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Major Manifestations of COVID-19 Associated Mucormycosis

Julie Ann Thomas*, Vinoth S, Komal Muneshwar, Ashok Mehendale

Department of Community Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India

ABSTRACT

Background: The Coronavirus outbreak has significantly destroyed mankind claiming countless lives all around the world. The clinical stretch of Coronavirus may vary in terms of severity extending from mild or subclinical condition to intensively severe pneumonia further sophisticated by fungal coinfections. Following the emergence of the pandemic, the emergence of innumerable secondary opportunistic fungal infections has created scope for another life threatening disease. Among these, mucormycosis has recently become a cause of anxiety due to its swift spread in patients with COVID-19 infection, during or after their treatment. The black fungus is a lethal obstacle reported commonly in COVID-19 positive patients worldwide. Many reports show that neutropenic patients are more vulnerable to these fungal infections due to immense utilisation of chemotherapy resulting in weak host defences. Diabetes mellitus is known to be one of the major factors that promote the occurrence of fungal infections. Prolonged use of steroidal drugs or antibiotics may result in development of a fungal disease. Late identification of the diagnosis, narrow range of treatment plan guidelines with a poor prognosis of COVID associated mucormycosis has alarmed many healthcare professionals with a possibility of occurrence of an epidemic. Thus, an urgent initiative to bring this scenario to the concern of public health by conducting surveillance programs, prompt diagnostic and management measures is essential. Nationwide public awareness and education on COVID-19 and its related complications is necessary to promote the safety and welfare of the society at a global level.

Aim: This study revolves to interpret the actual outline of this deadly infection by evaluating all the published case reviews to assess the various clinical forms of mucormycosis infection seen in COVID-19 affected patients (both active or revived) that involve its epidemiology, predisposing factor, clinical presentations, prognosis and treatment protocol with regard to COVID-19.

Key words: Mucormycosis, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), COVID-19 associated mucormycosis, Fungal infection, Rhino orbito cerebral, Pulmonary

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Corresponding author: Dr. Julie Ann Thomas
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INTRODUCTION

A massive outbreak of the 2019 novel Coronavirus otherwise called as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was initially reported in the huanan seafood wholesale market situated in Wuhan, China on December during the year 2019 [1]. The rapid emergence of this mysterious viral pneumonia has jeopardized the public health globally increasing the number of cases along with the range of affected regions [2,3].

According to the data available until 16th of April, 2020, Spain reported to have highest confirmed cases per million (3864), followed by Italy (2732), Korea (207), Iran (909), Bahrain (982), China (57), Japan (68) and in Saudi Arabia (168). On examining the mortality rates recorded by many countries, the figure again varies widely. Italy was reported to have the maximum mortality rate (13.1%) on April 16, 2020 whereas; Iran, China, Spain, France and Korea described lower mortality rates [4]. During the COVID-19 pandemic, children are being equally infected with the virus and its evolving variants in addition to adults [5].

Common clinical manifestations of COVID-19 are cough with production of sputum, high grade fever, dyspnea, myalgia and fatigue. Severe cases can ultimately lead to respiratory failure which initiates the need for advanced forms of ventilator support [6]. Radiologically, COVID-19 may show evidence of pneumonia with bilateral diffuse opacities [7]. Other symptoms which are less commonly seen include abdominal pain, diarrhea, haemoptysis, nausea and vomiting. Most severe cases eventually lead to organ dysfunction and death [8]. Symptoms that affect the neurological system include dizziness, headache, ataxia,

epilepsy, impaired consciousness, hyposmia and hypogeusia [9]. Adults, who develop severe respiratory symptoms, can result in multiple organ disorders, Acute Respiratory Distress Syndrome (ARDS) whilst the pediatric age groups rarely have notable respiratory symptoms and are usually asymptomatic. Moreover, children can get seriously affected by this infection resulting in a catastrophic multisystem inflammatory syndrome [10,11].

