (CNS) infection occurs from nearby paranasal sinus infection. During an episode of fungemia infection occurs due to seeding of brain. Most of the patients are intravenous drug users who have injected fungal contaminated material directly into the blood stream. CNS involvement has also been reported in HIV infected patients. Most of the patients presented with lethargy and symptoms suggestive of focal neurologic deficits.²¹
7. Disseminated disease — Disseminated disease is very rare and occurs in severely immunocompromised patients, patients with major burns and premature infants. The mortality rate in such patients is very high.¹⁶

3.5. Laboratory diagnosis and imaging

The outcome of Mucormycosis is very much influenced by quick diagnosis and prompt initiation of definitive therapy. The survival of the patient is improved and it also reduces the need for extensive surgical resection. For this a high index of suspicion in susceptible population is needed. Once clinically suspected, imaging along with other diagnostic methods like culture and histopathology are utilized to confirm the diagnosis.

Laboratory Diagnosis of mucormycosis includes KOH mount, culture and histopathology.

3.5.1. Potassium hydroxide (KOH) wet Mount

This is a quick test which helps in presumptive diagnosis of infection by fungi. In this wet mount, the hyphae typical of Mucorales are seen. However, the sensitivity varies as it is highly subjective and it is necessary to rule out artefacts like cotton fibres.²²

3.5.2. Calcofluor white (CFW) stain

This fluorochrome dye binds to the fungal cell wall component. Under fluorescent microscope the fungal elements will appear apple green or bluish against a background of white. KOH can also be added to CFW stain which further increases the sensitivity of this test.²²

3.5.3. Culture

Culture is a necessary tool to identify the fungal pathogen to the species level. The sample is inoculated in Sabouraud's Dextrose Agar (SDA). Mucorales usually show rapid growth where we can observe growth of cotton fluffy colonies within 72 hours. The fungal growth is identified by its colony characteristics in SDA and differing morphological features in Lactophenol Cotton Blue (LPCB) mount. The drawback of culture is low sensitivity of about 50% due to varied factors like sample collection, storage and processing. This can be overcome by proper communication and coordination between clinical and diagnostic team.²²

3.5.4. Histopathology

Histopathology as a diagnostic tool is very vital to identify whether the fungus grown in culture is a contaminant or a pathogen and to confirm invasion of blood vessels. Hematoxylin and eosin (H&E) stains show only the cell wall with no details or occasionally degenerate hyphae. Stains like periodic acid-Schiff (PAS) and Grocott methenamine-silver (GMS) are helpful as they highlight the fungal wall. The hyphae of Mucorales are wide, hyaline, ribbon like thin walled, pauciseptate which branch at right angle.²²

3.6. Treatment of Mucormycosis

Treatment include the combination of radical surgery and antifungal drugs accompanied by treating the risk factors like Diabetes mellitus.

3.6.1. Medical management

The drug of choice is Intravenous (IV) Amphotericin B (Liposomal).²³ For patients who show response to Amphotericin B, other antifungal drugs like Posaconazole or Icafonazole can be used as step down therapy. The outcome of patients is very much improved if antifungal treatment is started early.

3.6.2. Surgical management

Extensive surgical debridement of necrotic tissues should be undertaken as soon as diagnosis of Mucormycosis is suspected as it is associated with increased survival rate.²⁴

4. Conclusion

A high index of suspicion is needed for prompt diagnosis of Mucormycosis. It is imperative that in all cases of uncontrolled Diabetes mellitus especially in tropical countries like India presenting to health care facility with suspected infection at any site, mucormycosis should be included as one of the differential diagnosis. As invasive fungal diseases present with nonspecific clinical features, increasing awareness and education among clinicians about this deadly enemy is very crucial for early diagnosis and prompt initiation of appropriate therapy.²⁵ It is a real

challenge to diagnose mucormycosis. Along with clinical diagnosis, laboratory and imaging facilities are needed to confirm the diagnosis. So, it is the need of the hour to strengthen such facilities in hospitals. As we are reporting this case study along with a short review, we hope that this will help in expanding awareness among medical community about mucormycosis which is a lethal opponent of patients with Diabetes Mellitus.

5. Source of Funding

None.

6. Conflict of Interest

None.

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