

## *International Journal of Scientific Research and Reviews*

### **Mucormycosis in the Bed of Covid-19: Fighting the Deadly Enemy**

**Maheshwari Ujwala<sup>1</sup>, \*Kaur Navdeep<sup>1</sup>, Jamwal Shivani<sup>2</sup>, Munot Shweta<sup>1</sup> and Kale Vithal<sup>2</sup>**

<sup>1</sup>Dept. of Pathology, MGM Medical College, Kamothe, Navi Mumbai-410209, Maharashtra, INDIA

<sup>2</sup>Oral and Maxillofacial surgery, Oramax clinic, Panvel, Navi Mumbai-410206, Maharashtra, INDIA

#### **ABSTRACT**

COVID-19 patients who have comorbidities or those who are immunocompromised are more prone to develop severe bacterial and fungal superinfections and co-infections. There are also few cases reported of rhino-orbital mucormycosis in COVID-19 disease. We report 2 cases of COVID-19 Mucormycosis infection, clinical presentation and histopathological findings. We report 2 cases of mucormycosis. A 47-year-old COVID-19 positive female reported with dental pain in relation to left side for a history of roughly 7 days with infraorbital buckle swelling and submandibular space swelling, As CT and MRI established diagnosis of Rhino-orbito-maxillary mucormycosis, maxillectomy specimen was received for HPE examination. The second patient, a 67-year-old male was having ongoing COVID-19 pneumonitis presented with right sided ptosis, swelling of the face, jaw and retro-orbital pain with mild blood discharge in relation to right nostril. CT and MRI established diagnosis of Rhino-orbito-maxillary mucormycosis. Right sided eyeball with attached retro-orbital muscles attached along with optic nerve, mucosal tissue and right maxillary bone was sent for HPE examination. A diagnosis of mucormycosis was given on HPE examination of the specimen and were confirmed with special stains like PAS and GMS. Since the incidence of rhino orbital-cerebral mucormycosis is on a rising trend in patients recovered/treated for COVID-19 thus proving nightmare amongst this pandemic pertaining possibility of widespread use of steroids, monoclonal antibiotics, broad-spectrum antibiotics to combat high mortality and morbidity needs rapid and conclusive diagnosis so as to aid in treatment as early treatment can improve the prognosis of this dreadful fungal infection.

**KEYWORDS:** COVID-19, Mucormycosis, Fungal infections, Orbit

#### **\*Corresponding Author**

**Dr. Navdeep Kaur**

Resident

Dept. of Pathology

MGM Medical College,

Kamothe, Navi Mumbai-410209, Maharashtra, India

Email: [dr.navdeep.kaur87@gmail.com](mailto:dr.navdeep.kaur87@gmail.com), Mob. No: +918360208461

## **INTRODUCTION**

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a new type of coronavirus was first reported in Wuhan, China and later quickly spread to other parts of the world thus creating a pandemic situation.<sup>1</sup> The pandemic has caused more than 110 million cases and more than 2.4 million deaths globally.<sup>2</sup> COVID-19 patients who hospitalized in intensive care units (ICU) and have comorbidities or immunocompromised or have chronic respiratory diseases, corticosteroid therapy, intubation/mechanical ventilation are more prone to develop severe bacterial and fungal superinfections and co-infections.<sup>3</sup>

Corticosteroids like Methylprednisolone and Dexamethasone are thought to modulate inflammation mediated lung injury and thereby reduce progression of respiratory failure in Covid-19. Their side effects include increased secondary infections, manifestation of latent diabetes mellitus, dizziness, weight gain, insomnia and muscle weakness.