Mucormycosis is an infrequent, invasive and sometimes catastrophic fungal opportunistic illness. It is triggered by contact with mucor mould, which may be found abundantly in soil, air and even human noses and mucus. As it progresses through the respiratory tract, it erodes facial tissues [12]. It does not get transmitted from person to person. Over the last several decades, mucormycosis has become an essential fungal infection that has brought an elevated rate of mortality. Mucormycetes are fungi that can cause mucormycosis. They include *mucor* species, Saksenaea, *Syncephalastrum* species, *Absidia*, Apophysomyces and *Rhizomucor* [13]. The major cause for a huge number of cases is *Mucorales fungi*; hence, terms such as mucormycosis and zygomycosis or phycomycosis are commonly known to refer them [14,15]. The infection generally affects the brain, sinus cavities or lungs and is relatively common in individuals suffering or recovering from COVID-19. The *Mucorales* has gained importance over the last few years as the extent of cases presenting with predisposing factors for mucormycosis has eventually reached a huge scale. A study conducted by White, et al. noted that 26.7% of the COVID-19 affected individuals had invasive fungal infection [16].

Various conditions predisposing to this fungal infection, as found in many studies, include uncontrolled diabetes mellitus along with or without associated ketoacidosis, conditions as a result of iron overload, haematological malignancies with or without transplantation of stem cells, severe neutropenia for a prolonged period, neonatal prematurity, malnourishment, severe trauma, prolonged and increased intake of corticosteroids and illegal use of drugs intravenously [17]. Immunosuppressive medication suppresses immunological phagocytic effector functions, making individuals more vulnerable to invasive mould infections. The initial line of defence against *Mucorales* involves epithelial cells that meet at the primary sites of infection, like alveoli and skin epithelia [18]. Being a fatal fungal infection that has been reported widely in adults with a poor outcome and harmful consequences; optimal control of sugar levels, wise use of corticosteroids, conclusive diagnosis followed by interdisciplinary team management involving antifungal therapy, surgical debridement and comorbidity control are critical in ensuring the health and safety of such patients [19-21].

LITERATURE REVIEW

An extensive literature search was made within the following databases, namely, Google Scholars, PubMed and EMBASE from inception till October 2021 with usage of keywords such as COVID-19, fungal infection, rhino orbito cerebral mucormycosis, pulmonary mucormycosis and SARS-CoV-2. For possibly relevant articles, references from related reviews and collected publications were also evaluated.

DISCUSSION

Generally, based on its clinical features and anatomical site of occurrence, mucormycosis can be distributed into 6 major forms:

- Rhinocerebral (also known as rhino orbito cerebral mucormycosis).
- Gastrointestinal.
- Pulmonary.
- Disseminated.
- Cutaneous.
- Rare forms namely endocarditis, peritonitis and renal infection [22-24].

The most frequent sites of invasion are found to be the sinuses (39%) followed by the lungs and then the skin showing cutaneous manifestations (19%) [25] whereas, in children, only skin and gut are affected frequently. Pertaining to COVID-19, two major forms of mucormycosis observed in individuals affected are:

- Rhino Orbito Cerebral Mucormycosis (ROCM).
- Pulmonary Mucormycosis.

Rhino Orbito Cerebral Mucormycosis (ROCM)

Epidemiology, risk factors: Rhino orbito cerebral mucormycosis is a threatening fungal infection often seen to cause infarction of the infected tissues in immunocompromised hosts. Intracranial spread of this disease is a significant factor that exhibits poor prognosis [26]. The causative factors include uncontrollable glucose levels, hematological malignancies and a prolonged corticosteroid use [27]. The most frequent species responsible for the infection is mainly *Rhizopus oryzae*, followed by *Rhizopus* microspores [28]. In accordance with most reports, rhino orbito cerebral mucormycosis is rather a disease which is not quite common; however, its incidence seems to be escalating in the recent past. COVID-19 associated mucormycosis has been distributed worldwide. Reports from a systematic review which involved 101 such cases showed that more than half of the cases were seen in India while the rest were found in USA, Iran, UK, Italy, Turkey, France, Mexico, Brazil and Austria [29].

The association of Rhino Orbital Cerebral Mucormycosis (ROCM) with COVID-19 falls at stake when accompanied by the following risk factors [30].

- Uncontrolled diabetes.
- Associated immunodeficiency conditions (patients on blood transfusion, organ transplant, chronic renal disease).
- Long term corticosteroid therapy.
- Patients on mechanical ventilation/prolonged ICU stay.

- Immunomodulation treatments.
- Protein energy malnutrition.
- Iron and/or aluminium overload.
- Voriconazole treatment.
- Critically ill patients who have gone through invasive procedures.
- Long standing oxygen therapy.

