

## Post COVID-19 Mucormycosis: Review of Literature

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### ARTICLE INFO.

#### Keywords:

Mucormycosis; COVID-19;  
Diagnosis; Maxillofacial infection.

### Abstract

Mucormycosis is a fatal fungal infection which emerges as a serious complication of COVID-19. It increased significantly in prevalence in the last few years especially in immunocompromised patients. Clinically, it has different types, pulmonary mucormycosis, Gastrointestinal tract mucormycosis, renal mucormycosis, Cutaneous mucormycosis, disseminated mucormycosis, but the most common type to develop is Rhino-orbital-cerebral-mucormycosis (ROCM).

A fast definitive diagnosis is the most critical step to determine the type of treatment with either a surgical or pharmacological approach and to confine the spread of the infection to neighboring tissues to achieve a better prognosis with reconstruction of affected area and decrease the rate of mortalities.

The aim of this review is to discuss mucormycosis based on evidence from 1957 until 2022 taken from different countries, to shine light on causative factor, clinical presentation, radiographic appearance, its classifications and treatment using surgical and pharmacological pathways, also show the recent reconstruction methods performed, as well as its mortality rate.

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## 1 Introduction

Mucormycosis is named by Baker, an American pathologist, in 1957 to describe a severe Rhizopus infection. It is a fatal fungal sinonasal infection caused by Mucor, Rhizopus, and Absidia species in the head and neck that affects persons with weakened immune systems.<sup>1</sup> Mucormycosis, commonly known as phycomycosis, is a fungal infection that is extremely rare but showed great increase in its spread since covid 19 pandemic.<sup>2</sup>

## 2 Causative microorganism

Mucormycosis is most commonly caused by Mucorales. Mucor, Rhizopus, and many other Zygomycetes species may be to blame, hence, the disorder is described as zygomycosis. Rhizopus oryzae (R. oryzae) is the most common type and cause of rhinocerebral zygomycosis,<sup>3</sup> accounting for over 60% of all mucormycosis infections

in humans and 90% of the Rhino-orbital-cerebral mucormycosis ROCM variation.<sup>1</sup> These fungi can be found in soil, manure, and decaying organic matter all around the world, and they can also be cultured from healthy people's noses, throats, mouths, and faeces.<sup>3</sup> Inhalation, percutaneous contact, and ingestion are the most common ways for Mucorales fungi to enter the human body.<sup>4</sup>

In immunocompromised patients, mucormycosis induces angioinvasive infection.<sup>4</sup> The disease spreads throughout the body via the bloodstream.<sup>1</sup> Thrombosis and necrosis cause blackish staining of tissues, earning it the nickname the black fungi.<sup>5</sup>

### 3 Classification

1st classification: Clinically, mucormycosis shows six different types:

- Rhino-cerebral mucormycosis
- Pulmonary mucormycosis
- GIT mucormycosis
- Renal mucormycosis
- Cutaneous mucormycosis
- Disseminated mucormycosis

The most prevalent type is rhino cerebral mucormycosis. It is of a major concern to dentists. <sup>6</sup> The Second Classification: is the most common classification system for mucormycosis which divides Fungal Rhinosinusitis (FRS) into invasive or noninvasive disease based on histopathological findings of fungal elements invading tissues. <sup>7</sup>

- Invasive diseases are divided into:
  - (1) Acute invasive type.
  - (2) Chronic invasive type.
  - (3) Granulomatous type.
- The noninvasive diseases are divided into the following clinical forms:
  - (1) Localized colonization.
  - (2) Fungal ball.
  - (3) Eosinophil-related FRS that includes AFRS.<sup>7</sup>

### 4 Diagnosis

#### 4.1 Clinical picture

Smith and Krichner defined clinical criteria for Mucormycosis diagnosis in the 1950s: Black necrotic turbinate, blood-tinged nasal discharge and soft peri-orbital or peri-nasal swelling/dyscoloration or induration are some of the symptoms, and ptosis with drooping of eyelid lid edema, and ophthalmoplegia. There may be associated multiple cranial nerve palsies.<sup>8</sup>



