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Review Article

COVID-19 Associated Mucormycosis (CAM): A Narrative Review on Craniofacial Mucormycosis

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ABSTRACT:
The COVID-19 pandemic has caused a surge in the number of cases of mucormycosis. Most cases are temporally linked to COVID-19; hence, the entity is described as COVID-19-associated mucormycosis (CAM). The most common type of mucormycosis seen in the setting of COVID-19 is Rhino-orbito-cerebral Mucormycosis / Craniofacial Mucormycosis. It poses an important burden on immunocompromised patients, due to its persistently high mortality. Subjects with diabetes mellitus and multiple risk factors may be at a higher risk for developing mucormycosis. Concurrent glucocorticoid therapy probably heightens the risk of mucormycosis. The diagnosis and treatment of mucormycosis remain a challenge. The clinical presentation is nonspecific, and, when it becomes apparent that the patient most probably has mucormycosis, it is often too late to administer effective treatment. Early diagnosis is thus crucial and is the main target of current research. A high index of suspicion and aggressive management is required to improve outcomes. The management of mucormycosis is multimodal, including reversal of underlying risk factors, administration of antifungal agents, surgical intervention and various adjunctive therapies. Timely and adequately dosed antifungal therapy is necessary. Liposomal Amphotericin B in the initial dose of 5mg/kg body weight with strict metabolic control is the treatment of choice.
KEYWORDS: COVID-19 associated Mucormycosis, Craniofacial Mucormycosis, Immunosuppression, Diabetes Mellitus

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INTRODUCTION

The emergence and rapid spread of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a potentially fatal disease, continues to be a significant problem worldwide. It has been associated with a wide range of opportunistic bacterial and fungal infections. Both Aspergillosis and Candida have been reported as the main fungal pathogens for co-infection in people with COVID-19. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, particularly from India. This entity has been termed as COVID-19 Associated Mucormycosis (CAM) which occurs during active / recovering or post recovery phase of coronavirus infection.

Mucormycosis (previously called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These molds live throughout the environment. Mucormycosis is an opportunistic infection that typically affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury.

The primary reason that appears to be facilitating Mucorales spores to germinate in people with

COVID-19 is an ideal environment of low oxygen levels (hypoxia), high glucose, acidic medium, high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.

The most common type of mucormycosis seen in the setting of COVID-19 is Rhino-orbito-cerebral Mucormycosis / Craniofacial Mucormycosis.[1] The term ROCM refers to the entire spectrum ranging from the sino-nasal tissue invasion (limited sino-nasal disease), progression to orbits (limited rhino-orbital disease) to finally central nervous system involvement (rhino-orbital-cerebral disease). The increasing incidence of Rhino-orbito-cerebral mucormycosis (ROCM) in India has become a matter of immediate concern.

EPIDEMIOLOGY

The exact burden of mucormycosis is not known. The true incidence and prevalence may be higher than what appears. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries. India has the highest cases of the mucormycosis in the world. In developing countries like India, the incidence of diabetes mellitus is alarmingly high which leads to rise in the incidence of mucormycosis, with an overall mortality of 46%.[2]

ETIOLOGY

The causative agent of the mucormycosis is saprophytic fungi of the class Phycomycetes, order Mucorales, and the family Mucoraceae. These fungi include Mucor, Rhizopus, Absidia, Cunninghamella genera, and Apophysomyces elegans. The commonest cause of human infection is Rhizopus arrbizus.[3] Inhalation of spores from fungi living in soil or organic matter in immunocompromised patients is the most common route of invasion. Being an opportunistic infection, reduced host immunity and appropriate host environment such as hyperglycemia, iron overload favor the fungal invasion. It flourishes more in hot and humid climate and environment especially in tropical areas and summer season.

