ejpmr, 2021,8(6), 609-615

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ADVANCING COVID – 19 ASSOCIATED MUCORMYCOSIS

Malavika Ashok[1*], Aranya K. Sreekumar[1], Kavya Shyam[1] and Archana J.R.[1]

Sixth Year Pharm D Intern, Cosmopolitan PG Institute of Medical Sciences Hospital, Trivandrum, Kerala, India.

***Corresponding Author: Malavika Ashok**

Sixth Year Pharm D Intern, Cosmopolitan PG Institute of Medical Sciences Hospital, Trivandrum, Kerala, India.

Article Received on 20/04/2021 **Article Revised on 10/05/2021** **Article Accepted on 31/05/2021**

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by newly discovered novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). The disease pattern of COVID - 19 can range from asymptomatic to mild upper respiratory infection, it can also lead to a severe pneumonia with associated bacterial and fungal co-infections such as Mucormycosis caused by mold fungi (Zygomycetes), which is the third invasive mycosis in order of importance after candidiasis and aspergillosis. The rise in cases of mucormycosis is due to COVID - 19 which remain associated with impaired immune system of infected patient. A classic clinical sign of mucormycosis is the rapid onset of tissue necrosis with or without fever. Necrosis is the result of invasion of blood vessels and subsequent thrombosis. The standard management of mucormycosis requires early diagnosis, a reversal of risk factors and underlying illness, surgical debridement, and prompt administration of intravenous antifungals - usually Amphotericin B.

KEYWORDS: Mucormycosis, COVID – 19, SARS CoV – 2, Zygomycetes, Aspergillosis, Amphotericin B, Surgical debridement.

MUCORMYCOSIS – A PREAMBLE

Mucormycosis, being the third invasive mycosis infection in order of importance after candidiasis and aspergillosis, is caused by several species such as Rizopus, mucor species, syncephalastrum species, cunninghamella species etc. Mucorales and Entomophthorales are the two orders of the class Zygomycetes.[1]

Members of the order Mucorales are the aetiological agents of the disease known as 'mucormycosis', a fulminant disease with high rates of morbidity and mortality that mainly affects immunocompromised patients. However, species of the order Entomophthorales are the common cause for the chronic subcutaneous disease observed in immunocompetent patients. Either on grow non-selective or selective media, Mucorales grow well in them. Growth is expeditious, with mycelial elements expanding to the entire plate in only a few days.[3] Identification of the agents responsible for mucormycosis is based on macroscopic and microscopic morphological identification, carbohydrate metabolism and the maximum temperature favour with its growth.[1,3]

Here in this review literature we aim to highlight the correlation of Mucormycosis with COVID - 19 and delineate the clinical features, risks, diagnosis, management and prevention strategies.

PATHOPHYSIOLOGY

Through inhalation of airborne spores, percutaneous inoculation or ingestion, Mucorales enter deep tissues where they colonise into high number of patients but do not necessarily cause invasion.

After the spores have invaded the lungs or subcutaneous tissues, they come in contact with first line of defence, mononuclear and polynuclear phagocytes. The phagocytic cells of the healthy host kill the spores of Mucorales by generating oxidative metabolites and defensins (cationic peptides).[2,3,4] Severely immunocompromised neutropenic patients and those with phagocyte dysfunction are at greater risk of mucormycosis.

Ketoacidosis reduces the motility of these phagocytes towards the source of the infection and their ability for lysis by oxidative and non-oxidative mechanisms. High Iron concentration in the serum is another risk factor for Mucormycosis. Patients treated with deferoxamine have a high incidence of mucormycosis, probably because Mucorales use this chelate as a siderophore to obtain more iron.[5] It is well-known that administration of iron or deferoxamine to Mucorales infected animals reduces survival.[6,7.8] The increased risk of mucormycosis in patients with ketoacidosis may also be due to the release of iron bound to proteins.[2,9] If the spores escape phagocytosis, they can invade vessels, partly by efficacious adherence to endothelial cells, an ability that

Rhizopus *oryzae* maintains even when the fungus species is not viable.[9]

HISTORY AND PHYSICAL

There are five predominant clinical types of mucormycosis; of these, Rhinocerebral and Pulmonary infections are the most common.[10,11,12]

The classic sign of mucormycosis is presented with rapid onset of tissue necrosis with or without fever. As a result of invasion of blood vessels and thrombosis which eventually lead to Necrosis.