**Figure 1.** clinical photograph of a patient showing edema of the paranasal area involving cheek skin.<sup>8</sup>

The most obvious sign of infection in the oral cavity is a black area of eschar on palate. Looseness of teeth and fistula in the palpebral and cheeks area could be noticed. Other complications include vision loss, eye pain, and altered sensation in the infraorbital area are also common.<sup>8</sup>



**Figure 2.** clinical photograph showing extensive skin necrosis.<sup>8</sup>

The symptoms of this infection vary depending on the place of origin. Facial structures (nose, sinuses, eye, and brain) are the most commonly affected.<sup>8</sup>

From early 2021 to late 2022, early signs of stuffiness and nasal discharge, which might be blood colored, may misdiagnosed. A nasal endoscopy may reveal the presence of eschar or slough in advanced cases.<sup>8</sup> Other general symptoms such as stomach aches, nausea, vomiting, and bleeding can occur when the GI system is compromised. The damaged skin may appear as a darker red sensitive area with a deepening core due to tissue loss. There could be an ulcer, which can be very painful. Invasion into blood arteries causes thrombosis and death of nearby tissue due to a lack of vascularity.<sup>1</sup>

The widespread of mucormycosis is frequently found in people with pre-existing medical

conditions, determining which symptoms are related to mucormycosis can be difficult.<sup>4</sup> Pulmonary mucormycosis is most likely to develop in patients with significant neutropenia and graft-versus-host disease, on the other hand rhino orbital illness are more likely to develop in diabetic patients.<sup>9</sup>

Mucormycosis symptoms have been mistaken for odontogenic infection by general dentists unfamiliar with disease's clinical appearance, causing a delay in the start of definitive mucormycosis treatment and thus a poor outcome for the patient.<sup>1</sup>

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
<b>Stage 1: Involvement of the nasal mucosa</b> 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischemia, eschar	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
<b>Stage 2: Involvement of paranasal sinuses</b> 2a: One sinus 2b: Two ipsilateral sinuses 2c: Two ipsilateral sinuses and/or palatino/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
<b>Stage 3: Involvement of the orbit</b> 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anaesthesia	Signs in Stage 1 and 2 + conjunctival chemosis, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anaesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis, V1 and V2 nerve anaesthesia, and features of III, IV and VI nerve palsy indicating orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
<b>Stage 4: Involvement of the CNS</b> 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anaesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy, Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Table 1. Staging of Rhino-orbital-cerebral Mucormycosis.<sup>10</sup>

### 4.2 Radiographic picture:

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the current modalities used in the diagnosis of ROCM.<sup>8</sup>

In CT scan, the first noticeable feature is varying degrees of opacifications in the sinus with the majority of them being tumefactive. Nasal septal mucosa and nasal turbinate ulcerations and emphysematous nature are the early findings in CT imaging. Inflammation can be seen as thickening of the nasal and sinuses mucosae which is visible with or without fluid level.<sup>3</sup> Late findings include bony breach, orbital involvement, and intracranial extension but can appear early according to the pace of the disease as it can spread rapidly within hours.<sup>8</sup>

CT scans of the sinuses and lungs showing blood vessel invasion may indicate a fungal infection, but they may not confirm mucormycosis.<sup>8</sup> It can be used to distinguish between orbital mucormycosis and orbital cellulitis.<sup>1</sup>

Orbital extensions' findings on CT are: pre-septal edema, thickening of extraocular muscles, stranding at extraconal and intraconal orbital fat with or without enhancement, Phlegmon or inflammatory mass with or without abscess, optic nerve involvement.<sup>9</sup>

MRI gives better information on the soft tissue involvement which helps in the visualization of the route of invasion and the involvement of orbital soft tissue, perineural invasion, infratemporal fossa, intracranial structures. MRI can detect cavernous sinus invasion as well as vascular consequences such thrombosis and ischemia.<sup>8</sup> In ROCM, MRI with gadolinium contrast is the preferred approach. On axial or coronal slices, the characteristic 'black turbinate' sign indicates fungal rhinosinusitis.<sup>1</sup>