The virus invades the pancreas and destroys the insulin producing cells, thus raising the blood sugar and Angiotensin converting Enzyme-2 (ACE-2) levels [31]. Mucor produces keto reductase as a source of infection, allowing it to thrive in the acidic and glucose rich environment created by ketoacidosis [32]. Administration of steroids in the treatment course of COVID-19 elevates the sugar levels and reduces immunity, thus increasing the frequency of spread of the deadly 'black fungus'.

Pathogenesis: Angioinvasion with infarction and perineural spread are considered as the hallmark features of mucormycosis [33,34]. The infection initiates in the nasal cavity, extending to the sinuses of the face and may rapidly move to the brain and orbit, exhibiting as aggressive orbital and cerebral mucormycosis. The fungus gradually invades the nasal mucosa where extensive spores are formed. A necrotic lesion, eschar formation or blackish discharge in the nose or oral cavities indicates tissue necrosis. Arterial thrombosis and ischemic necrosis occur when it directly invades the blood vessel. Growth of infection into ethmoid and maxillary sinuses can involve the orbital region. Intracranial spread mostly occurs through the cribriform plate, ophthalmic artery and superior orbital fissure [35]. In COVID-19, airway epithelial injury, extended use of humidifiers without regular cleanliness, steam inhalation burns injuries, multiple swab tests have been proposed as a source of fungus invasion [36].

Clinical features: A majority of studies conducted worldwide showed that commonest symptoms associated with ROCM at presentation were nasal block, swelling of lid or ocular pain [37-41]. However, sudden loss of vision is also a rare feature observed in individuals [42]. According to a study conducted in August 2021, higher proportion of individuals had ptosis (72.7%), while only 34.7% individuals had facial oedema. Proptosis was seen in 60.6% while 58.1% ROCM patients showed pupil involvement [43]. Other symptoms can also be facial pain with numbness, diminished vision to complete ophthalmoplagia, blindness and in severe cases, cavernous sinus thrombosis [44]. Proptosis in ROCM may be caused by an increased intraorbital invasion, infiltration of extraocular muscles or any cerebral lesion outcome. Occurrence of ptosis could be related to muscles (myogenic), nerves (neurogenic) or mechanical factors [45]. Mucormycosis can affect any pain sensitive structure in the brain, causing unilateral headaches, on the side of the lesion [46]. In individuals with complete unilateral ophthalmoplagia, mucor spreads through the nasal cavity, PNS, pterygopalatine fossa, invade the soft tissues, retro orbital space, extraocular muscles, optic nerve and further extend to infiltrate the cavernous sinus, finally spreading to affect the contrary side [47]. The non-neurological features commonly reported are necrosis of palate with blackish discoloration over it, newly developed aching tooth or loosening of tooth primarily affecting the upper part of jaw [48].

Diagnosis of ROCM: The identification of ROCM is established on early clinical examination with appropriate investigations such as, CT scan of orbit, paranasal sinuses and brain. The preliminary microbiological examination includes KOH mount or calcofluor white stain. Nasal endoscopy with biopsy is one of the most economical and readily available diagnostic tools. Radiological investigations namely Contrast Enhanced CT (CECT) or gadolinium enhanced Magnetic Resonance Imaging (MRI) scans are done to show any suspected intracranial spread [49]. CT scan demonstrates nodular thickening of the mucosa with absent fluid levels and hyper dense content resulting in eroded bony sinus walls [50].

MRI contrast study reveals diffuse nodular mucosa within the sinuses and the typical 'black turbinate sign' (non-enhancement of left nasal turbinates') [51]. This radiological modality demonstrates variable signal intensity depending on the contents present in the sinuses, due to presence of manganese and iron in the fungal elements [52].

Prognosis and treatment: ROCM is considered as an emerging swiftly disseminating fungal infection especially when associated with immunocompromised conditions including COVID-19 and thus carry fatal prognosis involving the cavernous sinus [53]. The worrisome complication of rhino ocular mucormycosis is the development of cerebral mucormycosis. Contiguous spread from the primary access portal of the paranasal sinuses secondarily invades the nervous system. In 70% of situations, the CNS is affected due to rapid local infiltration via a network of valve less emissary veins. Although brain involvement is a poor prognostic indicator, an intensive surgical treatment at the earliest shows a significant impact on the prognosis.

