ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(2); 212-222

Original Research Article

Clinical Profile of Mucormycosis in Covid 19 in A Tertiary Care Centre: A Retrolective Study

Madhuri M Kirloskar[1] Jenny Koshy[2] Jeetendra Singh[3]

[1]Professor and Head, Department of Medicine, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik, 422003, Maharashtra, India.

[2]Junior Resident-3, Department of Medicine, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik, 422003, Maharashtra, India.

[3]Professor and Head, Department of Pharmacology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik, 422003, Maharashtra, India

Received: 03-12-2021 / Revised: 30-12-2021 / Accepted: 28-01-2022
Corresponding author: Dr. Jeetendra Singh
Conflict of interest: Nil

Abstract

Mucormycosis is a fungal infection which is caused by a rare type of opportunistic fungal pathogen called mucormycetes. It is a serious and potentially fatal fungal infection. A wide range of bacterial and fungal co-infections have been associated with COVID 19. The second wave of COVID 19 showed a sudden surge in mucormycosis. The most commonly observed form was rhino cerebral mucormycosis. Most of the patients had diabetes as a pre-disposing factor and had received steroids, oxygen therapy, biologicals and antibiotics as a part of treatment of COVID 19. COVID 19 in itself favours the growth of mucormycosis owing to the weakened immune system. While the diagnosis of mucormycosis still remains challenging the treatment mainly aims at managing co-morbid condition in high-risk group, anti-fungal therapy using Amphotericin B and azoles and surgical debridement.

In this article, we analysed, 71, histopathologically confirmed cases of mucormycosis associated with COVID 19 admitted and studied their clinical profile and risk factors associated with it.

Keywords: Mucormycosis, Mucormycetes, Fungal Infection.

Introduction

Mucormycosis is a rare fungal disease arising from the activity of organisms that belong to the Mucorales order, with Mucor spp., Rhizomucor, Leichtheimia spp. and Rhizopus being among the most notable causative agents[1]. The fungi normally thrive in soils, rotten wood, as well as decaying organic matter from compost piles and leaves. The disease is more likely to occur under immunocompromised condition as people are exposed to the spores of these microbes[2]. That said, mucormycosis may also evolve or get exacerbated after the occurrence of natural disasters, as well as where underlying medical conditions/events like diabetes

mellitus, hematologic malignancies, severe trauma, and solid organ/hematopoietic stem cell transplantation exist[3,4,5,6,7]. The disease is characterized by infarction of tissues and necrosis, even as the causative agents show a high tendency for angioinvasion[8]. It is, however, not unlikely to see various manifestations of the disease a situation that is reflected in the varied clinical presentations. Based on the localization; mucormycosis may be gastrointestinal, pulmonary, cutaneous, sinusitis – which could involve rhino-cerebral, rhino-orbital or pansinusitis – and it may even be disseminated[9]. More so, these variations also have an impact on the mortality rates; 70 – 90% mortality rate in cases of disseminated mucormycosis and 20 – 50% mortality rate in localized cases[9,10,11]. Generally, death appears to be unavoidable in the instances where mucormycosis is left untreated[9].

The outbreak of COVID-19 yet create a concern as per the prevalence of mucormycosis. This is primarily due to the availability of the enabling environments such as elevated glucose levels, hyperglycaemia, elevated ferritin levels, decreased count and activity of white blood cells, hypoxia, diabetic ketoacidosis, and metabolic acidosis which trigger the germination and/or growth of the spores[12]. More specifically, the severe inflammatory reaction and diffuse alveolar damage cause a decline in the CD4+ and CD8+ T cell count in COVID-19 patients, and this raises the susceptibility to an array of fungal infections[13,14], including mucormycosis which has an incidence rate of 0.005 in 1.7 million persons[15].

Material and methods:

A retrolective observational study was carried out in the MUCOR ward under Department of General Medicine in a tertiary care Institute from a period of FEBRUARY 2021 TO JULY 2021.

Eligibility criteria:

A] Inclusion Criteria:

1) All adult patients >18 yrs. of age
2) All histopathologically diagnosed mucormycosis cases with a history of RT-PCR positive or who is RT-PCR positive.

B] Exclusion Criteria:

1)Mucormycosis in covid 19 negative patients.
2)Any documented evidence of mucormycosis in the past.