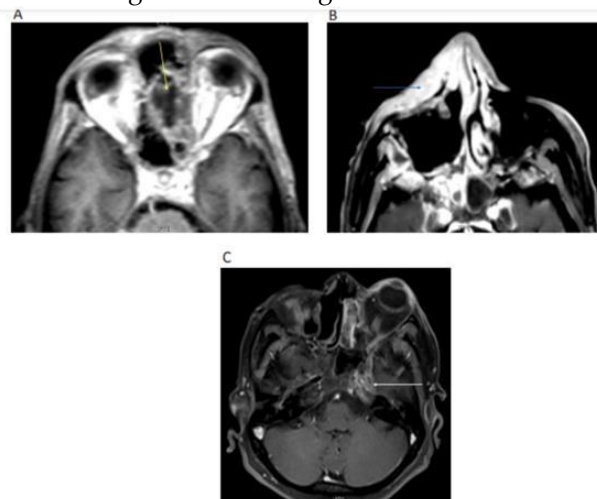


Figure 3. MRI post contrast enhancing patterns in mucormycosis. T1 post contrast MRI showing: A. hypointense pattern involving left ethmoid sinus B. Intense enhancement pattern in the left premaxillary region. C. Heterogeneous enhancement pattern in the left ethmoid and surrounding the left internal carotid artery.

Endoscopy is extremely recommended to diagnose mucormycosis if sinusitis is found. If sickness of the eye or brain is suspected, an MRI should be used instead of a CT scan because it is much more sensitive.<sup>9</sup>

Mucormycosis is strongly suggested by a reverse halo sign (RHS) in a patient with a low neutrophil count and blood malignancy.<sup>8</sup>

### 4.3 Histological features:

The gross specimens are collected for histopathological investigations by debridement of

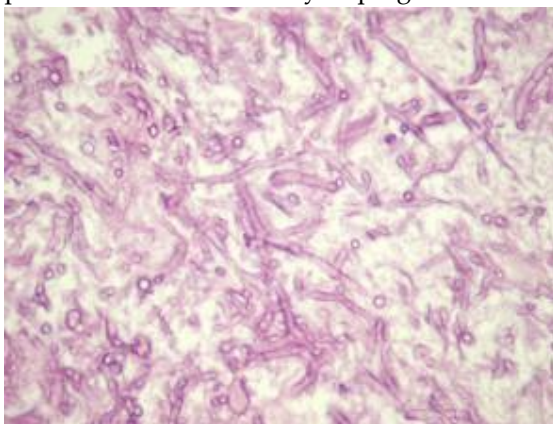
sinonasal tissue through endoscopic surgery, soft tissue debridement, maxillectomies, and orbital exenterations.<sup>11</sup>

Microscopic examination using Hematoxylin and eosin (H&E) stain shows: Mucorales which appear as nonpigmented amphophilic hyphae that have a thin wall, having a pale, and translucent appearance. Necrotic adipocytes form round to ovoid eosinophilic deposits with a crystalline internal structure.<sup>11</sup>

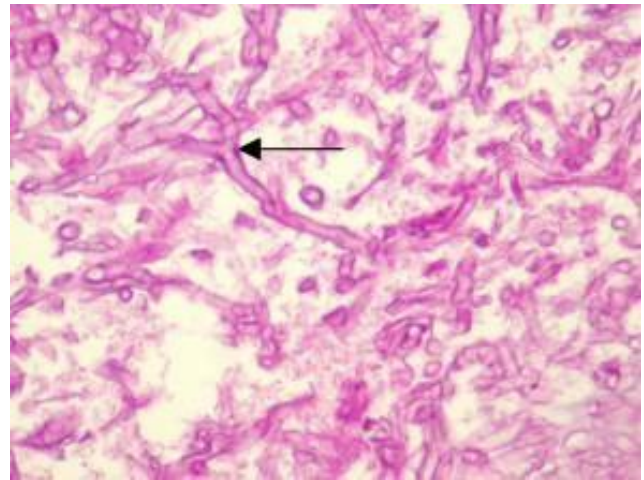
Special stains like Periodic acid Schiff (PAS) and Gomori Methenamine Silver (MGS) are used to highlight the hyphae as dark magenta and black colored structures.<sup>12</sup>

In Immunohistochemistry; tissue sections of patients with culture-proven invasive fungal infection are evaluated with conducted PCR .<sup>13</sup> Method used ELISA, Western blot, immunohistochemistry with anti-*R. arrhizus* monoclonal mouse antibody to target Cytoplasm, hyphae, walls and septae, of *R. arrhizus* WSSAs.<sup>14</sup> In situ hybridization targeting 5S and 18S ribosomal RNA sequences is still under research.<sup>14</sup>

