



A REVIEW ON: “RHINO ORBITO CEREBRAL MUCORMYCOSIS”

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ABSTRACT-

Rheno -orbital-cerebral mucormycosis (ROCM) is a fungal infection caused by opportunistic fungi of phylum zygomycota that starts in paranasal sinuses and spreads to the orbit and brain parenchyma. ROCM is a life-threatening infection with a death rate of more than 50%, any age group may be affected by this illness. ROCM is serious infection that effects the nose, eyes and brain, infection produced by a fungus of class phycomycetes, that is typically lethal. The fungi that cause Rheno -orbital-cerebral mucormycosis live in environment particularly in soil, decaying organic mater, such as leaves, animal dung etc. ROCM can cause due to fungi enter the body through a break in the skin, the most common illness of ROCM are diabetes mellitus, hemochromatosis, and transplantation such as organ, stem cell, bone marrow etc. Post COVID-19 patient with or without risk factor, renal failure, Intravenous drug users, Patient on immunotherapy, Corticosteroid treatment, HIV, Uncontrolled diabetes, Neutropenia etc. are the risk factor for Rhino-orbital-cerebral mucormycosis. CT and MRI test can help to evaluate the severity of infection or tissue damage, their finding are not specific to mucormycosis, because diagnosis may be challenging, treatment should begin as soon as feasible to prevent mortality and enhance outcomes. The prognosis of Rheno -orbital-cerebral mucormycosis is difficult; it may require both intravenous antifungal therapy and surgical excision, in some cases. Antifungal drugs used in ROCM are Amphotericin B, Isavuconazole, Posaconazole etc. Posaconazole is the most affective antifungal drug with true in-vitro interest towards the Mucorales. Supportive care, corticosteroid and remedial drugs are all choices for COVID-19 treatment. These people on the other hand, may be at risk for invasive mould infections as a result of their steroid use.

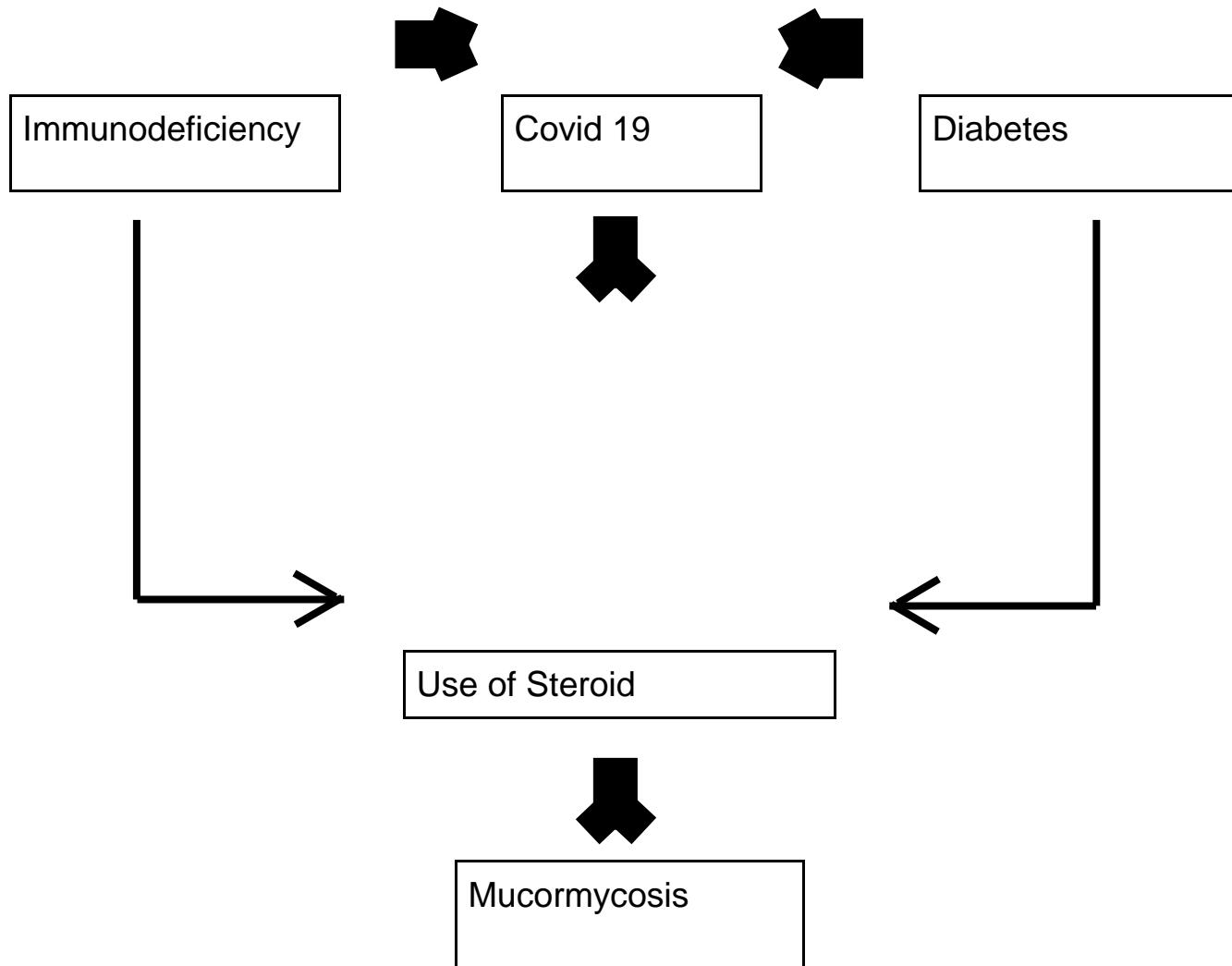
Key Words:

