Case Report

Post-Coronavirus Disease-2019 Rhino-orbital Mucormycosis: A Case Report

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ABSTRACT

Background: Rhino-orbital-cerebral mucormycosis (ROCM) is a rare, opportunistic, angio-invasive, and fatal infection caused by mold fungi of the genera Rhizopus, Mucor, and Rhizomucor. The global incidence of ROCM is 0.005-1.7 per million, with a fatality rate of 46%. Early diagnosis and treatment are crucial for this disease, as a delay of one week can increase the mortality rate to 66%.

Case: A 32-year-old male, a known case of coronavirus disease 2019 (COVID-19) for the past 15 days from Janakpur, Dhanusha, Nepal presented to the emergency department of Dhulikhel Hospital with a sudden onset of blurred vision in the left eye, left-sided ocular pain, and nasal bleeding for the last three days.

Observations: The patient was suspected of post-COVID-19 mucormycosis, and a nasal swab for potassium hydroxide (KOH) mount showed hyphae in microscopy. Intravenous and retrobulbar liposomal amphotericin B were administered as medical therapy, along with surgical debridement. A multidisciplinary approach was necessary for the treatment.

Conclusion: A long-term, multimodal treatment approach involving combined antifungal drug therapy (intravenous liposomal amphotericin B and retrobulbar amphotericin B), and timely surgical debridement leads to an improvement in both short-term and long-term outcomes.

Key words: Mucormycosis; rhino-orbital-cerebral mucormycosis.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has rapidly spread across the globe. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been linked to a broad spectrum of opportunistic fungal and bacterial infections (Kubin, 2019), with fungal infections being 10 times more prevalent than bacterial ones (Kwon, 2020).

Rhino-orbital-cerebral mucormycosis (ROCM) is an uncommon, opportunistic, angio-invasive, and often fatal infection caused by mold fungi belonging to the genera Rhizopus, Mucor, and Rhizomucor (Eucker, 2001). Rhizopus oryzae is the most common type, responsible for 90% of rhino-orbital-cerebral mucormycosis cases (Mandell, 2005). Recent cases of rhinoorbital mucormycosis have been observed in individuals with COVID-19. Factors facilitating mucorales spores to germinate in COVID-19 patients include elevated glucose levels (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), an acidic medium (metabolic acidosis, diabetic ketoacidosis), reduced phagocytic activity of white blood cells (immunosuppression—SARS-CoV-2 mediated, steroid-mediated), and an ideal environment of low oxygen (hypoxia) (Singh, 2021).

Globally, the incidence of ROCM is 0.005-1.7 per million, with a fatality rate of 46% (Jeong, 2019). However, when orbital and intracranial involvement occurs, the fatality rate rises to 50-80% (Deutsch, 2019). A 2021 study by John et al. concluded that 93% and 88% of mucormycosis-positive cases have diabetes mellitus and a history of corticosteroid use, respectively. Early diagnosis and treatment are imperative for this disease, as a delay of one week can double the mortality rate from 35% to 66% (Werthman, 2021). Even with early combined surgical and medical therapy, the prognosis remains very poor in mucormycosis (Singh, 2021).

CASE REPORT

A 32-year-old male from Janakpur, known to have COVID-19 for the past 15 days, presented to the emergency department of Dhulikhel Hospital with a sudden onset of blurred vision in the left eye, protrusion of the eyeball, left-sided headache, and ocular pain accompanied by nasal bleeding over the last 3 days. The headache was characterised by a dull, aching sensation radiating to the left eyeball, along with left-sided facial pain, jaw pain, and dysphagia. This discomfort persisted despite nonsteroidal anti-inflammatory drug use, reaching a severity that significantly restricted his daily activities. The sudden onset and pulsatile left-sided protrusion of the eyeball were associated with retrobulbar pain and ptosis.

During admission for acute interstitial pneumonia due to COVID-19, the patient was diagnosed with diabetes (routine blood sugar 400 mg/dl and HbA1c 7.6%). He underwent treatment with oxygen therapy, a six-day course of the steroid dexamethasone, five days of remdesivir, and six days of ivermectin and doxycycline.