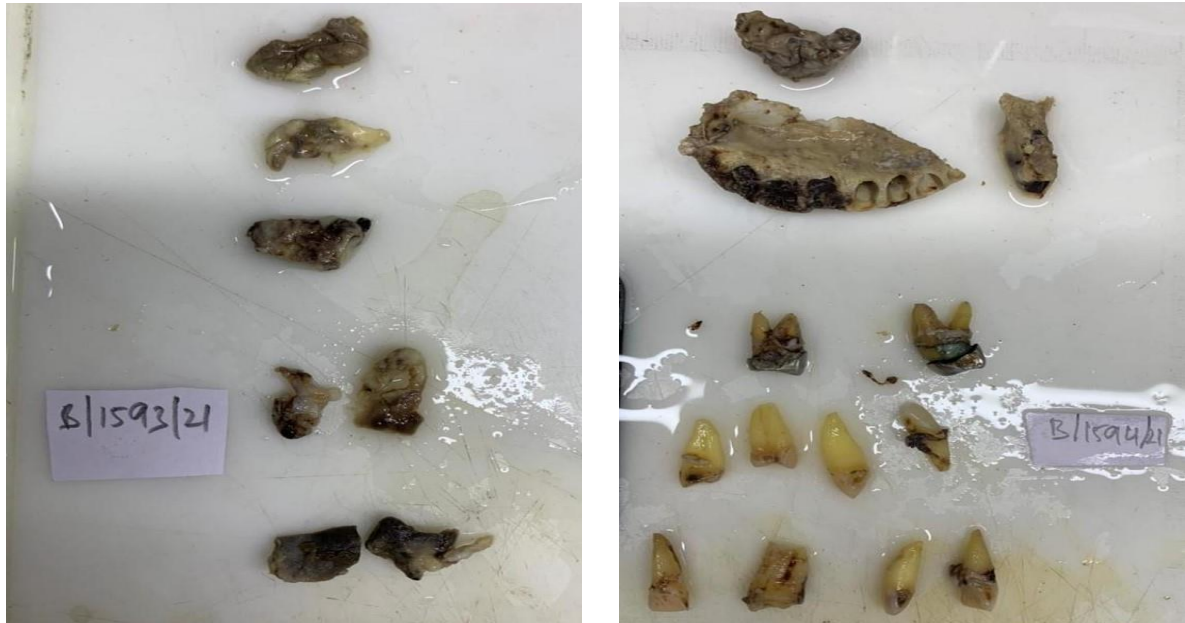
There are also few cases reported of rhino-orbital mucormycosis in COVID-19 disease. Mucormycosis is an uncommon, life-threatening fastest growing thermotolerant infection caused by fungi belonging to the subphylum Mucormycotina of the phylum Zygomycota. Among organisms responsible for causing mucormycosis, *Rhizopus* species are the most common cause of infection, followed by *Mucor*.<sup>5,6</sup> Mucormycosis is difficult to diagnosis which affects outcome and results in poor prognosis therefore early diagnosis and treatment is essential.

We report 2 cases of COVID-19 Mucormycosis infection with clinical presentation and histopathological findings.