CLASSIFICATION[3]

1. Rhino-orbital-cerebral Mucormycosis (ROCM) / Craniofacial Mucormycosis : infection that begins in the paranasal sinuses and then spreads to involve the orbit, face, palate and/or brain. It is the commonest clinical form of mucormycosis and is often fatal within a week of onset if left untreated. It is most commonly seen in neutropenic cancer patients, HSCT recipients and diabetes with uncontrolled ketoacidosis.
2. Pulmonary Mucormycosis : infection develops in lungs as a result of aspiration of infectious material or following inhalation or from hematogenous or lymphatic spread during dissemination. If untreated, haematogenous dissemination to other organs, particularly the brain will often occur. The infection is fatal within 2-3 weeks. It is most commonly seen in neutropenic cancer patients undergoing remission induction treatment.
3. Gastrointestinal Mucormycosis : rare condition in which all segments of the gastrointestinal tract can be involved, but lesions are most common in the stomach, colon and ileum. The disease is seldom diagnosed during life. It is usually encountered in malnourished infants or children.
4. Cutaneous Mucormycosis : Traumatic inoculation of spores can lead to excessive necrotic cutaneous infections. It is most often seen in patients with burns or other forms of local trauma.
5. Disseminated Mucormycosis : infection may spread through the bloodstream to affect another part of the body. This may follow any of the above four forms of mucormycosis, but is usually seen in neutropenic patients with a pulmonary infection. The commonest site of spread is the brain. Cerebral infection following haematogenous dissemination is distinct from rhinocerebral form of mucormycosis.
6. Other forms of Mucormycosis : isolated mucormycosis brain lesions have been reported in parenteral drug abusers.

PATHOPHYSIOLOGY[4]

Higher rates of mucormycosis cases in India are due to a combination of factors. COVID-19 leads to a weakened immune system, preventing the body from effectively protecting against infection. As a result, individuals recovering from COVID-19 are at high risk for mucormycosis. There is an increased incidence of infection in diabetic patients, especially diabetic ketoacidosis. Phagocytosis of leukocytes, neutrophils chemotaxis, and local inflammatory response is depressed in patients with diabetes mellitus. Figure 1[5] depicts the association between COVID-19 and Mucormycosis.

Mucormycetes enter the body either by inhalation of airborne spores, percutaneous inoculation or ingestion. Once the spores reach the lungs or subcutaneous tissues, they are destroyed by the first line of defence, mononuclear and polynuclear phagocytes in healthy individual. But when an immunocompromised host breathes in the spores of mucormycetes, the defence system is hampered, and it cause an infection commonly in the lungs or sinuses.

In case of Craniofacial / Rhino-orbito-cerebral mucormycosis, the infection starts in the nasal cavity and extends to adjoining paranasal sinuses. It gets

implanted and grows in the nasal cavity and sinuses. The humid environment of the nose and paranasal sinuses favours the growth and invasion of fungi. Early implantation of fungi is common in maxillary sinus with a mass of fungal growth called a fungal ball and no bone erosion. In undiagnosed or untreated cases, the infiltration of bone is common. It almost extends in all surrounding tissues. It then progresses to the brain via either ethmoid sinuses, orbital apex, and through bone erosion or through angioinvasion. Invasion of blood vessels by fungal hyphae damages the endothelium causing blood clots that occlude the blood vessels leading to ischemia and necrosis of surrounding tissue. This necrotic tissue is the nidus for organism growth, and it thrives there and subsequently invades the surrounding tissues through blood vessels. Ischemic necrosis of infected tissues can prevent delivery of leukocytes and antifungal agents to the foci of infection. This angioinvasion likely contributes to the capacity of the organism to hematogenously disseminate to other target organs. Consequently, damage of and penetration through endothelial cells or the extracellular matrix proteins lining blood vessels is likely to be a critical step in the pathogenicity.

CLINICAL PRESENTATION

Infection usually begins in the mouth or nose and enters the central nervous system via the eyes. Early stages may include one-sided eye pain or headache, and may be accompanied by pain in the face, numbness, fever, loss of smell, a blocked nose or runny nose. In advanced stages, the person may appear to have sinusitis. The face may look swollen on one side, with rapidly progressing black lesions across the nose or upper inside of the mouth. One eye may look swollen and bulging, and vision may be blurred. Affected skin may appear as a dusky reddish tender patch with a darkening centre due to tissue death. There may be an ulcer and it can be very painful. Invasion into the blood vessels can result in thrombosis and subsequent death of surrounding tissue due to a loss of blood supply. In most advanced cases, involvement of the brain leads to cavernous sinus thrombosis, cerebral infarct, hemiplegia, seizures or can develop mental status changes or coma or death.