71 patients fulfilling the above criteria were included in our study. The clinical profile of mucormycosis in COVID 19 and how mucormycosis patients responded to treatments, with reference being made to data from MRI/CT scans, KOH report, histopathological examination, and Hb1AC test were studied. The disease severity was also assessed based on Neelam Vaid et al[16]. A proposed grading system and experience of COVID 19 associated rhino orbito cerebral mucormycosis from an Indian tertiary care centre. The risk factors contributing for mucormycosis in covid 19 like diabetes mellitus, steroids, oxygen requirement during covid treatment were also assessed in this study.

Presentation of finding and results:

Table1: showing sample characteristics

Patient characteristics		**N (%)**
No. of (COVID-19) patients		71 (100)
Mean age		47.68
Gender	M	54 (76.05)
	F	17 (23.94)
Mean length of hospitalization (in days)		27.32

Survival rate	60 (84.5)
Death	11 (15.49)
Mucormycosis	71 (100)
Comorbidities	
Diabetes mellitus	48 (67.60)
Hypertension	9 (12.67)
Hypothyroidism	3 (4.22)
Cerebrovascular accident	2 (2.81)
Ischemic heart disease	1 (1.4)
Acute kidney injury	1 (1.4)
Acute renal failure	1 (1.4)
Diabetes	
Pre-existing DM	13 (18.3)
Recent DM	40 (56.33)
NO	18 (25.35)

The table above shows the characteristics of the sample population whose mean age is 47.68 years, 76.05% of them being male and the remaining 23.94% (17) being female. The mean length of days in the hospital is 27.32; the highest number of days a patient stayed in the hospital was for 60 days while the least is 5 days – although this particular patient left the medical centre against medical advice. There were 4 other patients that left the hospital against medical advice. Diabetes mellitus is the most prevalent comorbidity in this study as 67.60% of the patients had it, while hypertension is the second prevalent co-morbidity (12.95%). 56.33% (40) of the diabetes incidence were recent cases while the other 18.30% (13) were pre-existing ones.

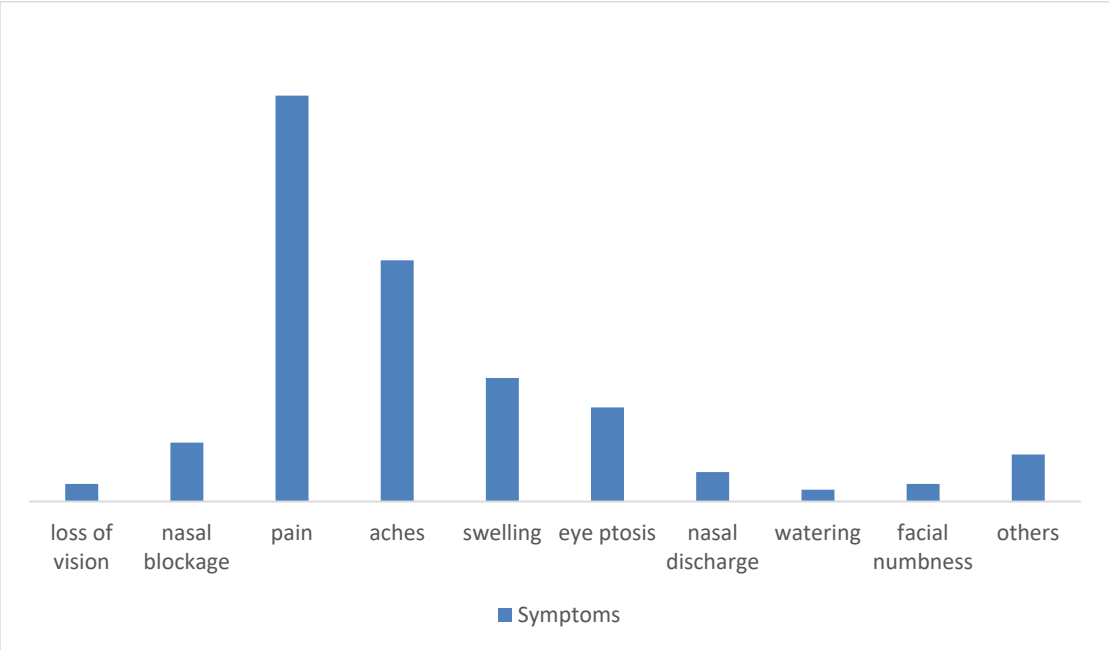

Figure 1: Showing the occurrence of mucormycosis

The figure above here shows the frequency at which different symptoms of mucormycosis occurred. Pain was the most commonly reported symptom, and this affected body parts like the jaw, face, eye, nasal and dental aspects. Aching sensation was the next frequently most occurring symptom with the head, tooth, ear, and jaw affected. Swelling over the eye, gum, cheek, preorbital space, face, and palate was also common. Some patients also reported bouts of eye ptosis, nasal discharge, eye watering, numbness, and nasal blockage loss/impairment of vision. There were yet instances where some patients had nasal bleeding, epistaxis, dizziness, oral ulcer, weakness, and breathlessness.