## **CASE PRESENTATION**

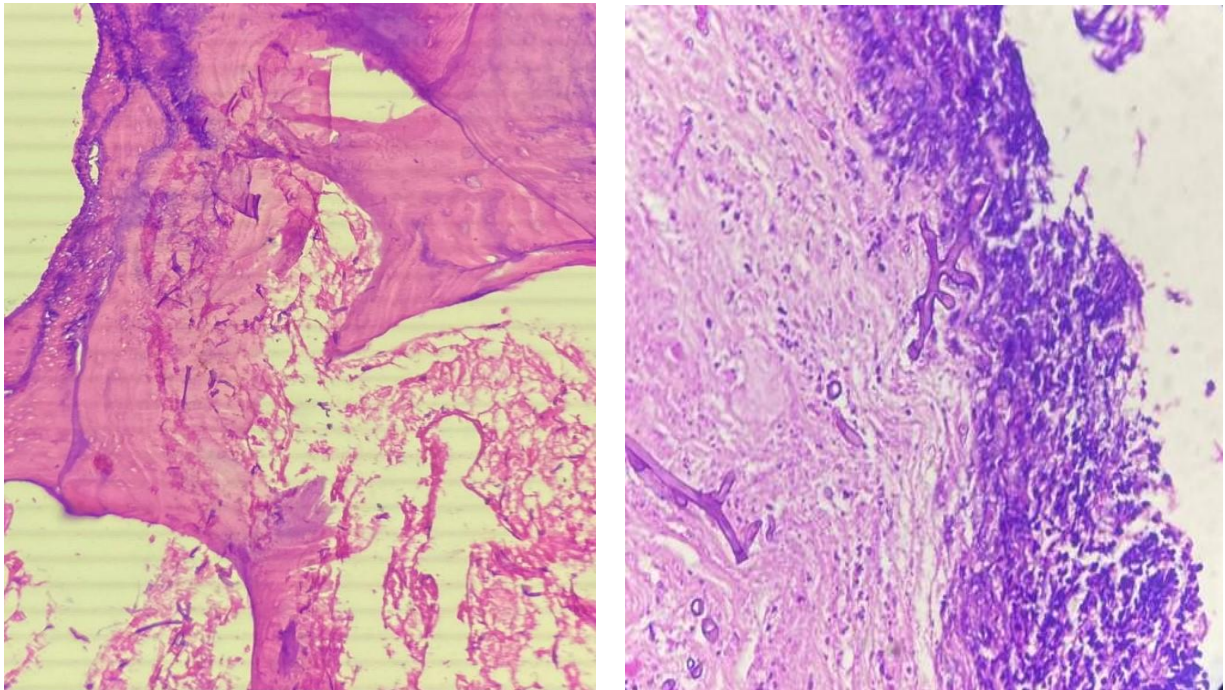
### ***Case Report 1***

A 47-year-old COVID-19 positive female reported with dental pain on the left side since 7 days with infraorbital buckle swelling and submandibular space swelling. Patient was diagnosed with diabetes during the treatment of COVID-19. Ptosis was evident, however pupil was reacting to light and visual acuity was 6/6. The right eye movements and vision were normal. The rest of the neurological examination was within normal limits. Rhinoscopy revealed evidence of necrotic tissue along the nasal septum. Samples for histopathology examination were taken. The oral examination revealed palatal necrosis. CT and MRI established diagnosis of Rhino-orbito-maxillary Mucormycosis, maxillectomy specimen was received for HPE examination.



**Figure1: Gross specimen showing nasal necrotic tissue and left maxilla with teeth and necrotic tissue**

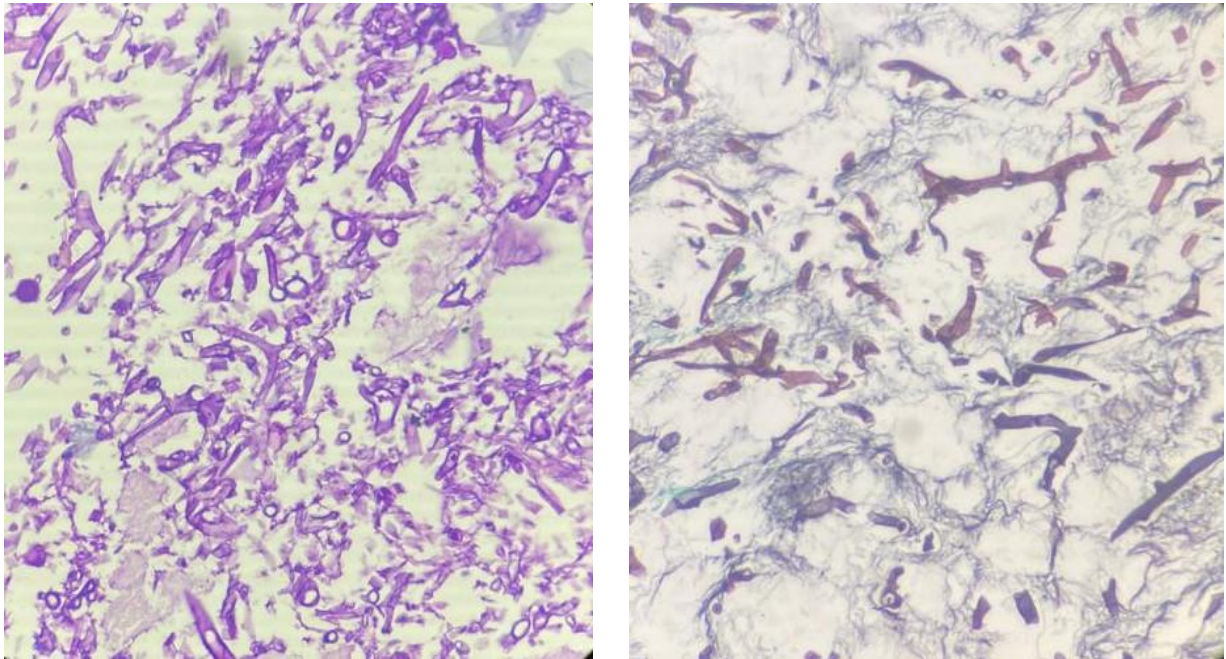
Microscopic examination revealed abundant necrosis along with chronic inflammatory cells consisting of lymphocytes and plasma cells. Plenty of right angle branching broad hyphae of mucormycosis along with spores were noted in nasal tissue and noted invading the marrow of the maxilla.