Oral manifestations may include:
•Swollen gums with pus discharge
•Unexplained tooth/ upper jaw mobility
•Palatal swelling
•Palatal ulcer
•Bone necrosis – Hard palate / Maxilla (Eschar)

In 1950, Smith and Krichner[6] gave a criterion for the clinical diagnosis of ROCM. It is considered to be gold standard. It is as follows:

i. Black, necrotic turbinates easily mistaken for dried, crusted blood,
ii. Blood-tinged nasal discharge and facial pain, both on the same side,
iii. Soft peri-orbital or peri-nasal swelling with discoloration and induration,
iv. Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and,
v. Multiple cranial nerve palsies unrelated to documented lesions.

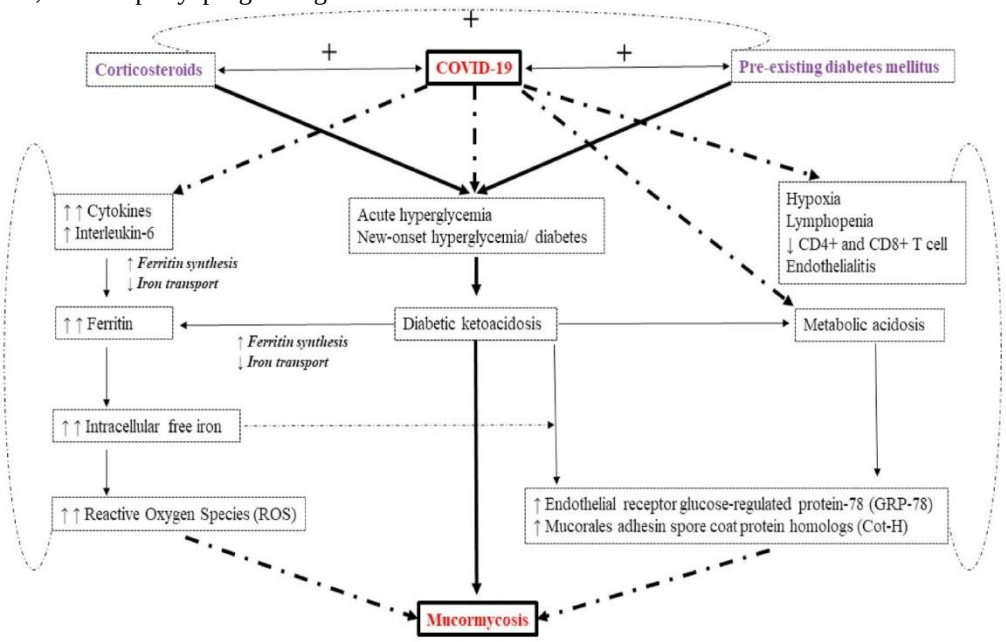

Figure 1: Schematic diagram showing the likely association between the novel coronavirus disease (COVID-19) and mucormycosis. [5]

INVESTIGATIONS[7]

- Direct microscopy - (90% sensitivity)
  Specimen : Deep or endoscopy-guided nasal swab, paranasal sinus, or orbital tissue.
  Stains used: KOH mount, LPCB mount and calcofluor white
  Key Features: Non-septate or pauci septate, irregular, ribbon like hyphae; wide angle of non-dichotomous branching (>/ 45-90 degrees) and greater hyphal diameter as compared to other filamentous fungi. These are 6-25 um in width. (Figure 2)

- Culture-
  Specimen : Deep or endoscopy-guided nasal swab, paranasal sinus, or orbital tissue.
  Stains used: Brain heart infusion agar, potato dextrose agar or preferably sabouraud dextrose agar with gentamicin or chloramphenicol and polymyxin-B but without cycloheximide, incubated at 30-37^0 C.
  Key Features: Rapid growth of fluffy white, grey or brown cotton candy -like colonies. The hyphae are coarse and dotted with brown or black sporangia.

- Molecular Diagnostics- (75% sensitivity)
  Specimen: Tissue sample (deep or endoscopy-guided nasal swab, paranasal sinus, or orbital tissue), culture or blood.
  Key features: Development of molecular biology tools has allowed the non invasive diagnosis of Mucormycosis. Polymerase chain reaction assay was designed with the aim to detect Mucorales DNA early in the course of infection of serum and it has shown tremendous success rate.