COVID 19, Mucor, Fungi, Posaconazole, Cunninghamella, Phycomycetes, Mucomyceta, Rizomucor, Ophthalmoplegia.

Introduction

In 1885, Paultauf initially described Mucormycosis, commonly known as Zygomycosis and Phycomycosis. Normal saprobic organisms of the class Zygomycetes, including genera as *Mucor*, *Absidia*, *Rhizopus*, and *Cunninghamella*, develop an opportunistic fungal illness. It is a rare, life-threatening, and rapidly progressing fungal infection caused by a phylum of microorganisms called Glomeromycota. Mucomyceta is a mould family that causes the fungal infection mucormucosis. The fungi can be found in a variety of places in the environment, including the soil, decaying organic materials such as leaves, animal manure, and rotten wood. *Rizopus* species, *Mucor* species, and *Rizomucor* species are the fungi that cause mucomycosis. This infection is more likely to arise if you have compromised immunity due to a sickness or health condition. A cut or a burn can potentially spread the fungus to your skin (cutaneous exposure). In some circumstances, the infection spreads to the wound or burn. While these moulds can be found in nature, not everyone who comes into contact with them will develop a fungal infection. If you have a compromised immune system, you may be more susceptible to developing this sort of infection. It is an opportunistic infection characterised by fungal hyphae invasion of blood vessels, infarction, and across of host tissue. Immunocompromised patients, particularly those with uncontrolled diabetes, have long been known to be susceptible to mucormycosis. Most people are exposed to microscopic fungal spores on a daily basis, so avoiding mucormycetes is probably impossible.

Kingdom	Fungi
Phylum	Zygomycota
Subphylum	Mucormycotina
Class	Phycomycetes
Order	A. Entomophthorales B. Mucorales
Family	Mucoraceae
General species	<i>Rizopius</i> <i>Mucor</i> <i>Absidia</i> <i>Apophysomyces elegans</i> <i>Cunninghamella genera</i>



Rhin- Orbito- Cerebral Mucormycosis

Rhino-orbital cerebral mucormycosis is an uncommon invasive fungus that starts in the paranasal sinuses and spreads to the orbits and brain parenchyma. ROCM is a life-threatening infection with a death rate of more than 50%. Early diagnosis, which determines the extent of an infection's spread, is critical because medical and surgical intervention can minimise mortality and morbidity. As a result, all radiology departments must be knowledgeable with the imaging characteristics of rhino-orbital mucormycosis. It is caused by the intake of spores through the nose and the development of coenocytic hyphae that can spread. They multiply in the sinuses after being inhaled, and can then go to the orbit by direct invasion via the nasolacrimal duct. It can spread from the orbital apex, the cavernous sinus, the cribriform plate, or blood arteries to obtain access to the brain.