During the clinical examination, the patient exhibited an afebrile state, a pulse rate of 65/min, blood pressure measuring 110/80 mmHg, oxygen saturation at 95%, and a respiratory rate of 20/min. Systemic examination yielded no noteworthy findings, and neurological

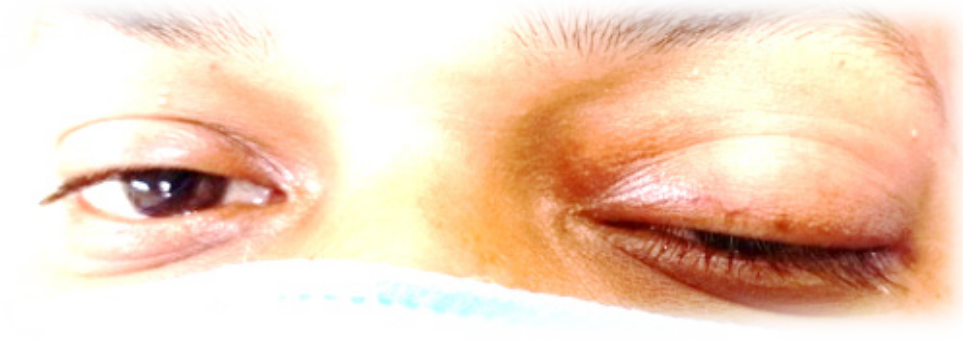


Figure 1: Left eye tosis.

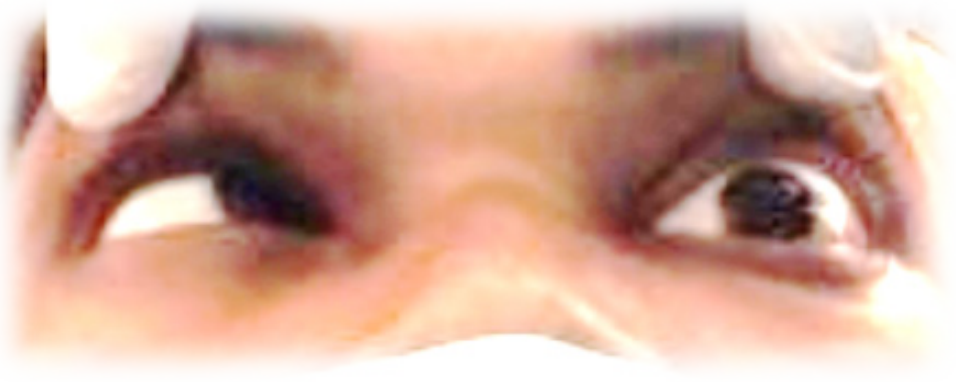


Figure 2: Ophthalmoplegia.

examination results were within normal limits. Visual acuity (VA) was assessed at 6/6 for the right eye and 6/36 for the left eye, with no improvement observed using a pinhole. The left eye examination revealed periorbital edema, eyelid congestion, and complete ptosis (Figure 1). Extraocular movement was restricted in superior, inferior, and lateral gaze (Figure 2). Pupil reactivity was normal, with no relative afferent pupillary defect (RAPD). Fundus examination of the right eye was unremarkable.

Baseline blood investigations conducted in the emergency department revealed total leukocyte count (TLC) at 6.810^3/uL, neutrophils (N) at 82% (normal range: 45-75%), lymphocytes (L) at 10% (normal range: 20-45%), monocytes (M) at 08% (normal range: 2-8%), eosinophils (E) at 0% (normal range: 1-6%), basophils (B) at 0% (normal range: 0-1%), hemoglobin (Hb) at 12.4 g/dL (normal range: 13-17), and platelets at 13010^3/uL (normal range: 150-450). Routine blood sugar (RBS) was measured at 293.0 mg/dL (normal range: 60-150).

Urine examination revealed sugar 2+, albumin 1+, and ketones positive (3+). MRI of the brain orbit and PNS with contrast displayed altered signal intensity in the sphenoid and left ethmoid and maxillary sinuses, along with

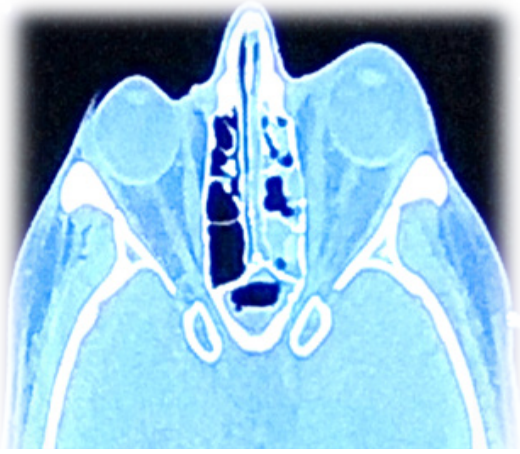


Figure 3: CT scan in axial section.