- Histopathology-
  Specimen- Nasal mucosa, paranasal sinus mucosa and debris or orbital tissue should be subjected to rapid diagnostic techniques such as frozen section, and squash and imprint and also processed for routine fixed sections.
  Stains used : Hematoxylin-Eosin, periodic acid- Schiff and grocott- Gomori's methenamine silver special stain.
  Key Features: Hyphae showing tissue invasion is confirmatory of invasive ROCM. Hyphae vary in width from 10-20 um in diameter and 6-50 in width on histopathology and are non-septate or pauci-septate. In the tissue, hyphae appear ribbon-like with an irregular pattern of branching. Wider, irregular, ribbon-like hyphae are more reliable diagnostic features.

- Imaging – [8]
  Techniques: Contrast enhanced MRI (preferred) and CT scan
  Key Features: Nasal and paranasal sinus mucosal thickening with irregular patchy enhancement is an early sign.
  Ischemia and non-enhancement of turbinates manifests as an early sentinel sign on MRI- black turbinate sign.
  The fluid level in the sinus and partial or complete opacification signifies advanced involvement of paranasal sinuses.
  Thickening of the medial rectus is the early sign of orbital invasion.
  Patch enhancement of the orbital fat, lesion in the area of superior and inferior orbital fissure and the orbital apex and bone destruction at the paranasal sinus and orbit indicate advanced disease.

ROCM has been diagnostically categorized into 3 categories:

- Possible –
  1. Typical symptoms and signs in an appropriate clinical setting of concurrent or recently (<6weeks) treated COVID-19
  2. No supportive evidence on diagnostic nasal endoscopy or contrast enhanced MRI or CT scan.

- Probable-
  1. Clinical supportive evidence
  2. Supportive diagnostic nasal endoscopic findings, or contrast enhanced MRI or CT scan.
  3. No evidence on direct microscopy or culture or histopathology with special stains or molecular diagnostics.

- Definite-
  1. Clinical supportive evidence
  2. Supportive diagnostic nasal endoscopic findings, or contrast enhanced MRI or CT scan.
  3. Confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics.

DIFFERENTIAL DIAGNOSIS:

Clinicians must have a high index of suspicion to differentiate craniofacial mucormycosis from other diseases having similar overlapping symptoms and involving similar sites. Differential diagnosis of ROCM include:

- Bacterial Sinusitis and Allergic Fungal Sinusitis
- Aspergillosis
- Cellulitis

- Nasal and Paranasal Malignancies
- Proptosis
- Migraine Headache
- Brain Tumour and Pseudotumor Cerebri
- Cavernous Sinus Thrombosis

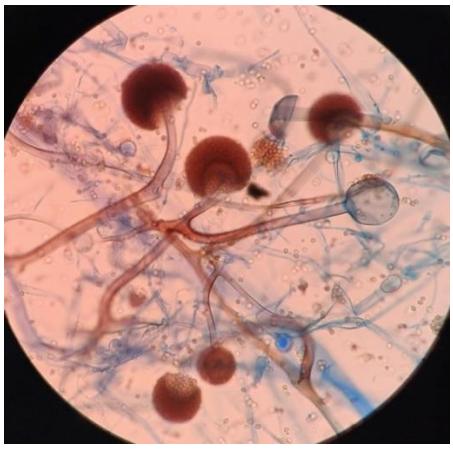

Figure 2: Lactophenol cotton blue (LCB) mount from the growth revealed aseptate hyphae with nodal rhizoids and short sporangiophores with terminal spherical sporangia filled with brownish sporangiospores, suggestive of Rhizopus microspores.[9]

MANAGEMENT[9]