**Figure2: Microphotograph showing Broad Fungal Hyphae (40x, H&E)**



Periodic Acid Schiff (PAS) and Grocott-Gomori's methenamine silver stain (GMS), special stain for fungus, was done subsequently confirming the diagnosis.



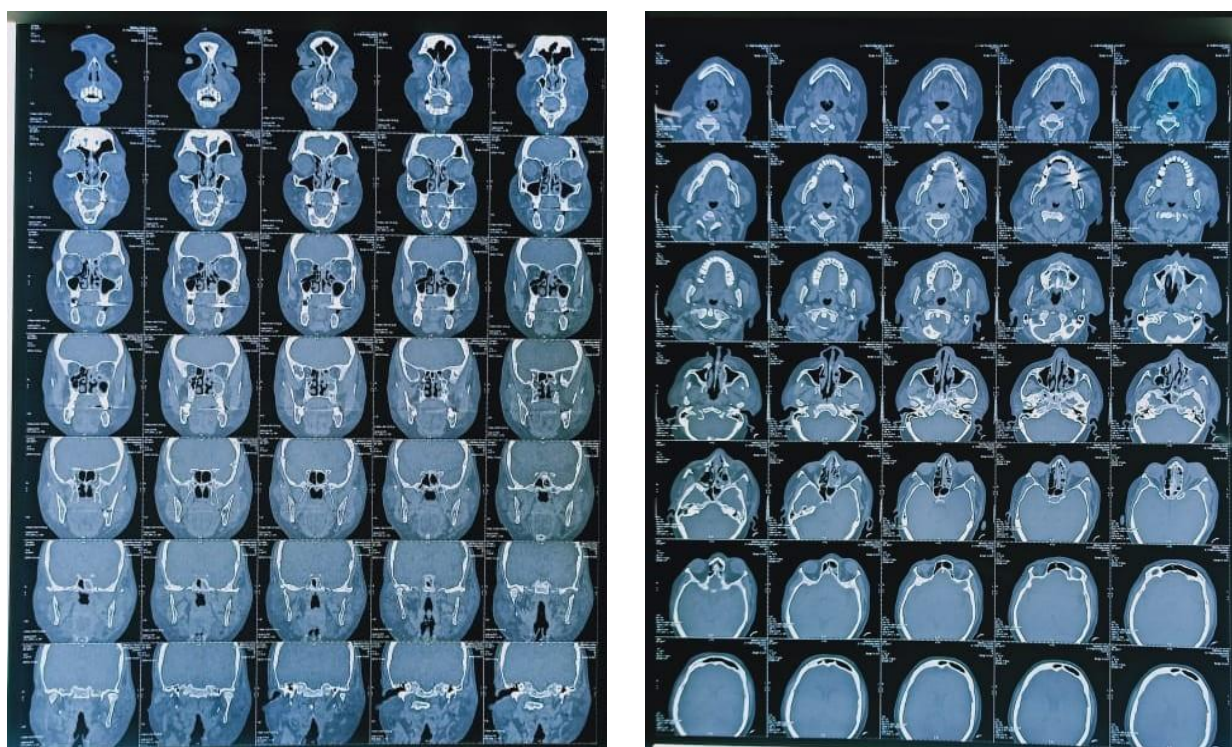
**Figure3: Microphotograph showing PAS and GMS staining Fungal Hyphae (40x)**

### ***Case Report 2***

A 67-year-old male was having ongoing COVID-19 pneumonitis presented with right sided ptosis, swelling of the face, jaw and retro-orbital pain with mild blood discharge in relation to right nostril. He also reported mild weakness of left side of his body. The right eye movements and vision were normal. The rest of the neurological examination was within normal limits. On oral examination necrotic patches in relation to the palate and buccal dehiscence of bone in relation to right molars. Rhinoscopy shows necrotic patches and mild blood discharge in relation to right nostril. So based on these clinical findings, CT and MRI scans were advised scans.