MRI/CT scans. The MRI/CT scans reveal that more than half of the patients – about 52.11% (37) – had sinusitis which affected the paranasal, maxillary, sphenoidal, ethmoidal and sinonasal spaces. Even more so, maxillary sinusitis occurred along with obliterated ostiomeatal complex in one instance. Again, occasions exist where sinusitis evolved with intracerebral, and intraorbital extensions. Erosions of the regions such as the maxillary sinus, sphenoid, ethmoid sinus, medial wall of the orbit and alveoli wall were also observed. Cellulitis was found to spread across the orbital, infraorbital and fascial spaces in a couple of patients. Mucosal thickening of the maxillary, sphenoid, ethmoid and frontal sinus, as well as granuloma, acute multiple infarct and internal carotid artery occlusion were found to appear less often.

Histopathological examination:

Based on the histopathological examination of the tissue specimens of the patients, nasal mucormycosis was found to be the most predominant with 64.79% (46) of the patients affected. This was followed by maxillary mucormycosis and orbital mucormycosis which affected 36.61% (26) and 15.49% (11) of the patients respectively. 9.86% (7) of the patients, however, had palatal mucormycosis. Occurring at a lesser frequency are orbital mucormycosis, middle meatus mucormycosis, teeth mucormycosis, nasolacrimal duct mucormycosis and aspergillosis.

Table 2: HbA1c results in mucormycosis patients

HbA1C (%)	Patients
4 – 5.9	13 (18.30)
6.0 – 6.4	5 (6.25)
6.5 – 7.9	24 (33.80)
≥ 8.0	27 (38.02)

The HbA1C result shows that 18.30% (13) of the patients had good to excellent score. Another 6.25% (5) of the patients had HbA1C between the prediabetic range even though two of those in this group already had diabetes. 33.80% (24) of the patients were observed to have HbA1C in the abnormal (diabetic) range [of 6.5 – 7.9], and it is interesting to note that two patients who had no history of diabetes mellitus were among this group. Finally, 38.02% (27) – including one patient not having diabetes mellitus – had HbA1C of 8 and above.

Table 3: Interventions

Mucormycosis	No. of patients (%)
Amphotericin	71 (100)
Posaconazole	42 (59.15)
Piperacillin-Tazobactam	6 (8.45)
Ceftriaxone	51 (71.83)
Cefotaxime	1 (1.4)
Surgical procedures Functional endoscopic sinus surgery Debridement Septoplasty Concha excision Craniotomy Maxillectomy Exenteration	 71 (100) 20 (28.16) 12 (16.90) 1 (1.4) 1 (1.4) 24 (33.80) 11 (15.49)

The table above shows how frequency of patients that underwent different therapeutic interventions for the treatment/management of mucormycosis; there were also series of therapies, including the use of antifungal agents, antibiotics, and surgical procedures. Antifungals, Amphotericin B and Posaconazole were administered to 100% (71) and 59.15% (42) – in respective order – of the patients. Also, 71.83% (51) of the patients had Ceftriaxone, while 1.4% (1) and 8.45% (6) of the patients respectively were administered Cefotaxime and Piperacillin-Tazobactam. Amphotericin B Liposomal formulation was administered in these patients in a dose of 5mg/kg/day and the duration of treatment individualized depending upon the extent and severity of the disease.In our study , the minimum duration of treatment was 21 days and maximum was 8 weeks. Concerning surgical procedures; all the patients had functional endoscopic sinus surgery performed on them, and this was either done along with debridement, septoplasty, craniotomy, or concha excision. Maxillectomy and exenteration of the eye were the other surgical procedures that were performed on some patients. It should be noted that only 45.07% (32) of the patients had mucormycosis taken care of through the administration of a triad of an antifungal, antibiotic and functional endoscopic sinus surgery.