Limited / Mild disease	Moderate / Severe disease
<p>Retropulsion has almost no resistance.</p> <p>There are extra-ocular motions.</p> <p>The ability to vision exists.</p> <p>Orbital imaging reveals a small amount of illness.</p>	<p>Retropulsion that is significantly positive.</p> <p>Frozen globe or restricted ocular motility.</p> <p>The ability to vision does not exist.</p> <p>Orbital connection is extensive.</p>

Signs and symptoms

Rhino-orbital cerebral mucormycosis symptoms are typically non-specific, with a wide range of severity. Sinusitis, nasal discharge, and epistaxis are among the first symptoms of Mucormycosis. Over the skin of the orbit, palate, and nasal mucosa, there is a black eschar. The gangrene of the nasal and oral mucosa is visible as a black eschar. This disease's indications and symptoms are mostly followed:

- Blurring of vision
- Severe Headache
- Eye or Facial swelling (usually unilateral then bilateral)
- Proptosis
- Ophthalmoplegia
- Orbital pain
- Facial asymmetry
- Cavernous sinus thrombosis
- Toothache

Risk factors

- Uncontrolled Diabetes
- Transplantation (organ, stem cell, Bone marrow)
- Neutropenia
- Human immunodeficiency virus (HIV)
- Corticosteroid treatment
- Patient on immunotherapy
- Intravenous drug users
- Hemochromatosis
- Renal failure
- Post COVID patients with or without Risk Factor

Age Factor:-

ROCM is not a disease that affects people as they become older. Any age group might be affected by this illness. In comparison to women, it is most often seen in men. The age group most often afflicted is 41 to 60 years old.

Causes

Rheno-orbital-cerebral mucormycosis is a fungal infection caused by fungi of phylum zygomycota. Large quantities of them have been isolated from soil or decomposing organic substances like fruit and bread. Airborne sporangiospores and/or tiny hyphal components are hypothesised to be breathed by humans into their oral and nasal mucosa. Ingestion of these components or contamination of wounds with them can also cause infection. The spores are easily retained by the phagocytic reaction of an immunocompetent host.

The infection may become established if the spores germinate and hyphae form. Immunocompromised patients, particularly those with diabetes or immunological weakness, are more likely to develop this condition. The fungi that cause Rhino-orbital-cerebral mucormycosis live in environment particularly in soil, decaying organic matter, such as leaves, compost piles, animal dung etc. Rhino-orbital-cerebral mucormycosis can cause due to fungi enter the body through a break in the skin such as kidney transplantation, a burn, organ transplantation.

ROCM in COVID-19 patients:

COVID-19 is a respiratory virus that continues to be a serious public health concern across the world. Fever, dry cough, tiredness, and shortness of breath are frequent signs of the illness, which can develop to acute respiratory distress syndrome in severe instances (ARDS). COVID-19 infection has been linked to a variety of bacterial and fungal illnesses. During therapy with corticosteroids, a patient with COVID-19 infection developed rhino-facial mucormycosis. During this pandemic, perineural extension of fungal infection was seen in post-COVID-19 immunocompetent mucormycosis patients.

The unprecedented rise in cases of COVID-19 associated mucormycosis pushed medical health to the edge even before the onslaught of the COVID-19 pandemic could settle. The most consistent associations leading to the most common manifestation of mucormycosis, Rhino-Orbito-Cerebral Mucormycosis, appear to be hyperglycemia and corticosteroids. Rhino-Orbito-Cerebral Mucormycosis (ROCM) has arisen as another medical emergency with inadequate evidence on all aspects, from prevention to care, as the second wave fades. ROCM is a disease that progresses quickly and has a death rate of about 40%. Visual deterioration, periorbital swelling, proptosis, facial pain or numbness, headache, nasal obstruction, or nasal bleed in the acute phase of COVID-19 or in the post-COVID-19 phase must all be treated with a high index of suspicion; neurological manifestations such as encephalopathy, focal neurological deficit, or seizures may also be seen.

Treatment options for COVID-19 include supportive care, corticosteroids, and remedial medicines. These individuals, on the other hand, may be vulnerable to invasive mould infections as a result of the use of steroids. Diabetes affects Covid-19 infection management even further.