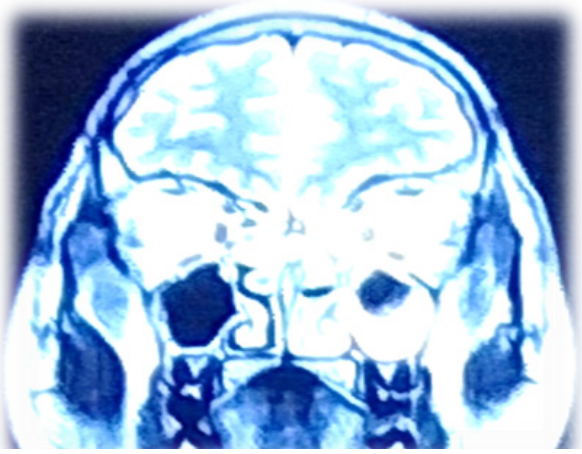


Figure 4: CT scan in coronal section.

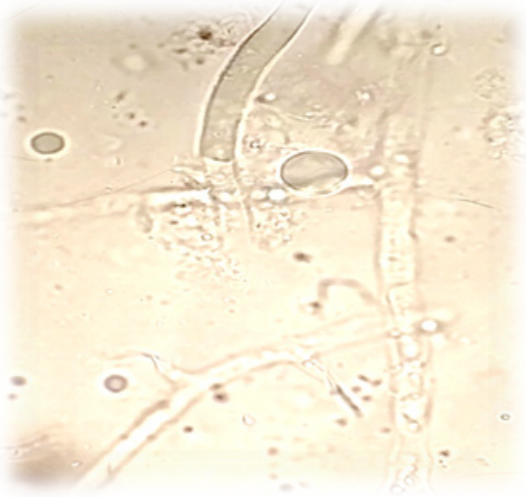
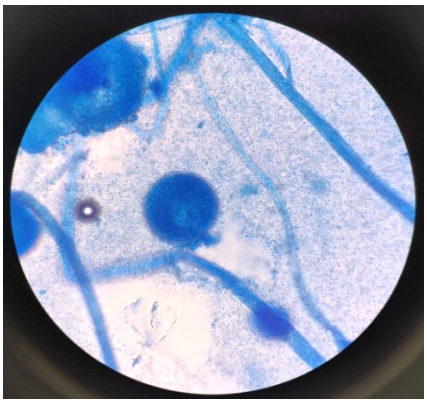


Figure 5: KOH stain showing hyphae.

inflammatory changes suggestive of invasive sinusitis. Thickened medial and inferior rectus muscles with enhancement on the left side, mild intraconal fat stranding with a bulky left optic nerve, presumably of inflammatory etiology, were also observed (Figures 3 and 4). No evidence of venous sinus thrombosis was found.

Considering the patient's history, clinical evaluation, blood investigations, and MRI findings, a suspicion of post-COVID-19 mucormycosis arose, leading to the collection of a nasal swab for KOH mount. The microbiological examination of the nasal swab from the inferior turbinate area revealed non-segmented fungal hyphae (Figure 5).

A multidisciplinary approach involving Ophthalmology, Otolaryngorhinology, Medicine, and Dental teams was initiated. Nasal endoscopy was performed, and tissue from the suspected diseased area was sent for microscopic examination on KOH mount, fungal culture, and biopsy. Fungal culture in SDA agar exhibited



Figures 6, 7: Cottony white mucor colonies on Grayish black background.

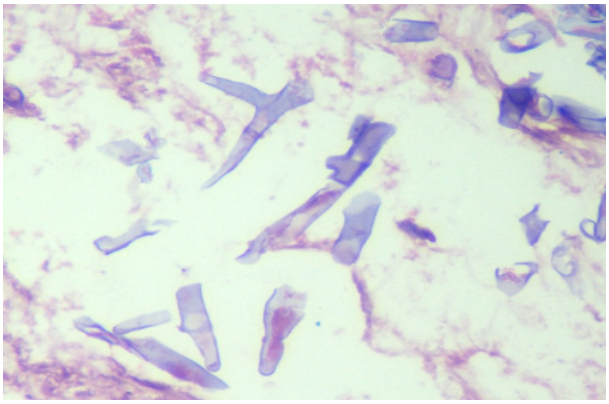


Figure 8: HPE showing fungal hyphae at 90 degree.

the growth of Rhizopus species (Figure 6 and 7). Histopathological examination under the microscope with haematoxylin and eosin (H/E) stain and periodic acid–Schiff stain (PAS) stain (Figure 8) revealed features consistent with mucormycosis.