- Rhinocerebral mucormycosis is the most common form in patients with diabetes and with renal transplants.[13] It also occurs in neutropenic cancer patients and hematopoietic stem cell transplant or solid organ transplant recipients. Symptoms include unilateral facial edema, headaches, nasal or sinus congestion or pain, serosanguinous nasal discharge and fever. Ptosis, proptosis, loss of extraocular muscle function, and vision disturbance may occur as the infection spreads. The applicable diagnostic signs include necrotic black lesions on the hard palate or nasal turbinate and drainage of black pus from eyes.
- Hematologic malignancy or profound neutropenia are the commonest reasons for Pulmonary Mucormycosis. The non-specific symptoms include fever, cough, chest pain, and dyspnea. Angioinvasion leads to tissue necrosis, which may ultimately cause cavitation and/or hemoptysis.
- Cutaneous mucormycosis may be primary or secondary. Primary infection is usually caused by direct entry of the fungus into damaged skin and is most often seen in patients with burns or other forms of local skin trauma, and can occur in patients who are not immunosuppressed. Primary infection produces an acute inflammatory response with pus, abscess formation, tissue swelling, and necrosis. The lesions may become red and indurated and progress to black eschars. Secondary cutaneous infection is generally seen when there is hematogenous spread of pathogen occurs. Lesions typically begin as erythematous, indurated, and painful cellulitis and then progress to an ulcer covered with a black eschar.
- Gastrointestinal mucormycosis is less common than the other clinical forms and occurs as result from ingestion of the organism. Predominant in malnourished patients or premature infants. The commonly affected sites are stomach, colon, and ileum. Abdominal pain with distension, nausea and vomiting are the commonest nonspecific symptoms where gastrointestinal bleeding can also occur. It is the most common form of mucormycosis among neonates and is challenging to diagnose partly because of its clinical resemblance to necrotizing enterocolitis, a far more common disease.[14]
- Disseminated mucormycosis may follow the above described forms of mucormycosis but is usually seen in neutropenic patients with a pulmonary infection. The commonest site of spread is the brain, but the spleen, heart, skin, and other organs can also be affected.

DIAGNOSTIC TESTS AND INVESTIGATIONS

Diagnosis of mucormycosis is challenging because the signs and symptoms are similar to many conditions including other types of infection. Based on the identification of characteristic symptoms, detailed patient history, clinical evaluation and a variety of specialized tests a final diagnosis has to be made. Comparing to diagnosis of other fungal infections and treatment of mucormycosis is more difficult and challenging because under normal laboratory conditions, sporulation fails and culture results from the biopsies are often negative due to unviable organism in necrotic tissues.[15,16,17]

The diagnosis is comparatively easy in the case of rhino-orbital and mucocutaneous involvement but when deep tissues are invaded as in case of pulmonary mucormycosis, the samples, and correct diagnosis is more burdensome to obtain.[18,19]

Fungal culture is used to identify the mold in affected tissue where a sample of affected tissue is taken, which test can determine the presence and type of fungal infection involved. However, sometimes a fungal culture does not reveal a fungal infection despite the presence of infection and tests using cultures of clinical samples have limited sensitivity. There are many reports of negative culture results both ante-mortem and post-mortem, which is due to the aggressive processing of the specimen before plating especially when the samples are biopsy specimens. Thus, a fungal culture providing negative results does not rule out mucormycosis. Tests using sputum have sensitivity values less than 25% in pulmonary forms and the specificity remains unknown, although it is generally believed to be low.[16,19]

Even though culture is contemplated as the gold standard for recognizing the infective agent, detecting Mucor-like hyphae in the involved tissues by histopathologic examination is also used to confirm mucormycosis.[20] Histopathological testing alone does not provide the genus and species, and therefore be complemented with culture. Histological invasion, particularly of vessels, the hyphae of zygomycetes appeared as wide, ribbon-like, pauci septate hyphae with right-angle branching is diagnostic in an appropriate clinical context.[21]

If an infection is positive in histopathology study for infection, but a fungal culture is negative, polymerase chain reaction (PCR) may be used. PCR can recognize the causative species of the infection and small fragments of DNA including genetic material of infectious organisms like fungi. Freshness of the tissue specimens is important for the accuracy of PCR assays.