Management fundamentally involves control of risk factors (like hyperglycemia), adequate surgical debridement and medical management with antifungal therapy [54]. According to a study by roden MM in 2005, 61% of cases survived when treated with amphotericin deoxy cholate, while 57% cases survived by surgery alone. The combination of both showed a survival rate of 70% among 929 cases. Unfortunately, only 3% of subjects survived without any intervention. Amphotericin B (liposomal) is currently considered the preferred drug and has become successful in majority of the patients having COVID-19 associated ROCM (88%) [55]. Dosage depends on the stage of the disease. A full dose of liposomal amphotericin B is instituted 5 mg per kg of body weight is given for initial stages and up to 10 mg per kg of body weight in case of severe stages. The liposomal form is preferred due to its low level of nephrotoxicity; hence larger doses may be administered for an extended

duration to provide the exact therapeutic effect. Oral antifungal therapy in a step down manner is necessary in 3-6 months [56,57]. Isavuconazole can be used either combined with liposomal amphotericin B or used as a salvage therapy or as monotherapy. At the same time, an Indian study conducted in 2016 indicated the efficiency of Posaconazole as salvage therapy for ROCM that showed complete resolution in 67% of the cases [58].

Orbital exenteration and PNS debridement are believed to be the primary management techniques for ROCM. Debridement of all necrotic and inflamed tissues is warranted. Previous reports state that orbital exenteration is indicated in case of proptosis, ophthalmoplagia, cranial and ocular involvement [59,60].

Pulmonary mucormycosis

Invasive pulmonary mucormycosis is a deadly fungal infection which has recently been identified as a secondary complicating ailment evident in COVID-19 disease especially among critically ill patients. *Rhizopus arrhizus***,** the causative fungi is found in nearly 70% of all cases of mucormycosis, leading to several clinical diseases in adults [61]. When compared to nonpulmonary COVID-19 mucormycosis, COVID-19 Associated Pulmonary Mucormycosis (CAPM) has a greater mortality rate. COVID-19 Associated Pulmonary Mucormycosis (CAPM) has limited data available because it is uncommon [62]. The majority of cases are discovered after COVID-19 has been detected for more than 8 days. Hypoxemia caused by COVID-19 and the overuse of glucocorticoids are both linked to the development of mucormycosis in late stages. An epidemiological study conducted in India showed that age greater than 54 years, ICU admission and introduction of *Mucorales* in the lungs or brain were all linked to a higher exposure to death [63]. Individuals with neutropenia, corticosteroid usage and induction chemotherapy are more likely to develop pulmonary mucormycosis [64].

Clinical manifestations: SARS-CoV-2 and *Rhyzomucor* species infects the lung tissue, which is the most prevalent area of infection, causing cough, dyspnea, chest pain, fever and bleeding in airways [65,66]. Moulds that cause pulmonary mucormycosis damage the bronchial airways and lung parenchyma. It can cause cavitation and pericarditis if it spreads into the chest wall as lesions [67]. Different organs may be known to be involved, primarily affecting the lungs often (58%), with a death toll of up to 80% due to its rapid clinical course [68].

Diagnosis and treatment: Any patient with a known history of diabetes mellitus who shows respiratory manifestations like cough or exhibits a skin lesion must be properly evaluated for associated mucormycosis and initiate adequate treatment as soon as possible in order for an effective recovery. Diagnosis is usually established by clinical suspicion and histopathological study [69]. A high resolution CT scan and subsequent BAL should be performed as soon as respiratory impairment occurs in a highly immunocompromised patient diagnosed with COVID-19 [70]. CT scan is an economically cheaper and effective investigation for visualizing bony destruction. CT scans show pulmonary or sinus irregularities before any other modalities. Most patients with mucormycosis have a typical reverse halo sign characterized by ground glass opacity at the centre covered peripherally by a dense area of consolidation. A multifocal pneumonic pattern, vascular cut off signals which is an abrupt end of a branch of pulmonary artery, cavitations and diffused lesions in the peripheral region are furthermore detected. The magnitude and size of the underlying lesions indicates the extent of infectious agent to the pleura and complications such as haemorrhage or infarction owing to vascular invasion is imminent. In individuals with neutropenia the development of pulmonary infiltrates implies the presence of angioinvasion, tissue injury, thrombosis, haemorrhage, necrosis and edema [71].