Table 4: showing steroid and its relationship with mucormycosis

Grade of severity	Steroid (n=71, 100%)		Total
	Taken	Not taken	
1	15 (21.16%)	1 (1.40%)	16
2	19 (26.76%)	3(4.22%)	22
3	28 (39.43%)	3 (4.22%)	31
4	2 (2.81 %)	0 (0%)	2
TOTAL	64 (90.14%)	7 (9.85%)	71

Table 5: showing Remdesivir and its relationship with mucormycosis

Grade of severity	Remdesivir doses (n=71, 100%)				TOTAL
	< 6 doses	6 doses	> 6 doses	No dose	
1	6 (8.45%)	2 (2.81%)	3 (4.22%)	5 (7.04%)	16
2	6 (8.45%)	4 (56.33%)	2 (2.81%)	10 (14.08%)	22
3	10 (14.08%)	7 (9.85%)	0 (0%)	14 (19.71%)	31
4	1 (1.40%)	0 (0%)	0 (0%)	1 (1.40%)	2
TOTAL	41 (57.74%)			30 (42.25%)	71

Table 6: showing oxygen therapy and its relationship with mucormycosis

Grade of severity	Oxygen therapy (n=71, 100%)			TOTAL
	<10 days	>10 days	Not taken	
1	4(5.63%)	6 (8.45%)	6 (8.45%)	16
2	11(15.49%)	5 (7.04%)	6 (8.45%)	22
3	9 (12.67%)	7 (9.85%)	15	31
4	1 (1.40%)	0 (0%)	1 (1.40%)	2
TOTAL	25(35.21%)	18 (25.35%)	28 (39.43%)	71

Table 7: showing grade of mucormycosis and its outcome

Grade of severity	Death
1	0 (0%)
2	0 (0%)
3	6 (8.45%)
4	2 (2.81%)
Total	8 (11.26%)

The patients were classified as per Neelam Vaid et al. 2021[16] with most cases being in Grade 3(severe)[16]. 90.14% patients who received steroids as a part of therapy for COVID 19 developed mucormycosis.

57.74 % patients receiving Remdesivir suffered from Mucormycosis later. It was only 39.43 % of patients who didn't receive O 2 therapy while the rest 60.57 % patients who received O 2 developed mucormycosis. The death rate in mucormycosis accounted for a total of 11.26 % ascertaining the severity of the disease.

Discussion:

Rhino -orbito-cerebral mucormycosis followed by pulmonary mucormycosis is the common form of mucormycosis and has a slightly male predominance as observed in our study as well[17,18].

The fungal disease is more prevalent in patients with co-morbid conditions like diabetes and particularly those who had been given steroids or were on oxygen support for the treatment of COVID 19[19]. In addition, poor clinical hygiene and previously neglected diabetes paved way for the opportunistic environment for the fungal infection[19]. Gut associated lymphoid tissue protects the human body against various pathogens and infectious agents[20]. Exccessive use of steroids impairs the gut epithelial barrier allowing toxins and bacteria to leak into the bloodstream thereby providing a favourable environment for the fungus to grow[21]. During Covid 19 different antibiotics, steroids, vitamins and zinc etc. were used which causes a dysbiosis of gut and nasal microbiomes[21].

Amongst the COVID 19 patients only 7 patients didn't receive steroids the rest 90.14 % patients received steroids which shows a strong association of the use of steroids and development of mucormycosis

Steroids act mainly through:

1) Interaction with glucocorticoid receptors thereby causing hyperglycaemia
2) Defect in function of macrophages and neutrophils[19].

This downregulates the expression of proinflammatory cytokines secreted by macrophages like tumor necrosis factor alfa, interleukin 1 beta, interleukin 6 etc.[19,22,23]

Tocilizumab a monoclonal antibody approved for the use in COVID 19 acts as an immunosuppressant and controls inflammation which in turn reduces the patient's immunity and poses risk of contracting CAM[24,25,26]. It can be noted that the administration of biologicals like Remdesivir may have a causal relationship with development of mucormycosis as 50.70% patients who received remdesivir contracted mucormycosis though its thorough association is yet to be studied.

The widespread use of steroids and monoclonal antibodies and antibiotics against COVID 19 leads to development/ exacerbation of pre-existing fungal diseases[27].