Diagnosis by imaging is also difficult.[22] Radiology and computed tomography scans usually show invasion of the sinuses, invasion of the surrounding bone structures and displacement of the orbit in cases of rhino-orbital lesions. Magnetic resonance imaging is the technique of choice when intra-cranial structures are affected. Pulmonary mucormycosis generate lesions which is non-specific and cannot be differentiated from invasive aspergillosis.

During anti-Aspergillus therapy the presence of progressing multifocal pulmonary sinusitis suggests mucormycosis. Computerized Tomography (CT) scanning can be used to determine the exact location and extent of an infection, where CT may be taken off from lungs, sinuses, facial structures, or other areas of the body. A CT scan of the lungs can reveal a reverse halo sign in individuals with pulmonary mucormycosis, this diagnostic clue is an area of tissue death (necrosis) which resembles the ground glass on the film is suggestive of mucormycosis infection.[22,23]

Newer molecular and antigenic tools are indispensable for the early detection of mucormycosis. PCR in fresh tissue samples are more sensitive than tissue or blood culture methods for an accurate and dependable diagnosis of this infection.

INTRODUCTION TO SARS – CoV-2

Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by newly discovered novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), first reported in Wuhan (Hubei province), China.[24,26] This infection has spread rapidly across the world forming a global pandemic, resulted in more than 10 million confirmed COVID - 19 cases, including more than half a million deaths[27].

The disease pattern of COVID - 19 can range from asymptomatic to mild upper respiratory infection, it can also lead to a severe pneumonia with associated bacterial and fungal coinfections, requiring critical care and mechanical ventilation.[25,26]

The COVID - 19 symptoms have expanded since the first days of the disease's presentation, which initially included dry cough and high-grade fever, to various multisystem problems such as shortness of breath, loss of sense of smell, loss of taste functions, diarrhoea, generalised malaise, acute cardiac injury and secondary infections. Early identification of the high-morbidity conditions is significant for optimal treatment and improved outcomes.

SARS-CoV-2 infection triggers both innate and adaptive immune responses. Innate immune response includes a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines, and adaptive immune responses are carried out by T and B cells. These responses are capable of resolving an infection.

A dysfunctional immune response may occur in some cases, which present as severe COVID-19 infections this can cause significant lung and even systemic pathology. This can make these patients vulnerable to secondary infections.[28,29]

As well as due to the associated comorbidities and immune compromised conditions these patients are prone to develop severe opportunistic infections.

There are reports of the development of severe opportunistic infections in patients affected with COVID-19 disease such as oropharyngeal candidiasis, pulmonary aspergillosis, bloodstream candida infections etc.[30,31] Furthermore, there are isolated case reports of rhino-orbital mucormycosis in COVID -19 patients.

CORRELATION BETWEEN MUCORMYCOSIS AND SARS CoV- 2 INFECTION

Mucormycosis is a type of invasive fungal infection caused by mold fungi. In 60% of mucormycosis cases in humans, Rhizopus *oryzae* is the commonest aetiology which is responsible for 90% of the rhino cerebral form whereas pulmonary mucormycosis is a relatively rare fungal disease, which is arduous to diagnose early and lacks effectual treatment.[32]

The rise in cases of mucormycosis is due to COVID – 19, which remain correlated with the impaired immune system of infected patient.