Amphotericin-B is considered as the primary drug of treatment for better patient outcomes. Those patients with compromised renal function ought to be commenced on triazoles (posaconazole and isavuconazole) due to the nephrotoxic nature of amphotericin B. Triazoles work by blocking ergo sterol production in the membrane of the fungal cell [72]. These broad spectrum triazoles can be taken in oral and parenteral forms. As stated by The European confederation of medical mycology mucormycosis guidelines, an early surgical treatment such as local debridement or thorough resection to remove the infected tissue is equally effective besides systemic antifungal treatment [73].

CONCLUSION

COVID-19, which itself is a threatening disease has association with a significant number of secondary infections, the common cause being dysregulation of the immune system. Additionally, the extended use of corticosteroids or broad spectrum antibiotics in the course of COVID-19 treatment plan may eventually result in the exacerbation of pre-existing fungal diseases. Mucormycosis has been identified as a threat to all susceptible individuals. Both physicians and ophthalmologists should stay alert and be cognizant of the different presentations of these invasive opportunistic fungal infections with more focus on the causative factors. All COVID-19 patients prone to secondary infections should be kept at strict surveillance. Early diagnosis and treatment should be enabled to subsequently reduce the escalating frequency of mortality and morbidity. Prompt approach and intervention towards diabetes mellitus is an essential step. The administration of therapeutic medications should be supervised regularly to attain a successful curative effect at the least possible dose in a short duration.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients affected with 2019 novel Coronavirus in Wuhan, China. Lancet 2020; 395:497-506.
2. Deng SQ, Peng HJ. Characteristics of and public health responses to the Coronavirus disease 2019 outbreak in China. J Clin Med 2020; 9:575.
3. Han Q, Lin Q, Jin S, et al. Coronavirus 2019-nCoV: A brief perspective from the front line. J Infect 2020; 80:373-377.
4. Al-Tawfiq JA, Leonardi R, Fasoli G, et al. Prevalence and fatality rates of COVID-19: What are the reasons for the wide variations worldwide? Travel Med Infect Dis 2020; 35:101711.
5. Leibel SL, Sun X. COVID-19 in early life: Infants and children are affected too. Physiol 2021; 36:359-366.
6. Vieira JM, Ricardo OMP, Hannas CM, et al. What do we know about COVID-19? A review article. Rev Assoc Med Bras 2020; 66:534-540.
7. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020; 323:1488-1494.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-1069.
9. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77:683-690.
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 2020; 323:1239-1242.
11. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med 2020; 383:334-346.
12. Al-Khikani FH. Mucormycosis "Black fungus" new challenge associated with COVID-19. Biomed Biotechnol Res J 2021; 5:267.
13. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 2005; 41:634-653.
14. Spellberg B, Edwards Jr J, Ibrahim A, et al. Novel perspectives on mucormycosis: Pathophysiology, presentation and management. Clinical Microbiol Rev 2005; 18:556-569.
15. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: A review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 2004; 10:31-47.
16. White PL, Dhillon R, Cordey A, et al. A national strategy to diagnose Coronavirus disease 2019 associated invasive fungal disease in the intensive care unit. Clin Infect Dis 2021; 73:1634-1644.
17. Ribes JA, Vanover Sams CL, Baker DJ, et al. Zygomycetes in human disease. Clin Microbiol Rev 2000; 13:236-301.
18. Ghuman H, Voelz K. Innate and adaptive immunity to *Mucorales*. J Fungi 2017; 3:48.
19. Scott MM, Williams KW, Rossi J, et al. Leptin receptor expression in hindbrain Glp-1 neurons regulates food intake and energy balance in mice. J Clin Invest 2011; 121:2413-2421.
20. Hussain S, Baxi H, Riad A, et al. COVID-19 Associated Mucormycosis (CAM): An updated evidence mapping. Int J Environ Res Public Health 2021; 18:10340.
21. Bhandari S, Bhargava S, Samdhani S, et al. COVID-19, diabetes and steroids: The demonic trident for mucormycosis. Indian J Otolaryngol Head Neck Surg 2021; 1-4.
22. Goodman NL, Rinaldi MG, Balows A. Agents of zygomycosis, manual of clinical microbiology, 5th edition, DC ASM Press, Washington, 1991; 674-692.
23. Lopes JO, Pereira DV, Streher LA, et al. Cutaneous zygomycosis caused by Absidia corymbifera in a leukemic patient. Mycopathologia 1995; 130:89-92.
24. Stas KJ, Louwagie PG, Van Damme BJ, et al. Isolated zygomycosis in a bought living unrelated kidney transplant. Transpl Int 1996; 9:600-602.
25. Torres Narbona M, Guinea J, Martínez-Alarcon J, et al. Impact of zygomycosis on microbiology workload: A survey study in Spain. J Clin Microbiol 2007; 45:2051-2053.
26. Yohai RA, Bullock JD, Aziz AA, et al. Survival factors in rhino orbital cerebral mucormycosis. Surv Ophthalmol 1994; 39:3-22.
27. Shinde RV, Karande GS, Mohite ST, et al. Rhino orbital mucormycosis in diabetes mellitus. J Clin Diagn Res 2013; 7:1145-1147.
28. Mallis A, Mastronikolis SN, Naxakis SS, et al. Rhinocerebral mucormycosis: An update. Eur Rev Med Pharmacol Sci 2010; 14:987-992.
29. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021; 15:102146.
30. Rawson TM, Moore LS, Zhu N, et al. Bacterial and fungal coinfection in individuals with Coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020; 71:2459-2468.
31. Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel Coronavirus from Wuhan: An analysis based on decade long structural studies of SARS Coronavirus. J Virol 2020; 94:e00127-e00120.