Diagnosis:

The patient's history, physical exam, and risk factors for a fungal infection are used to provide a presumptive diagnosis. It's tough to make a definite diagnosis. Although tests like CT and MRI can assist determine the degree of infections or tissue damage, their results are not unique to mucormycosis. It can be difficult to diagnose, thus therapy should begin as soon as possible to reduce mortality and improve outcomes. It may also minimize the necessity for or degree of surgical resection, deformity, and pain, according to studies. The necessity for haste arises from the fact that by the time a preliminary diagnosis is confirmed, the patient has often suffered irreversible tissue damage. Although no sufficiently powered trials testing 1,3 beta-D-glucan in different types of mucormycosis have been performed, it is generally observed that 1, 3 beta-Dglucan detection test is negative in Mucorales infections. No circulating antigen detection test (similar to galactomannan detection for invasive aspergillosis) is available for the diagnosis of mucormycosis. There is currently no standardised blood polymerase chain reaction (PCR) test. A sinus and chest CT should be conducted in addition to brain imaging, regardless of the original clinical site involved, especially if there are suggestive signs and symptoms. This is significant since the therapeutic method for brain lesions differs.

Treatment:

Mucormycosis is a difficult disease to cure. It may require both intravenous antifungal therapy and surgical excision in some cases, necessitating the use of a multidisciplinary team in a facility environment. The medicine of choice is liposomal amphotericin B, which should be started as soon as possible. Treatment with antifungals such as posaconazole or isavuconazole has also been described. Controlling diabetes, reducing steroid use, and discontinuing immunomodulating medicines are all critical, according to doctors. The treatment includes an IV infusion of normal saline (IV) followed by an infusion of amphotericin B and antifungal medication for at least 4-6 weeks to maintain appropriate systemic hydration. Hyperbaric oxygen treatment is an effective adjuvant therapy for diabetic individuals with rhinocerebral or severe cutaneous disease who have mucormycosis.

Common antifungal medications that your doctor may prescribe for mucormycosis include:

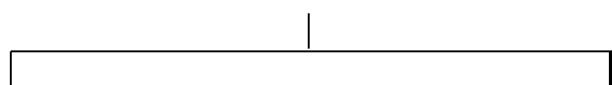
- Amphotericin B (given through an IV)

- Posaconazole (given through an IV or orally)
- Isavuconazole (given through an IV or orally)

Early antifungal administration and extensive surgical debridement are carried out empirically whenever the possibility of rhino-orbital cerebral mucormycosis is suspected based on risk factors, clinical features, and/or radiologic findings. A three-pronged approach of reversal of immunosuppressive state, administration of IV antifungals, and extensive surgical debridement is usually undertaken.

The treatment must be continued until the clinical signs and symptoms of infection, as well as the resolution of radiological signs of active disease and the elimination of predisposing risk factors such as hyperglycemia, immunosuppression, and other predisposing risk factors, have been resolved; this could take a long time. If liposomal Amphotericin B (deoxy cholate) is not available and renal functions and serum electrolytes are within normal ranges, conventional Amphotericin B (deoxy cholate) in the dose range of 1-1.5 mg/kg may be utilized. Antifungal medications are required to treat mucormycosis. These can only be used with a health care provider's prescription. Surgery around the eyes and nose may be required in some circumstances. Do not self-medicate — if these medications are not used appropriately, they might cause injury.

ROCM may be possible or proved.



Surgical debridement is required immediately. Glycemic management is really important.



Inj Amphotericin B(1.0-1.5 mg/kg/day) or Inj Amphotericin B lipid complex 5mg/kg/day or Inj Liposomal amphotericin B 5-10 mg/kg/day (intra cranial involvement 10 mg/kg/day)



Continue treatment until the initial imaging findings are resolved and the host immune system has been restored.

Prevention:

In the COVID19 era, preventing ROCM requires the cautious use of steroids (both dose and duration), the management of comorbidities (particularly diabetes), and the maintenance of sanitation and cleanliness. The Indian recommendations for COVID19 currently do not support the use of medications like posaconazole for prophylaxis. Posaconazole prophylaxis is only recommended for individuals with neutropenia and graft-versus-host disease with moderate strength, according to international standards.

ROCM has been classified into three categories: plausible, probable, and proved. Despite the need to make every effort to achieve a certain diagnosis, starting antifungal medication in even probable instances has a positive risk–benefit ratio. When the author recommends clinical follow-up with endoscopy and radiology without the use of antifungal medicines in the case of potential ROCM, pharmacological therapy for prophylaxis becomes obsolete.