SARS-CoV-2 infection manipulates the immune system by affecting T lymphocytes, especially CD4+ and CD8+ T cells, which is highly involved in the pathological process of COVID -19 infection. The significant reduction of the absolute number of lymphocytes (lymphopenia) and specifically of T cells involved in the most severe COVID -19 cases, is associated with the worst outcome compromising the immune system and might expose patients to a higher risk of developing opportunistic infections.[33,34]

In Sargin F, et al., (2021), the patient had uncontrolled glucose level observed owing to the possibility of a long-term diabetes that has not been diagnosed before and suggests the reason behind the underlying cause of mucor infection. Steroidal therapy to the patient can be another underlying cause for the development of mucor infection.[35]

Lymphopenia is common in patients infected with SARS-COV2 and may rise preponderance to mucor infection with further suppression of the immune system. This susceptibility has been documented especially by mucor infections observed in AIDS patients with lymphopenia suggesting that lymphopenia associated

with COVID -19 may also be a primary risk factor for mucor infection.

The spores of the inhaled fungus are destroyed by the phagocytic cells, but in immunocompromised individuals, the vascular endothelium is infected by the spores through invasion.

As in fungal infection, host response involves both cellular and humoral immunity where, the latter plays a major role in offering defence against fungal infection. It has been also reported that cellular immunity associated with Th1-type offer a protective response against fungal infection via secreting IFN-y.

Contradictorily, the response of Th2 via IL4 and IL10 triggers and facilitate fungal infection and pathological outcomes. Furthermore, the mononuclear immune cells at the site of infection start infiltration and generates a delayed immune activity favouring fungal infections.

The central research institution across the globe such as CDC emphasizes rise in mucormycosis cases after COVID-19 disease.

The poor and or impaired immune functioning is major cause of rise in mucormycosis cases and clinical findings further confirmed in COVID – 19 patients. The cell mediated immunity i.e. Th1 and IFN-y are primarily involved in providing protection during viral infections.

However, novel SARS-CoV-2 infection remains associated with impaired functioning of not only cellular but also humoral immunity triggering higher risk for fungal infection.[36]

In short, the multiple risk factors present in the patients or the comorbid illnesses in severe COVID-19 patients, along with the additional immunosuppression caused by glucocorticoids, increases the net effect of an immune suppression, thereby making liable to invasive mold infections.[37]

MANAGEMENT OF MUCORMYCOSIS IN SARS Cov – 2

The standard guidelines in management of mucormycosis involves early diagnosis, a reversing risk factors and underlying illness, surgical debridement, and immediate intravenous antifungals - usually amphotericin B. This include the prompt management of hyperglycaemia, acidosis, electrolyte imbalance and cessation of immunosuppressive drugs.

The recent discovery for the management of mucormycosis advocate Liposomal Amphotericin B at a dose of 5–10 mg/kg per day in high doses intravenously as initial therapy and without central nervous system involvement, a dose of 5 mg/kg is recommended.

It is understood that from a randomised controlled trial of 201 patients with invasive mold disease administrated liposomal amphotericin B used at 3 mg/kg/day showed equal efficacy but safer and better tolerated 10 mg/kg/day dose amphotericin B.[37]

The initial starting dose is 5 mg/kg IV daily, with a maximum dose of 10 mg/kg IV and the duration of treatment depends upon the patient's clinical picture.

Surgical debridement of infected tissue is mandatory to limit the further spread of infection. Aggressive surgical debridement of necrotic tissue should be promptly done which may involve lobectomy, partial pneumonectomy in accordance with the site of disease. Similar to necrotizing fasciitis, this advocates aggressive surgical management and often carried dramatic morbidity.

Without restoring immune status, the outcomes are unfortunately very bad even with the standard antifungal therapies and surgical debridement

Posaconazole or Isavuconazole has some evidence as second-line therapy in mucormycosis. As for rescue management, Posaconazole 200 mg IV four times daily is recommended. Amphotericin and Posaconazole combination are not supported by guidelines. Hyperbaric oxygen is used as an adjuvant therapy. The elevated oxygen pressure improves the ability of neutrophils to kill the fungi and enhances wound healing.[38]

Management of rhino-orbital cerebral mucormycosis also involves medical as well as surgical management which is regarded as an emergency.

A three-step approach of reversal of immunosuppressive state, administration of IV antifungals, and extensive surgical debridement is usually undertaken.