32. Chen X, Liao B, Cheng L, et al. The microbial coinfection in COVID-19. Appl Microbiol Biotechnol 2020; 104:7777-7785.
33. Frater JL, Hall GS, Procop GW, et al. Histologic features of zygomycosis: Emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med 2001; 125:375-378.
34. Sravani T, Uppin SG, Uppin MS, et al. Rhinocerebral mucormycosis: Pathology revisited with emphasis on perineural spread. Neurol India 2014; 62:383-386.
35. Mane RS, Watve JK, Mohite AA, et al. Rhinocerebral mucormycosis: A deadly disease on the rise. Indian J Otolaryngol Head Neck Surg 2007; 59:112-115.
36. Bhuyan A. Experts criticise India's complacency over COVID-19. Lancet 2021; 397:1611-1612.
37. Pakdel F, Ahmadikia K, Salehi M, et al. Mucormycosis in patients with COVID-19: A cross sectional descriptive multicentre study from Iran. Mycoses 2021; 64:1238-1252.
38. Fouad YA, Abdelaziz TT, Askoura A, et al. Spike in rhino orbital cerebral mucormycosis cases presenting to a tertiary care center during the COVID-19 pandemic. Front Med 2021;8:645270.
39. Mishra N, Mutya VS, Thomas A, et al. A case series of invasive mucormycosis in patients with COVID-19 infection. Int J Otorhinolaryngol Head Neck Surg 2021; 7:867-870.
40. Nehara HR, Puri I, Singhal V, et al. Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India. Indian J Med Microbiol 2021; 39:380-383.
41. Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids-An unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multicentric analysis. J Maxillofac Oral Surg 2021; 20:418-425.
42. Sen M, Lahane S, Lahane TP, et al. Mucor in a viral land: A tale of two pathogens. Indian J Ophthalmol 2021; 69:244-252.
43. Bhattacharyya A, Sarma P, Sharma DJ, et al. Rhino orbital cerebral mucormycosis in COVID-19: A systematic review. Indian J Pharmacol 2021; 53:317-327.
44. Mitra S, Janweja M, Sengupta A, et al. Post COVID-19 rhino orbito cerebral mucormycosis: A new addition to challenges in pandemic control. Eur Arch Otorhinolaryngol 2021; 279:2417-2422.
45. Mertens A, Barche D, Scheinpflug L, et al. Rhinocerebral mucormycosis. Laryngorhinootologie 2018; 97:550-554.
46. Maheshwari S, Patil M, Shendey S, et al. Mucormycosis creeping along the nerves in an immunocompetent individual. J Radiol Case Rep 2019; 13:1-10.
47. Umemura A, Suzuka T. A case of rhinocerebral mucormycosis presenting orbital apex syndrome. No shinkeigeka 1998; 26:439-442.
48. Dubey S, Mukherjee D, Sarkar P, et al. COVID-19 associated rhino orbital cerebral mucormycosis: An observational study from Eastern India, with special emphasis on neurological spectrum. Diabetes Metab Syndr 2021; 15:102267.
49. Ballester DG, Gonzalez Garcia R, Garcia CM, et al. Mucormycosis of the head and neck: Report of five cases with different presentations. J Craniomaxillofac Surg 2012; 40:584-591.
50. Bhavani PN, Shivanand VP, Satish DP. Imaging findings of rhino orbitocerebral mucormycosis in a COVID-19 patient. Eurorad 2021.
51. Safder S, Carpenter JS, Roberts TD, et al. The “black turbinate” sign: An early MR imaging finding of nasal mucormycosis. Am J Neuroradiol 2010; 31:771-774.
52. Parsi K, Itgampalli RK, Vittal R, et al. Perineural spread of rhino orbitocerebral mucormycosis caused by Apophysomyces elegans. Ann Indian Acad Neurol 2013; 16:414-417.
53. Bae MS, Kim EJ, Lee KM, et al. Rapidly progressive rhino orbito cerebral mucormycosis complicated with unilateral internal carotid artery occlusion: A case report. Neuro Intervention 2012; 7:45-49.
54. Sen M, Honavar SG, Bansal R, et al. Epidemiology, clinical profile, management and outcome of COVID-19 associated rhino orbital cerebral mucormycosis in 2826 patients in India Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol 2021; 69:1670-1692.
55. Hoenigl M, Seidel D, Carvalho A, et al. The emergence of COVID-19 associated mucormycosis: Analysis of cases from 18 Countries. 2021.
56. Skiada A, Pavleas I, Drogari Apiranthitou M, et al. Epidemiology and diagnosis of mucormycosis: An update. J Fungi 2020; 6:265.
57. Sipsas NV, Gamaletsou MN, Anastasopoulou A, et al. Therapy of mucormycosis. J Fungi 2018; 4:90.
58. Manesh A, John AO, Mathew B, et al. Posaconazole: An emerging therapeutic option for invasive rhino orbito cerebral mucormycosis. Mycoses 2016; 59:765-772.
59. Ravani SA, Agrawal GA, Leuva PA, et al. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol 2021; 69:1563-1568.
60. Nithyanandam S, Jacob MS, Battu RR, et al. Rhino orbito cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol 2003; 51:231-236.
61. Ibrahim AS, Spellberg B, Walsh TJ, et al. Pathogenesis of mucormycosis. Clin Infect Dis 2012; 54:S16-S22