COVID 19 associated mucormycosis was seen in patients' weeks to months after they developing COVID 19 or while they were suffering from COVID 19[28,29]. COVID 19 has shown to deteriorate the immune response which additionally paves the way for secondary opportunistic infections[28,29]. Three possible mechanism being:

1) Reduction in T – cells due to COVID related lymphopenia
2) Increase in pro – inflammatory markers
3) damage to pulmonary tissues[22,23]

Uncontrolled diabetes aids in developing mucormycosis by the following mechanisms:

1) Mucormycosis thrives on high glucose[31].
2) Lowering the immune response leading to reduced granulocyte phagocytosis with modified polymorphonuclear leukocyte response[32].

Also, free available iron which is a resource for mucor to grow is high in patients of COVID 19 as steroids cause hyperglycaemia which in turn leads to glycosylation of transferrin and ferritin and reduces the binding of iron thereby increasing free iron and COVID 19 increases cytokines like interleukins which increases free iron by increasing synthesis and decreasing transport of iron. Glucose regulator protein 78 expression is enhanced on the endothelial cells which then facilitates angio-invasion, tissue necrosis and hematogenous dissemination[33].

Prolonged use of ventilators and humidifiers were also associated with a rise in covid. The use of industrial oxygen in place of medical oxygen has been proposed to be a potential link in the rise of covid as according to the WHO medical use of oxygen differs from that of industrial oxygen in terms of purity, storage and distribution process. Hence the industrial oxygen is most likely to be contaminated and it needs an upgradation by undergoing deep cleaning and disinfection process before medical use. But the acute crisis that lead to shortage of oxygen on one hand and the time and costs involved in treating the industrial oxygen might have led to the conversion of many industrial oxygen cylinders to medical use thereby enhancing the risks of mucormycosis[34]. Out of 71 patients, 43 (60.56%) patients who received O_2 therapy developed COVID 19. Thus, it can

be ascertained that steroids and oxygen therapy do have a role in the COVID 19 patients developing mucormycosis which again shows a causal relationship of COVID 19 mucormycosis and O_2 therapy.

It could be said that the significance of amphotericin B in the treatment/management of mucormycosis is made apparent in this study. However, one has to exercise caution before drawing a conclusion on this especially since this study is not based on monotherapy. More significantly, it is worth noting that functional endoscopic sinus surgery (FESS) is equally important in the treatment of mucormycosis. Without attempting to water down the effect of amphotericin B, the finding from this study showed that the drug works in conjunction with surgery and some additional unknown factors. It was observed that two of the patients who were only administered amphotericin B [as monotherapy] eventually died, and this is despite the surgical procedures they underwent. As per the treatment, the patients were given Ceftriaxone, which is an antibiotic, and then subjected to FESS with either septoplasty or debridement. Notwithstanding, it is important to take note of the extent to which the severity of a patient's condition, as well as underlying medical conditions can affect a treatment outcome. As it was observed; a patient who had taken all the therapeutic interventions, except maxillectomy, had a negative mucormycosis report eventually died – even after having a revision FESS. So, it suffices that mucormycosis treatment goals be more driven towards safely addressing comorbidities in tandem with mucormycosis-centred therapies, a situation that could ultimately make monotherapy less viable. Though the effect of mucormycosis on HbA1C has not been widely reported, but this should be focused on in subsequent studies considering that they were non-diabetic patients that had their HbA1C scores within diabetic ranges.

Conclusion:

COVID-19-associated mucormycosis patients in this study fall in the middle-age range, with an average age of 48.11 years, and diabetes mellitus was the most common comorbidity amongst them followed by hypertension.

Sinusitis and erosions were also quite frequent amongst these patients, and the fact that some patients had to suffer these across different regions simultaneously even as they were placed under oxygen therapy and hospitalized for days goes to show the manifestation of severe COVID-19. The results from histopathological examination showed that nasal and maxillary mucormycosis were the two most prevalent types, and in some cases, certain patients had disseminated mucormycosis with two or more regions involved. Generally, pain, swelling and aches around different parts of facial/orbital aspects, as well as ptosis were common among COVID-associated mucormycosis patients.

The use of steroids, oxygen therapy, use of biological and COVID 19 in itself could be responsible for providing favourable growth medium for mucormycosis. Most of the patients presented in Grade 2 and 3 of grading system of mucormycosis. It was in light of the considerable symptomatic manifestations and sequelae of the disease that it became essential to adopt surgical interventions, especially function endoscopic sinus surgery and others (exenteration, maxillectomy, debridement, septoplasty, craniotomy and concha excision) along with the use of amphotericin and other antimicrobial agents to promote the survival of patients having COVID-19-associated mucormycosis.