Debridement of nasal turbinates and irrigation with liposomal Amphotericin B (AMB) were performed four times every third day. A test dose of 1 mg of AMB in 100 ml of normal saline was administered over two hours without any adverse reactions. Intravenous liposomal Amphotericin B, 5 mg/kg, six vials (50 mg each) with 500 ml 5% Dextrose with eight units of regular insulin over three hours, was given once daily for two weeks for mucormycosis and to manage increased blood sugar levels. Retrobulbar injection liposomal amphotericin B (1 ml superiomedially) was given every alternate day for five times (50 mg vial of Amphotericin B diluted in 14 ml of distilled water – 3.5 mg/ml). Topical eye drops of Ofloxacin were administered four times a day. Functional endoscopic sinus surgery and orbital decompression were performed (Figure 9), and the patient complained of left side upper jaw ache with loosening of the left upper third molar, which was managed by extraction by the dental team.

On the first day of admission, before the administration of retrobulbar liposomal Amphotericin B injection, the patient's vision in the left eye was hand movement close to the face. There was ptosis with complete internal and external ophthalmoplegia in the left eye. At one week of admission, VA of the left eye was perception of light close to the face with internal and external ophthalmoplegia, ptosis, and RAPD. On fundus examination, the disc was hyperemic, elevated with blurred margins. The posterior pole was normal. On the tenth day of admission, VA of the left eye further deteriorated to non-perception of light (NPL). Nasal KOH mount was conducted, showing no fungus after two weeks of IV Amphotericin B. The patient was switched to oral Posaconazole 300 mg twice a day for day one, then once a day for three months. At discharge, VA of the left eye was NPL, complete ophthalmoplegia, RAPD was present, the disc was pale, but ptosis had improved (Figure 10). Despite the aggressive treatment, the vision of the left eye could not be saved.