**Figure 4: Preoperative Photograph showing ptosis and buccal dehiscence and palatal necrosis**



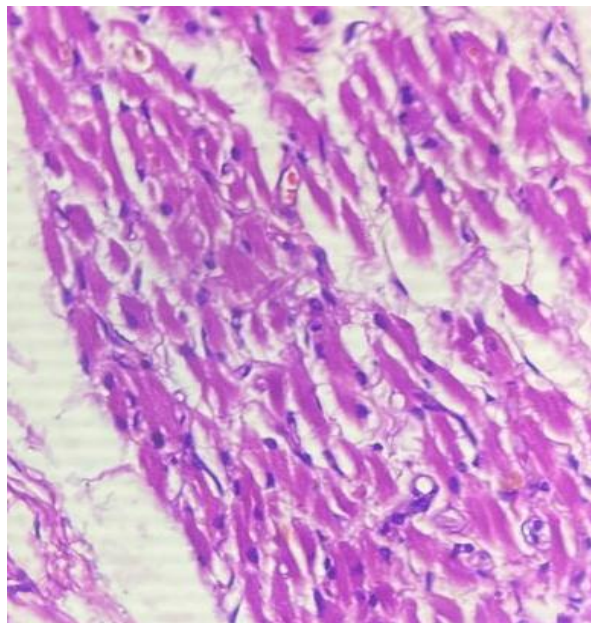
**Figure 5: MRI reveals bone erosion of the posterior wall of the Right Orbit**





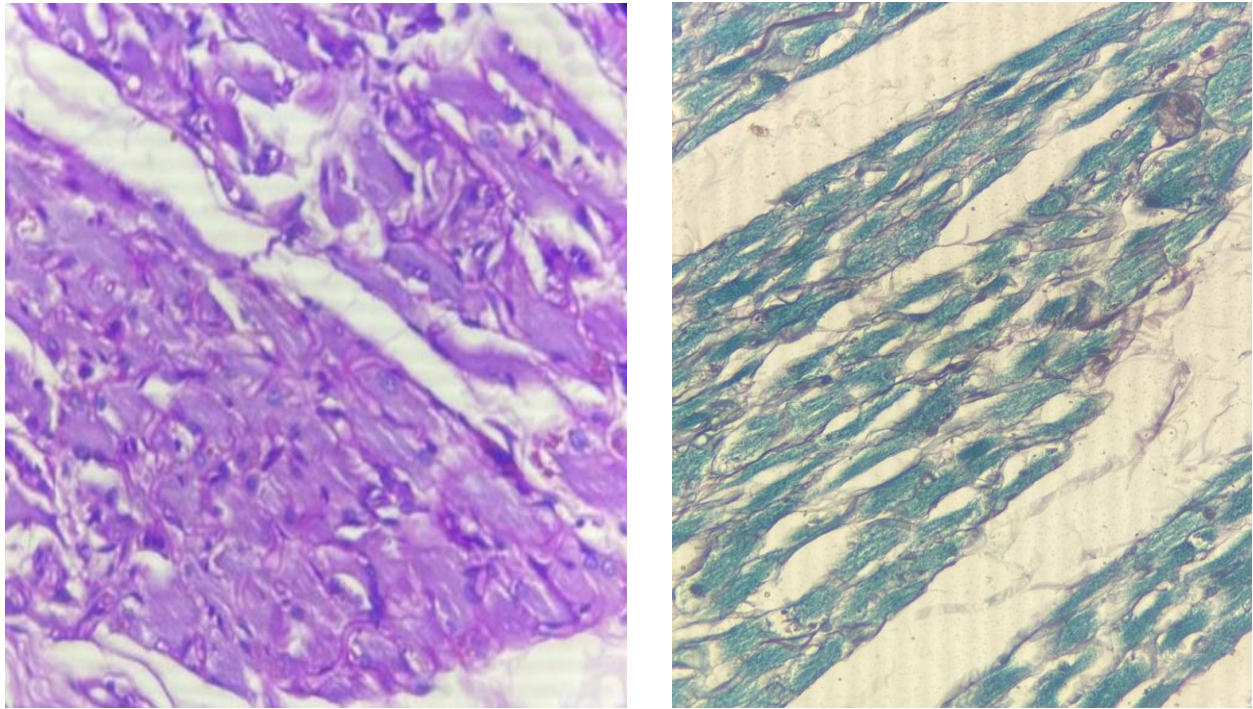
**Figure 6: Gross specimen received as eye contents, maxilla and necrotic tissue**

Histopathological analysis of the biopsy sample reveal fungal colonies of broad aseptate hyphae at an obtuse angle involving the eye, however optic nerve was uninvolved and invading the marrow of maxilla.