And, going by the result, it was obvious that the therapeutic interventions overseen

by multidisciplinary team of medical practitioners were significant in improving treatment outcomes. More so, the findings from this study showed yet again the significance of combination therapy in the treatment/management of mucormycosis. Plus, it is apparent that amphotericin B alone may not be effective in certain cases hence the need to carry out multiple surgical procedures on some patients in order to improve the rate of survival can be recommended. Also, the duration of treatment with amphotericin didn't have any direct effect on the prognosis of the patient and hence a multidisciplinary approach with antifungals, antibiotics and surgical debridement was found to improve the prognosis of the patient.

References:

1. Kwon-Chung, K.J. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: Molecular mycologic perspectives. Clin. Infect. Dis. 2012, 54 (Suppl. 1), S8–S15.
2. Lelievre L., Garcia-Hermoso D., Abdoul, H., Hivelin M., Chouaki, T.; Toubas, D.; Mamez, A.C.; Lantieri, L.; Lortholary, O.; Lanternier, F.; et al. Posttraumatic mucormycosis: A nationwide study in France and review of the literature. Medicine (Baltimore) 2014, 93, 395–404.
3. Andresen, D.; Donaldson, A.; Choo, L.; Knox, A.; Klaassen, M.; Ursic, C.; Vonthethoff, L.; Krilis, S.; Konecny, P. Multifocal cutaneous mucormycosis complicating polymicrobial wound infections in a tsunami survivor from Sri Lanka. Lancet 2005, 365, 876–878.
4. Rao, C.Y.; Kurukularatne, C.; Garcia-Diaz, J.B.; Kemmerly, S.A.; Reed, D.; Fridkin, S.K.; Morgan, J. Implications of detecting the mold Syncephalastrum in clinical specimens of New Orleans residents after hurricanes Katrina and Rita. J. Occup. Environ. Med. 2007, 49, 411–416.
5. Warkentien, T.; Rodriguez, C.; Lloyd, B.; Wells, J.; Weintrob, A.; Dunne, J.R.; Ganesan, A.; Li, P.; Bradley, W.; Gaskins, L.J.; et al. Invasive mold infections following combat-related injuries. Clin. Infect. Dis. 2012, 55, 1441–1449.
6. Davoudi, S.; Graviss, L.S.; Kontoyiannis, D.P. Healthcare-associated outbreaks due to mucorales and other uncommon fungi. Eur. J. Clin. Investig. 2015, 45, 767–773.
7. Legrand M, Gits-Muselli M, Boutin L, Garcia-Hermoso D, Maurel V, Soussi S, et al. Detection of circulating Mucorales DNA in critically ill burn patients: Preliminary report of a screening strategy for early diagnosis and treatment. Clin. Infect. Dis. 2016, 63, 1312–1317.
8. Yasmin, F.; Najeeb, H.; Naeem, A.; Dapke, K.; Phadke, R.; Asghar, M.S.; Shah, S.M.I.; De Berardis, D.; Ullah, I. COVID-19 Associated Mucormycosis: A Systematic Review from Diagnostic Challenges to Management. Diseases 2021, 9, 65.
9. Roden, M.M.; Zaoutis, T.E.; Buchanan,W.L.; Knudsen, T.A.; Sarkisova, T.A.; Schaufele, R.L.; Sein, M.; Sein, T.; Chiou, C.C.; Chu, J.H.; et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin. Infect. Dis. 2005, 41, 634–653.
10. Skiada, A.; Pagano, L.; Groll, A.; Zimmerli, S.; Dupont, B.; Lagrou, K.; Lass-Florl, C.; Bouza, E.; Klimko, N.; Gaustad, P.; et al. Zygomycosis in Europe: Analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) working Group on Zygomycosis between 2005 and 2007. Clin. Microbiol. Infect. 2011, 17, 1859–1867.