62. Muthu V, Agarwal R, Dhooria S, et al. Has the mortality from pulmonary mucormycosis changed over time? A systematic review and meta-analysis. Clin Microbiol Infect 2021; 27:538-549.
63. Patel A, Agarwal R, Rudramurthy SM, et al. Multicentre epidemiologic study of Coronavirus disease associated mucormycosis, India. Emerg Infect Dis 2021; 27:2349-2359.
64. Riley TT, Muzny CA, Swiatlo E, et al. Breaking the mold: A review of mucormycosis and current pharmacological treatment options. Ann Pharmacother 2016; 50:747-757.
65. Pasero D, Sanna S, Liperi C, et al. A challenging complication following SARS-CoV-2 infection: A case of pulmonary mucormycosis. Infection 2021; 49:1055-1060.
66. Bayram N, Ozsaygılı C, Sav H, et al. Susceptibility of severe COVID-19 patients to rhino orbital mucormycosis fungal infection in different clinical manifestations. Jpn J Ophthalmol 2021; 65:515-525.
67. Danion F, Aguilar C, Catherinot E, et al. Mucormycosis: New developments into a persistently devastating infection. Semin Respir Crit Care Med 2015; 36:692-705.
68. Lin E, Moua T, Limper AH, et al. Pulmonary mucormycosis: Clinical features and outcomes. Infection 2017; 45:443-448.
69. Dimaka K, Mallis A, Naxakis SS, et al. Chronic rhinocerebral mucormycosis: A rare case report and review of the literature. Mycoses 2014; 57:699-702.
70. Zurl C, Hoenigl M, Schulz E, et al. Autopsy proven pulmonary mucormycosis due to *Rhizopus microsporus* in a critically ill COVID-19 patient with underlying hematological malignancy. J Fungi 2021; 7:88.
71. Yasmin F, Najeeb H, Naeem A, et al. COVID-19 associated mucormycosis: A systematic review from diagnostic challenges to management. Diseases 2021; 9:65.
72. Hof H. A new, broad spectrum azole antifungal: Posaconazole mechanisms of action and resistance, spectrum of activity. Mycoses 2006; 49:2-6.
73. Cornely OA, Alastruey Izquierdo A, Arenz D, 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:e405-e421.