Successful management of mucormycosis is based on a multimodal approach, including reversal or discontinuation of underlying predisposing factors , early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies. A multi-disciplinary team comprises of experts in diagnosis - Radiologist, Microbiologist, Pathologist, Molecular Biologist; medical team - Infectious disease Specialist, Neurologist; and surgeons - Oral and Maxillofacial Surgeon, Otorhinolaryngologist, Ophthalmologist, Neurosurgeon and Plastic Surgeon. Mortality can be reduced by early initiation of treatment. Early diagnosis is crucial in order to promptly initiate therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery, and improving outcome and survival. The European Confederation of Medical Mycology (ECMM) and the Mycoses Study Group Education and Research Consortium (MSG ERC) have issued comprehensive management guidelines. [10]

- Medical Treatment - It spreads rapidly and is highly invasive, so, needs aggressive therapy. I.v. Liposomal Amphotericin B in the initial dose of 5mg/kg body weight (10 mg/kg body wt in case of CNS involvement) with strict metabolic control is the treatment of choice. Each vial contains 50 mg. It should be diluted in 5% or 10% dextrose, it is incompatible with normal saline/ Ringer Lactate. Conventional Amphotericin B (deoxycholate) in the dose 1-1.5mg/kg may be used if liposomal form is not available and renal functions and serum electrolytes are within normal limits. 4 to 6 weeks of Amphotericin B therapy is required to eradicate the disease. If amphotericin-B is contraindicated because of impaired renal function : Isavuconazole IV 200mg thrice a day on day 1-2, 200mg once a day on day 3: or Posaconazole IV 300mg twice a day on day 1, 300 mg once a day from day 2 is given. It has to be continued till a favourable response is achieved and disease is stabilized which may take several weeks following which step down to oral Posaconazole or Isavuconazole can be done. A study conducted by *Catilin et. al.*[11] showed a survival benefit of patients with Rhino-orbito-cerebral mucormycosis who were treated with a combination of amphotericin B with caspofungin.

- Surgical treatment [12] - Surgical intervention is an invasive technique that involves the removal of involved body tissue and fungal growth supervened by drainage and irrigation of sinuses. Some studies recommend surgical removal of the fungal ball after drug therapy whereas some define immediate surgical debridement after diagnosis followed by slow intravenous administration of amphotericin B. The type of surgical procedure depends upon the site or sinuses involved. In case of sino-nasal manifestations, aggressive debridement of paranasal sinuses is done with or without turbinectomy, partial or complete maxillectomy or medial orbital wall resection. Proper clearance of involved tissue needs >1 cm excision of healthy tissue to eradicate the disease. Sinus irrigation is done with Amphotericin B 1mg/ml. Topical administration of antifungal in the debrided area is very useful. In case of limited involvement of orbit with vision preserved, retrobulbar Amphotericin B 3.5mg/ml is given. Orbital exenteration is needed in cases of severe orbital involvement. Intracranial involvement necessitates craniotomy and debridement. Recent advances in technology has led to Endoscopy and MRI/CT guided debridement for precise surgery at specific sinuses or sites. Surgery sometimes changes the configuration of body parts when it involves removal of the palate, eye structures or

nasal cavity which can be prosthetically rehabilitated at later stages.

- Alternative and Subsidiary treatment - Hyperbaric oxygen provides oxygen-rich environment to neutrophils to kill fungi. Rapid correction of metabolic abnormalities is mandatory in patients with uncontrolled diabetes and suspected of mucormycosis. Diabetic ketoacidosis should be treated with insulin and oral hypoglycaemic agents after consulting physicians. Corticosteroids and other immunosuppressive drugs should be tapered quickly and to the lowest possible dose. Some studies show that granulocyte-macrophage colony-stimulating factor and/or interferon-γ may enhance the immune response against certain Mucorales and thus potentially help treat the infection.

PREVENTION:

It may be possible to reduce the incidence of ROCM in the setting of COVID-19 patients by following steps:

- Judicious use of systemic corticosteroids in compliance with the current preferred practice guidelines of COVID-19.
- Keep in check the glucose levels and proper regulation of glucose levels in hyperglycaemic patients.
- Strict aseptic precautions while administering oxygen.
- Change your toothbrush once you test negative for COVID.
- Disinfect toothbrush each time after use with antiseptic mouthwash.
- COVID recovered patients are advised to use separate toothbrush holder.
- Gargles with 2% Povidone Iodine.
- Steam Inhalation is recommended to keep sinuses clear.
- Take high protein and low sugar diet.