11. Zilberberg, M.D.; Shorr, A.F.; Huang, H.; Chaudhari, P.; Paly, V.F.; Menzin, J. Hospital days, hospitalization costs, and inpatient mortality among patients with mucormycosis: A retrospective analysis of US hospital discharge data. BMC Infect. Dis. 2014, 14, 310.
12. Singh, A.K.; Singh, R.; Joshi, S.R.; Misra, A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab. Syndr. Clin. Res. Rev. 2021, 15, 102146.
13. Chen, N.; Zhou, M.; Dong, X.; Qu, J.; Gong, F.; Han, Y.; Qiu, Y.; Wang, J.; Liu, Y.; Wei, Y.; et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020, 395, 507–513.
14. Yang, W., Cao, Q., Qin, L., Wang, X., Cheng, Z., Pan, A., Dai, J., Sun, Q.; Zhao, F., Qu, J., et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J. Infect. 2020, 80, 388–393.
15. Jeong,W., Keighley, C., Wolfe, R., Lee, W.L., Slavin, M., Kong, D.C., Chen, S.C.-A. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin. Microbiol. Infect. 2019, 25, 26–34.
16. Neelam Vaid et al. A proposed grading system and experience of COVID 19 associated rhino orbito cerebral mucormycosis from an Indian tertiary care centre. Indian J Otolaryngol Head Neck Surg. 2021 Nov 15: 1–8
17. Chakrabarti A. The recent mucormycosis storm over Indian sky. Indian J Med Microbiol. 2021.
18. Jose A, Singh S, Roychoudhury A, Kholakiya Y, Arya S, Roychoudhury S. Current Understanding in the Pathophysiology of SARS-CoV-2-Associated Rhino-Orbito-Cerebral Mucormycosis: A Comprehensive Review. J Maxillofac Oral Surg. 2021.
19. Manoj Kumar, devojit Kumar sarma et al. MUcormycosis in COVID 19 pandemic: Risk factors and linkages.Current research in microbial sciences Volume 2,December 2021,100057.
20. R.D'Inca, M.Klooareg,et al. Intrauterine growth restriction modifies the developmental pattern of intestinal structure, transcriotomic profile and bacterial colonization in neonatal pigs.J.Nutr.,140(5)(20210: 925-931.
21. B.A. Paray, M.F. Albeshr, et al. Leaky gut and autoimmunity: an intricate balance in individuals' health and the diseased state.int. J.Mol.Sci.,21(24) (2020).
22. Narayanan S, Chua JV, Baddley JW. COVID-19 associated Mucormycosis (CAM): risk factors and mechanisms of disease. Clin Infect Dis. 2021.
23. Devnath P, Dhama K, Tareq AM, Emran TB. Mucormycosis coinfection in the context of global COVID-19 outbreak: A fatal addition to the pandemic spectrum. Int J Surg. 2021; 92:106031.
24. Bhogireddy R, Krishnamurthy V, Jabaris SSL, Pullaiah CP, Manohar S. Is Mucormycosis an inevitable complication of Covid-19 in India? Braz J Infect Dis. 2021:101597.
25. Bakshi SS, Kalidoss VK. COVID 19 infection and mucormycosis—a dangerously increasing combination. Egypt J Otolaryngol. 2021;37(1)
26. Thakar A, Lal D. "Black fungus": a perspective on the coronavirus disease 2019 (COVID-19)-associated rhino-orbital mucormycosis epidemic in India. Int Forum Allergy Rhinol. 2021.
27. Salil Mehta,Abhay Pandey.Rhino-Orbital Mucormycosis Associated with COVID 19.Cureus.2020 Sep;112(9):e10726.Published online

2020 2020 Sep 30.doi:10.7759/cureus.10726.PMCID: PMC7599039.PMID:33145132.
28. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'Em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;101019.
29. Rodriguez-Morales AJ, Sah R, Millan-Oñate J, Gonzalez A, Montenegro-Idrogo JJ, Scherger S, et al. COVID-19 associated mucormycosis: the urgent need to reconsider the indiscriminate use of immunosuppressive drugs. Ther Adv Infect Dis. 2021; 8:20499361211027065.
30. Bayram N, Ozsaygılı C, Sav H, Tekin Y, Gundogan M, Pangal E, et al. Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. Jpn J Ophthalmol. 2021;65(4):515–25.
31. Saidha PK, Kapoor S, Das P, Gupta A, Kakkar V, Kumar A, et al. Mucormycosis of Paranasal Sinuses of Odontogenic Origin Post COVID19 Infection: A Case Series. Indian J Otolaryngol Head Neck Surg. 2021:1–5.
32. MrigeshBhatia.Expert review of anti-infective therapy 2021,https://doi.org/10.1080/14787210.2021.1960822.accessed on 26 Jan 2022.
33. Awadhesh Kumar Singh, RituSingh, etal.Diabetes Metab Syndr.2021 July-August ;15(4):102146.