Conclusion:

Diabetes, which is a prominent risk factor for ROCM in developing nations, has resulted in a rise in the incidence of ROCM. Early and effective diagnosis and therapy of this severe infection can be facilitated by health-care monitoring

programs, physician awareness, and collaboration between mycologists and pathologists. Patients with haematological malignancies who come with periorbital pain and edema or blood-stained nasal discharge with multiple cranial nerve palsy have a poor prognosis and should be suspected of ROCM.

Reference:

- Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol* 1994;39(1):3-22.
- Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. *Manual of Clinical Microbiology*. Washington, DC: ASM Press, 1995.
- Hamilos G, Samonis G, Kontoyiannis DP. Pulmonary mucormycosis. In: Baddley JW, Pappas PG, Seminars in respiratory and critical care medicine. © Thieme Medical Publishers; 2011;32(06):693-702.
- Petrikos G, Tsiotis C. Recent advances in the pathogenesis of mucormycoses. *Clin Ther*. 2018;40(6):894-902.
- Galletti B, Freni F, Meduri A, et al. Rhino-Orbito-Cerebral mucormycosis in diabetic disease mucormycosis in diabetic disease. *J Craniofac Surg* 2020;31:e321-4.
- C. Vaughan, A. Bartolo, N. Vallabh, S.C. Leong *Clin Otolaryngol*, 43 (6) (2018), pp. 1454-1464, 10.1111/coa.13175 Epub 2018 Aug 8. PMID: 29947167
- Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: a tale of two pathogens. *Indian J Ophthalmol*. 2021;69(2):244.
- Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. *Clin Infect Dis*. 2008;47(4):503-9 [PubMed] [Google Scholar]
- Walsh T.J., Gamaletsou M.N., McGinnis M.R., Hayden R.T., Kontoyiannis D.P. Early Clinical and Laboratory Diagnosis of Invasive Pulmonary, Extrapulmonary, and Disseminated Mucormycosis (Zygomycosis) *Clin. Infect. Dis.* 2012;54:S55-S60. doi: 10.1093/cid/cir868. [PubMed] [CrossRef] [Google Scholar]
- Charles Patrick Davis, MD, PhD Medical Editor: Mary D. Nettleman, MD, MS, MACP. Medically Reviewed on 5/10/2021
- Tragiannidis A, Groll AH. Hyperbaric oxygen therapy and other adjunctive treatments for zygomycosis. *Clinical Microbiology and Infection*. 2009 Jan 1;15:82-6.
- Sundar S, Chakravarty J. Liposomal amphotericin B and leishmaniasis: dose and response. *Journal of global infectious diseases*. 2010 May;2(2):159.
- O'Neill MB, Alessi SA, George BE, Piro J. Disseminated RCM: A case report and review of literature. *J Oral Maxillofac Surg*. 2006;64:326–33. [PubMed] [Google Scholar]
- Damm N, Allen, Bouquot, editors. 5th ed. New Delhi: Elsevier A division of Reed Elsevier India Private Limited; 2006. *Oral and maxillofacial pathology*. [Google Scholar]
- Hibbett DS, Binder M, Bischoff JF, Blackwell M, Cannon PF, Eriksson OE, et al. A higher-level phylogenetic classification of the Fungi. *Mycol Res* 2007;111:509-47.
- Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41:634–653. [PubMed]
- Ibrahim, A. S., Spellberg, B., Walsh, T. J., & Kontoyiannis, D. P. (2012). Pathogenesis of mucormycosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 54 Suppl 1(Suppl 1), S16-22
- Cox, G., Kauffman, C., & Thorner, A. (2019). Mucormycosis (zygomycosis). *Uptodate*
- Honavar SG. Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-Orbito-Cerebral Mucormycosis in the Setting of COVID-19. *Indian J Ophthalmol* 2021;69:13615.
- EVIDENCE BASED ADVISORY IN THE TIME OF COVID-19. Downloaded from: <https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis ADVISORY FROM ICMR In COVID19 time.pdf>. [Last accessed 2021 May 13].
- Warwar RE, Bullock JD. Rhino-orbital-Cerebral mucormycosis: a review. *Orbit*. 1998 Jan 1;17(4):237-45.
- Wali U, Balkhair A. Cerebro-rhino orbital mucormycosis: an update. *Journal of infection and public health*. 2012 Apr 1;5(2):116-26.

23. Pillsbury HC, Fischer ND. Rhinocerebral mucormucosis. Archives of Otolaryngology. 1977 Oct 1;103(10):600-4.
24. Gamaletsou MN, Sipsas NV, Roilides