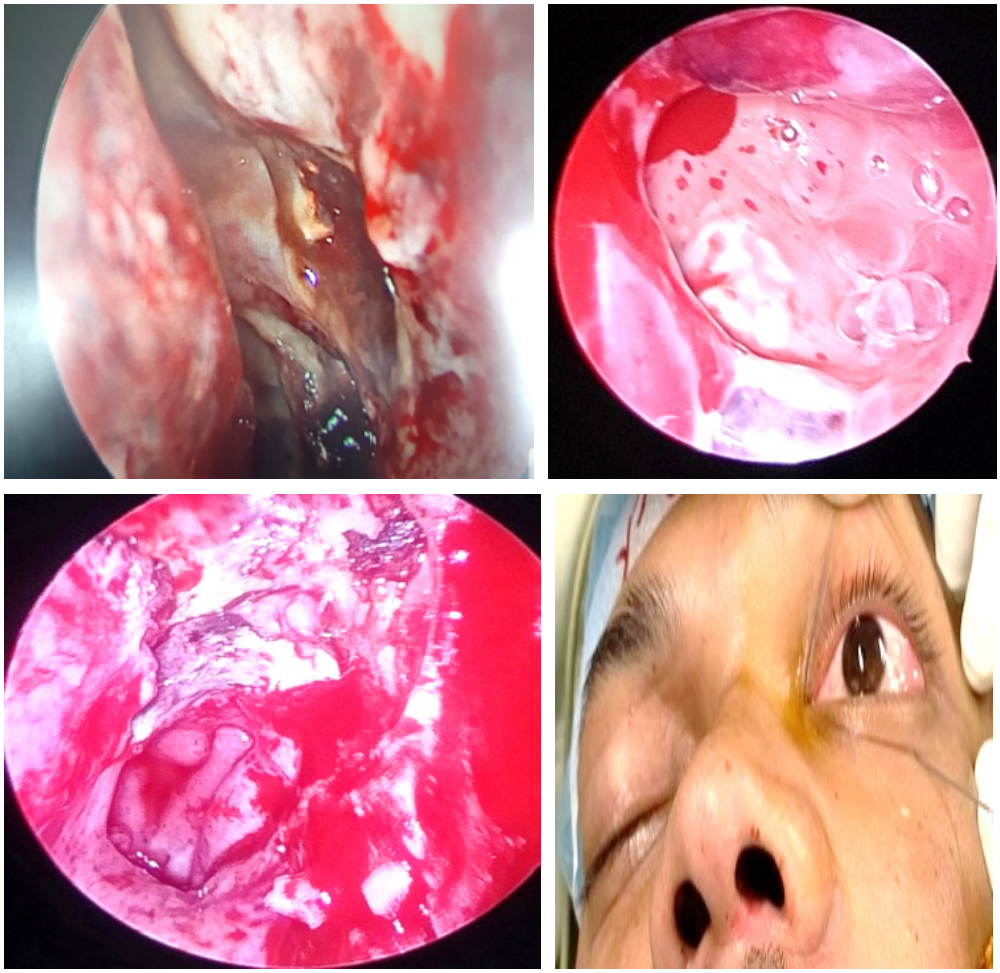


Figure 9: Functional endoscopic sinus surgery for invasive mucormycosis.

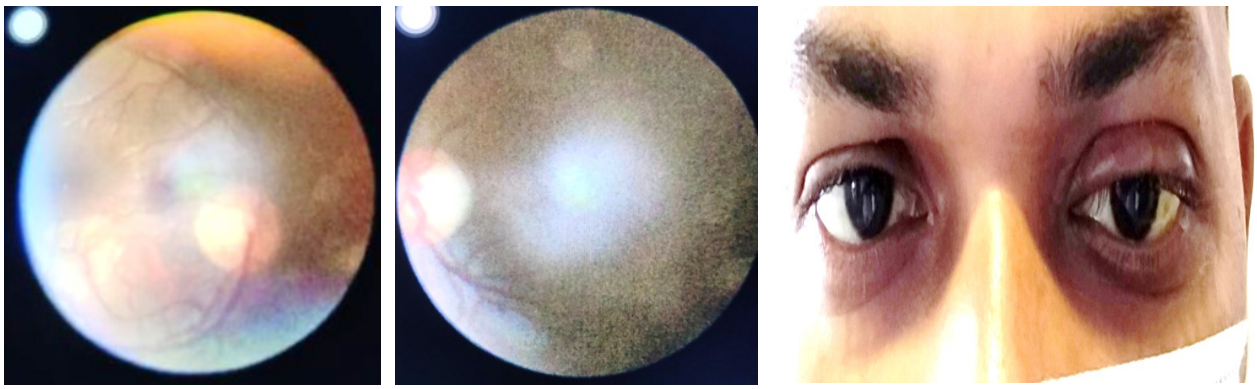


Figure:10 Fundus photograph and clinical picture at the day of discharge.

DISCUSSION

Mucormycosis spores and germ tubes adhere to and damage endothelial cells, causing angioinvasion (Ibrahim, 2005). This series of events results in ischemic necrosis of host tissues, including the ophthalmic artery, orbital wall, and ophthalmic nerves. Ophthalmic manifestations of this disease may include ophthalmoplegia, decreased vision, ptosis, and proptosis, with proptosis being the most common (Prakash, 2019). Additional symptoms may encompass periorbital pain and chemosis (Karadeniz, 2015). Various otorhinological signs such as sinusitis, epistaxis, facial edema, facial palsy, and palatal necrosis may also be present.

Negative culture reports can lead to delayed diagnoses since the success rates of tissue cultures are only 33–50% (Jiang, 2016; Badiee, 2013). A multidisciplinary approach is imperative for the management of mucormycosis, and concurrent management of underlying risk factors, such as ketosis, is crucial. Liposomal amphotericin B is the primary treatment choice, but close monitoring of renal and liver function parameters is necessary. Timely debridement of infective and necrotic tissue is essential. Posaconazole serves as an effective oral antifungal alternative, and hyperbaric oxygen may decrease acidosis by increasing oxygenation and phagocytic activity.

A challenging decision in rhino-orbital mucormycosis management is whether to exenterate the orbit. Patients treated with orbital exenteration and sinus debridement still face a high risk of treatment failure/ mortality in 89% of cases, especially in severe systemic disease (Nithyanandam, 2003). Some series even suggest that exenteration may be detrimental to survival, allowing further disease dissemination (Songu, 2008; Pelton, 2001). A retrospective case series indicated that for limited sino-nasal disease, surgical sino-nasal debridement achieved success in 94.4% of cases. The indication for orbital exenteration remains unclear, and a review of 179 invasive fungal sinusitis cases suggested its necessity in cases of orbital apex necrosis and retinal artery thrombosis (Blitzer, 2019).