**Figure 7: Microphotograph showing Broad Fungal Hyphae invading orbital muscle (40x, H&E)**

Periodic Acid Schiff (PAS) and Grocott-Gomori's methenamine silver stain (GMS), special stain for fungus, was done subsequently confirming the diagnosis.



**Figure 8: Microphotograph showing PAS and GMS staining Fungal Hyphae (40x)**

## **DISCUSSION**

COVID-19 as a new disease entity with a high infectivity rate and associated fatality, it is also associated with certain morbidities induced by novel therapeutic protocols resulting in additional challenges. Bacterial co-infection in patients with COVID-19 has been reported in many cases; but fungal infection is also reported although only in severe cases. Song et al., in his study, noted that the fungal infections are more likely to develop during the middle and late phase of COVID-19 infection.<sup>7</sup> Mucormycosis is a rapidly aggressive and angio-invasive infection. It is categorized on the basis of clinical presentation and affected organs as rhino-cerebral, cutaneous, disseminated, gastrointestinal, or pulmonary.<sup>8</sup> The factors contributing to the development of the infection are uncontrolled diabetes mellitus, use of the immunosuppressive therapy, hospital-acquired infections, previous lung pathologies, stem cell transplants, and organ transplant patients on immune-suppressants, leading to secondary infections.<sup>8</sup> Mortality is high, ranging between 50% and 80%, with factors including intracranial or orbital involvement, irreversible immune suppression, and mucormycosis leading to poorer outcomes.<sup>9,10</sup>

On inhalation of the spores into the oral and nasal cavity, individuals with an intact immune system infection rarely develops because the fungal spores are phagocytosed by macrophages. But in individuals with uncontrolled diabetes mellitus and immunocompromised patients with their weak immune system infection spreads to the paranasal sinuses and to orbit via ethmoid and maxillary sinuses or through nasolacrimal duct resulting in orbital cellulitis.<sup>11</sup>

Patients with mucormycosis usually present as per the site of infection like headache, fever, lethargy, painful eyes, nasal or sinus congestion, facial swelling, partial loss of vision, coughing, shortness of breath, bloody vomits, facial cellulites, anesthesia, nasal discharge, necrotic turbinates.<sup>12</sup> Mehta S et al reported two cases having clinical features which pointed towards fungal maxillary osteomyelitis.<sup>13</sup>

Diagnosis of invasive rhino orbito-maxillary mucormycosis is dependent on clinical presentation and by detection of broad aseptate hyphae with right-angled branching which is pathognomonic of mucormycosis on histopathological examination of the biopsy. Imaging like CT scan and MRI plays an important role in defining the extent of involvement.<sup>14</sup> Alternate techniques for tissue diagnosis include immunohistochemistry, polymerase chain reaction (PCR) for fungal DNA and in situ hybridization.<sup>15</sup>

Since the fatality of mucormycosis is very high which may be triggered by the use of steroids, a life-saving treatment for severe and critically ill Covid-19 patients. The Steroids minimizes the end organ damage but they also reduce immunity and increase blood sugar levels in both diabetics and non-diabetic Covid-19 patients. This reduction in immunity can cause mucormycosis. Similar observations have been reported by Amanda et al from America and by Chaudhary et al from Delhi.<sup>16,17</sup> Exenteration is however, not required in all cases of orbital mucormycosis.<sup>18</sup> Eight cases of sino-orbital mucormycosis were managed successfully without exenteration as reported by Kohn et al.