DENTIST PERSPECTIVE ON COVID-19 ASSOCIATED MUCORMYCOSIS

In Dentistry, COVID-19 Associated Mucormycosis (CAM) has gained increasing interest. Since initial symptoms of mucormycosis are mostly related to oral cavity ranging from bad breath, odontalgia, fascial pain, or loosening of teeth, the patients seek to get dental care initially. We emphasize to consider the condition as differential diagnosis for patients with impaired immune response presenting with spreading sinusitis, facial swelling, cellulitis or palatal ulcers. Hence, A dentist can play a very crucial role in timely diagnosis of craniofacial mucormycosis. The patients who have recovered from Covid-19 should be advised to seek regular dental check-ups for at least a month or more. A degree of clinical suspicion, early histopathologic diagnosis and prompt aggressive surgical evaluation along with systemic Amphotericin - B can save lives.

CONCLUSION

From review of literature, Awareness of, and due attention to warning symptoms and signs, and a high index of clinical suspicion, early diagnosis may help optimize the outcome of ROCM in the setting of COVID-19. Also, The health experts suspect the overuse of medication is a potential contributing factor for mucormycosis infection. So, the public healthcare authority should ensure the rational use of steroids and antibiotics to manage the ongoing pandemic and the government should stop the over-the-counter use of antibiotics and steroids immediately.

REFERENCES

1. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al.; MucoCovi Network. Multicenter epidemiologic study of coronavirus disease–associated mucormycosis, India. Emerg Infect Dis. 2021 Sep [*date cited*]. https://doi.org/10.3201/eid2709.210934
2. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. J Fungi (Basel). 2019 Mar 21;5(1):26. doi: 10.3390/jof5010026. PMID: 30901907; PMCID: PMC6462913.
3. Richardson, M.D. and Warnock, D.W. (2012). Mucormycosis. In Fungal Infection (eds M.D. Richardson and D.W. Warnock). https://doi.org/10.1002/9781118321492.ch13
4. Ashraf S. Ibrahim, Brad Spellberg, Thomas J. Walsh, Dimitrios P. Kontoyiannis, Pathogenesis of Mucormycosis, *Clinical Infectious Diseases*, Volume 54, Issue suppl_1, February 2012, Pages S16–S22, https://doi.org/10.1093/cid/cir865
5. Singh AK, Singh R, Joshi SR, Misra A, Mucormycosis in COVID-19: Asystematic review of cases reported worldwide and in India, Diabetes & Metabolic Syndrome: ClinicalResearch & Reviews (2021), doi: https://doi.org/10.1016/j.dsx.2021.05.019.
6. SMITH HW, KIRCHNER JA. Cerebral mucormycosis; a report of three cases. AMA Arch Otolaryngol. 1958 Dec;68(6):715-26. doi: 10.1001/archotol.1958.00730020739010. PMID: 13593957.
7. Honavar, Santosh G Code Mucor, Indian Journal of Ophthalmology: June 2021 - Volume 69 - Issue 6 - p 1361-1365 doi: 10.4103/ijo.IJO_1165_21
8. Lone PA, Wani NA, Jehangir M. Rhino-orbito-cerebral mucormycosis: Magnetic resonance imaging. Indian J Otol 2015;21:215-8.
9. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, Puri GD, Chakrabarti A, Agarwal R. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia. 2021 May;186(2):289-298. doi: 10.1007/s11046-021-00528-2. Epub 2021 Feb 5. PMID: 33544266; PMCID: PMC7862973.
10. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al Global guideline for the diagnosis and management of mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium Lancet Infect Dis. 2019;19:405–21
11. Caitlin Reed, Richard Bryant, Ashraf S. Ibrahim, John Edwards, Jr., Scott G. Filler, Robert Goldberg, Brad Spellberg, Combination Polyene-Caspofungin Treatment of Rhino-Orbital-Cerebral Mucormycosis, *Clinical Infectious Diseases*, Volume 47, Issue 3, 1 August 2008, Pages 364–371.
12. Abu El-Naaj I, Leiser Y, Wolff A, Peled M. The surgical management of rhinocerebral mucormycosis. J Craniomaxillofac Surg. 2013 Jun;41(4):291-5.