In this case, as there was no intracranial involvement, retinal artery thrombosis, or necrosis of the orbital apex as indicated by MRI, and considering the social stigma in the patient's geographical region, orbital exenteration was avoided.

CONCLUSION

In conclusion, this case report reveals intriguing findings. A long-term, multimodal treatment approach involving combined antifungal drug therapy (intravenous liposomal amphotericin B and retrobulbar amphotericin B) and timely surgical debridement can lead to improvements in both short-term and long-term outcomes.

REFERENCES

Badiee P, Arastefar A, Jafarian H (2013). Comparison of histopathological analysis, culture and polymerase chain reaction assays to detect mucormycosis in biopsy and blood specimens. Iran J Microbiol; 5(4): 406-410. PMid: 25848513

Blitzer A, Lawson W, Meyers BR, et al. (1980). Patient survival factors in paranasal sinus mucormycosis. Laryngoscope; 90: 635-648. DOI: 10.1288/00005537-198004000-00010

Deutsch PG, Whittaker J, Prasad S (2019). Invasive and non-invasive fungal rhinosinusitis - A review and update of the evidence. Medicina (Kaunas); 55(7): 319. DOI: 10.3390/medicina55070319

Eucker J, Sezer O, Graf B, et al. (2001). Mucormycoses. Mycoses; 44(7): 253-260. DOI: 10.1111/j.1439-0507.2001.00656.x

Ibrahim AS, Spellberg B, Avanessian V, et al. (2005). Rhizopus oryzae adheres to, is phagocytosed by, and damages endothelial cells in vitro. Infect Immun; 73(2): 778-783. DOI: 10.1128/iai.73.2.778-783.2005

Jeong W, Keighley C, Wolfe R, et al. (2019). The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin Microbiol Infect; 25 (1): 26-34. DOI: 10.1016/j.cmi.2018.07.011

Jiang N, Zhao G, Yang S, et al. (2016). A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC Ophthalmol; 16(1): 10. DOI: 10.1186/s12886-016-0189-1

Kubin CJ, McConville TH, Dietz D, et al. (2021). Characterisation of bacterial and fungal infections in hospitalised patients with coronavirus disease 2019 and factors associated with health care-Associated Infections. Open Forum Infect Dis; 8(6): ofab201. DOI: 10.1093/ofid/ofab201

Kwon WJ, Li G, Zheng M, et al. (2020). Superinfections and coinfections in COVID-19 - Separating the signal from the noise. Stanford University School of Medicine Infectious Disease. Available at: https://www.medpagetoday.com/infectiousdisease/covid19/86192

Masci JR, Wormser GP (2005). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th Edition. Clin Infect Dis; 41(2): 277. DOI: 10.1086/431221

Nithyanandam S, Jacob MS, Battu RR, et al. (2003). Rhino-orbito-cerebral mucormycosis: A retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol; 51(3): 231-236. PMid: 14601848

Pelton RW, Peterson EA, Patel BC, et al. (2001). Successful treatment of rhino-orbital mucormycosis without exenteration: The use of multiple treatment modalities. Ophthalmic Plast Reconstr Surg; 17(1): 62-66. DOI: 10.1097/00002341-200101000-00012

Prakash H, Chakrabarti A (2019). Global epidemiology of mucormycosis. J Fungi (Basel); 5(1):26. DOI: 10.3390/jof5010026

Singh AK, Singh R, Joshi SR, et al. (2021). Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr; 15(4): 102146. DOI: 10.1016/j.dsx.2021.05.019

Songu M, Unlu HH, Gunhan K, et al. (2008). Orbital exenteration: A dilemma in mucormycosis presented with orbital apex syndrome. Am J Rhinol; 22(1):; 98-103. DOI: 10.2500/ajr.2008.22.3121

Uğurlu SK, Selim S, Kopar A, et al. (2015). Rhino-orbital mucormycosis: Clinical findings and treatment outcomes of four cases. Turk J Ophthalmol;, 45(4): 169-174. DOI: 10.4274/tjo.82474

Werthman-Ehrenreich A (2021). Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med; 42: 264.e5-264.e8. DOI: 10.1016/j.ajem.2020.09.032