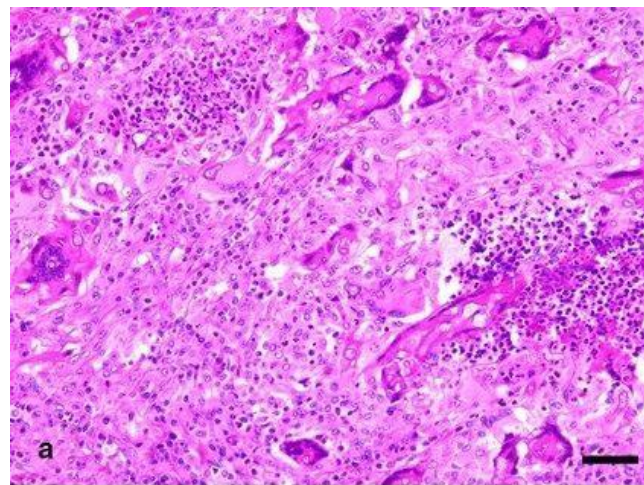
Immunohistochemistry test is useful in compensating the limitations of histomorphologic diagnosis in distinguishing between aspergillosis and mucormycosis.<sup>15</sup> Molecular techniques for mucormycosis still does not have helpful antigen-antibody methods. On the other hand, 1,3 beta-D Glucan detection test is observed to be negative in Mucorales infections, thus ruling out the possibilities of infection by *Aspergillus*.<sup>14</sup>



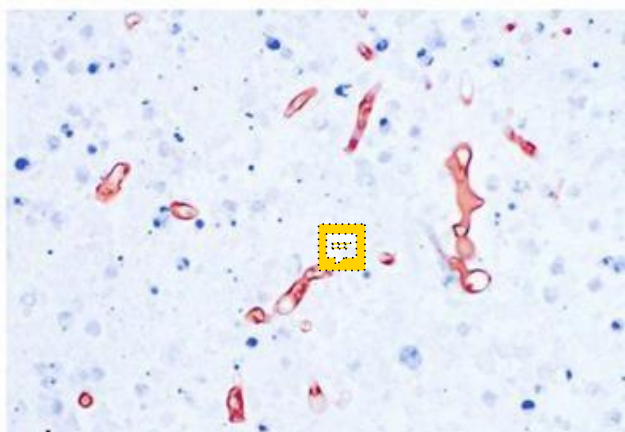
A)



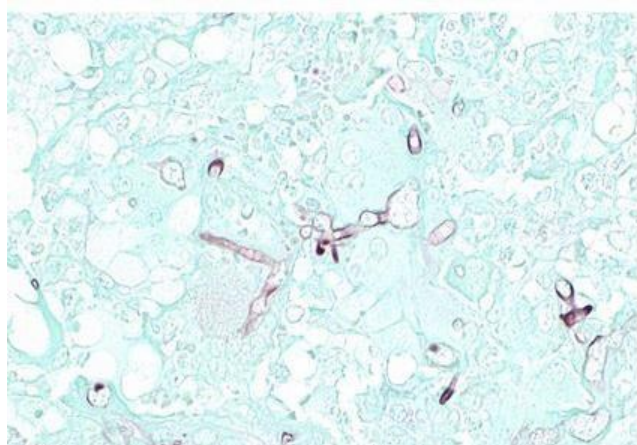
B)  
**Figure 4 A&B.** Mucormycosis organisms on haematoxylin and eosin sections <sup>16</sup>



**Figure 5.** Fungal granuloma in the right lung (H&E, bar = 50  $\mu$ m). <sup>15</sup>



**Figure 6.** Positive reaction of anti-Rhizomucor antibody on the hyphae (Immunohistochemistry [AEC], bar = 20  $\mu$ m)<sup>15</sup>



**Figure 7.** Dilated or ballooned out hyphae up to 20  $\mu\text{m}$  in diameter (Grocott's methenamine silver, bar = 20  $\mu\text{m}$ )<sup>15</sup>