To handle this severe fungal infection combined surgical and antifungal therapy is being tried which significantly lowered 90-day mortality compared with treatment with antifungals alone.<sup>19,20</sup> The main focus should be on the evaluation of the incidence and the prevention of fungal infection in the course of COVID-19 and immediate patient management should be started.<sup>21,22</sup>

## **CONCLUSION**

Invasive rhino-orbital-cerebral mucormycosis is a severe, fatal infection requiring multidisciplinary approach. Clinicians should be vigilant to evaluate for mucormycosis in patients with COVID-19 infection. Mucormycosis should be kept in mind when dealing with a case of orbital cellulitis or orbital apex syndrome with uncontrolled diabetes and immunodeficiency disorders. Early diagnosis, urgent systemic antifungal therapy and sinus debridement surgery are of extreme importance for successful eradication of infection and patient survival. Further research is needed to evaluate the potential link between these two infections.



## REFERENCES

1. Mak GC, Cheng PK, Lau SS, et al. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. *J Clin Virol.* 2020;129:104500. doi:10.1016/j.jcv.2020.104500.
2. World Health Organization Coronavirus disease 2019 (COVID-19) dashboard. Available online: <https://covid19.who.int> (Accessed February 20, 2021).
3. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: We should be prepared. *J Mycol Med.* 2020;30(2):100971. doi:10.1016/j.mycmed.2020.100971
4. Methylprednisolone for patients with COVID-19 severe acute respiratory syndrome - full text view. ClinicalTrials.gov. [https://clinicaltrials.gov/ct2/show/NC\\_T04323592](https://clinicaltrials.gov/ct2/show/NC_T04323592).
5. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev.* 2000; 13:236–301. [PubMed: 10756000]
6. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev.* 2005; 18:556–569. [PubMed: 16020690]
7. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: A clinical and diagnostic perspective from China. *Mycopathologia* 2020;1-8. doi: 10.1007/s11046-020-00462-9.
8. Papadogeorgakis N, Parara E, Petsinis V, Vourlakou C. A case of successfully treated rhinocerebral mucormycosis: Dental implications. *Int J Dent* 2010;2010. doi: 10.1155/2010/273127
9. Deutsch PG, Whittaker J, Prasad S. Invasive and non-invasive fungal rhinosinusitis—a review and update of the evidence. *Medicina* 2019;55:1–14.
10. Hirabayashi KE, Idowu OO, Kalin-Hajdu E, et al. Invasive fungal sinusitis: risk factors for visual acuity outcomes and mortality. *Ophthalmic Plast Reconstr Surg* 2019;35:535–542.
11. Roden MM, Zaoutis TE, Buchanan WL et al (2005) Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 5(41):634–653
12. Tugsel Z, Sezer B, Akalin T. Facial swelling and palatal ulceration in a diabetic patient. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2004;98:630–6. doi:10.1016/j.tripleo.2004.07.006
13. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. *Cureus.* 2020;12(9):10726. doi:10.7759/cureus.10726.
14. Superinfections and coinfections in COVID-19 MedPage Today. <https://www.medpagetoday.com/infectiousdisease/covid19/86192>.
15. Mukherjee B, Raichura ND, Alam MS (2016) Fungal infections of the orbit. *Indian J Ophthalmol* 64:337–345
16. Werthman-Ehrenreich A. Mucormycosis with orbital compartment Syndrome in a patient with COVID-19. *Am J Emerg Med.* 2021;264:64-8.
17. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant *Candida auris* infections in critically ill coronavirus disease patients, India, April-July 2020. *Emerg Infect Dis.* 2020;26(11):2694-6.
18. Qingli L, Orcutt JC, Seifter LS (1989) Orbital mucormycosis with retinal and ciliary artery occlusions. *Br J Ophthalmol* 73:680–683 23. Ibrahim AS, Kontoyiannis DP (2013) Update on mucormycosis
19. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. *Clin Microbiol Infect.* 2020;26(7):944.e9–e15.

20. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Chen SCA, et al. Contemporary management and clinical outcomes of mucormycosis: A systematic review and meta-analysis of case reports. *International Journal of Antimicrobial Agents*. 2019;53(5):589–597.
  21. Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V, et al. Sino-orbital mucormycosis in a COVID-19 patient: A case report. *Int J Surg Case Rep*. 2020;82:105957.
  22. Garg D, Muthu V, Sehgal IS. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. *Mycopathologia*. 2021;186(2):289–98.
-