### 5 Association with covid 19:

Researchers have discovered that when fungal spores enter a COVID-19 infected individual through an aerosol vector, affecting the sinuses and lungs, it primarily affects immunocompromised patients -more prevalent in male patients who are elderly<sup>8</sup> -admitted to hospitals, while it can also harm those with good immunity.<sup>1</sup>

Mucormycosis is particularly common in patients who have just been treated for COVID-19 with steroids and other anti-inflammatory medicines.<sup>1</sup> In 2020, India was the first country to report case series of COVID-19 associated mycormycosis.<sup>17</sup>

### 6 Management:

Pharmacological treatment with Amphotericin B lipid-based formulations has successfully treated mucormycosis as the first line of treatment.<sup>18</sup> Surgical debridement is the preferred treatment for the upper respiratory tract lesions.<sup>18</sup> Some patients may benefit from supplemental treatment with hyperbaric oxygen, recombinant cytokines, and/or granulocyte transfusions.<sup>18</sup>

In immunocompromised patients, the key for proper management is first to control hyperglycemia as in diabetic patient or any other risk factor then appropriate surgical debridement, and antifungal medications are the mainstays of mucormycosis treatment.<sup>3</sup>

Prognosis and choice of treatment of patient depend on infected area. Previous studies found that surgical sino-nasal debridement was

successful in 94 percent of those with mild sino-nasal illness. But rhino-orbital disease when treated with orbital exenteration along with sinus debridement had a treatment failure with progression/mortality in 89% of the cases.

Other medication like isavuconazole was approved by the Food and Drug Administration (FDA) as an antifungal drug for the treatment of invasive mucormycosis infections based on experiment that compared isavuconazole to amphotericin B in the treatment of mucormycosis.<sup>19</sup>

The determination between septate (e.g., *Aspergillus*) and non-septate hyphae (e.g., *Mucorales*) is of clinical significance, as this strongly affects antifungal treatment.<sup>20</sup> For example respiratory infections in COVID-19 can developed aspergillosis in some patient and Triazole antifungal drugs known as azoles, are the primary treatment for aspergillosis.<sup>21</sup>

### 7 Reconstruction:

Skin flaps and muscle flaps with a skin paddle have been utilized equally and reflect individual preferences. Free abdominal flaps have also been used. Osteocutaneous flaps allow for future dental repair. ALT flaps to osteocutaneous flaps were preferred in exenterated orbits.<sup>22</sup>

Surgical removal of sick tissues is a life-saving measure, but it comes at the expense of appearance and function. Advances in free flap surgery allow for the surgical restoration of previously inoperable defects and the introduction of vascularized tissue into previously damaged areas.<sup>23</sup>

When treatment plan includes repairing with a surgical obturator, its drawbacks would be difficulties in speaking and swallowing. After surgical debridement, immediate insertion of surgical obturators would help a patient with rhinocerebral mucormycosis undergoing surgical resection regain function, cleanliness, and mental stability. A closed mouth water rinsing test is used to ensure complete obturation. A soft liner is used as an interim obturator in the defect area.<sup>24</sup>

Deep resections leave important tissues exposed, which, might increase morbidity and mortality in patients if not covered. Immediate reconstruction can be done safely based on clinical criteria and if there is no evidence of hyphae invasion on

wound edges.<sup>25</sup>



(a)



(b)



(c)



(d)

**Figure 8.** (a) Surgical obturator, (b) Maxillary defect, (c) Impressions made with hydrocolloid impression material, (d) Insertion of Surgical obturator immediately after surgery.<sup>24</sup>

## 8 Mortality:

Despite recent breakthroughs in diagnosis and

treatment, mucormycosis is a deadly condition with high fatality rates.<sup>5</sup> Mucormycosis kills up to 50% of patients if left untreated.<sup>4</sup>

Lung infections are more likely to be more fatal than infections of the upper respiratory tract.<sup>18</sup> Carotid artery invasion can lead to cerebral ischemia, which can be fatal.<sup>26</sup> Orbital or cerebral involvement is linked to a poor outcome in mucormycosis, early endoscopic nasal inspection, diagnosis, and treatment are critical.<sup>27</sup>

## 9 Conclusion:

Post Covid-19 mucormycosis is a fungal infection that if left untreated may be fatal. Fast diagnosis and proper treatment to the patient is the best way to avoid its complications especially in immunocompromised patients to decrease the mortality rate.

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