Early definite diagnosis is practically challenging, whereas the delay in initiating the treatment will further exasperate the morbidity and mortality. Prompt antifungal administration and extensive surgical debridement are carried out empirically whenever the possibility of rhino-orbital cerebral mucormycosis is suspected based on risk factors, clinical features, and or radiologic findings. Granulocyte colony-stimulating factor may enhance white blood cell count and may help to improve host defences.

For definite histopathologic confirmation, debridement provides adequate tissue biopsy. Dissection is usually continued until normal, well-perfused bleeding tissue is attained, since mucormycotic tissues are less likely to bleed due to extensive thrombosis of vessels. Removal of the palate, nose cartilage, and orbit would cause significant disfigurement. The orbital involvement may need orbital decompression or exenteration. The relevance of routine orbital exenteration or the timing exenteration is currently unclear, and cases with orbital involvement have also been successfully managed without exenteration.[39]

RISK FACTORS

Mucormycosis or black fungus is a complication caused by a fungal infection. People get mucormycosis by coming in contact with the fungal spores in the environment. It can also develop on the skin after fungus enters the skin through a cut, scrape, burn or other skin trauma.

Mucormycosis can involve many different organs. The most common site of infection is Rhinocerebral, followed by cutaneous, lung, disseminated, and gastrointestinal tract.

The risk factors for mucormycosis include uncontrolled diabetes mellitus, immune dysregulation due to viral infection like Covid - 19 or other infections, weakening of immune system, hematologic malignancy, stem cell transplant, solid organ transplant, neutropenia, deferoxamine therapy, cancer, some biological agents use, voriconazole therapy, prolonged intensive care unit or hospital stay and corticosteroid use.[40]

Some risk factors are more closely associated with specific sites of involvement. Solid organ transplant is more uniquely associated with lung infection, whereas diabetes mellitus is more closely associated with the Rhinocerebral form. Diabetes is one of the major risk factors. Because growth of the fungi is stimulated by a high blood glucose concentration, infection is rare in patients with well-controlled blood glucose levels.

PREVENTION

- Maintain personal hygiene including thorough scrub bath
- The use of glucocorticoids in mild COVID-19 cases (without hypoxemia) or the utilization of higher doses of glucocorticoids should be avoided
- In the absence of a clear benefit, drugs targeting immune pathways such as tocilizumab should be discouraged
- The disease can be managed by controlling diabetes, discontinuing immune modulating drugs, reducing steroids
- Do not use unwashed mask continuously for more than 3days
- Masks should be ideally washed after a person returns home from outside every time, just in hot water or some disinfectant or cleansed with a sanitiser at least
- Control hyperglycaemia by regularly monitoring blood glucose levels.
- Use clean, sterile water for humidifiers during oxygen therapy
- Use antibiotics and antifungals rationally[37]

STRATEGIES TO TACKLE MUCORMYCOSIS

- Control of hyperglycaemia, early treatment with liposomal amphotericin B, and surgery are essential for the successful management of mucormycosis
- Discontinue immune modulating drugs
- Start antifungal therapy for at least 4-6weeks
- Empirical treatment is necessary before histologic identification and culture
- Extensive surgical debridement to remove all necrotic materials of tissue injury[41]

CONCLUSION

The rise in cases of mucormycosis is due to COVID – 19, which remain correlated with the impaired immune system of infected patient. Diabetes is one of the major risk factors because the growth of fungi is stimulated by a high blood glucose concentration, infection is rare in patients with well-controlled blood glucose levels. If infection is confirmed, early surgical intervention and intravenous anti-fungal treatment should be advocated for management, as a better prognosis and less fulminant disease course can be achieved in cases of post-coronavirus mucormycosis. This also include the prompt management of hyperglycaemia, acidosis, electrolyte imbalance and cessation of immunosuppressive drugs. Identifying the risk factors and the comorbidities is mandatory to reverse the condition and reduce the mortality in patients.

REFERENCE

1. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect, 2004; 10(1): 31–47.
2. Waldorf AR. Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol Ser., 1989; 47: 243–271.
3. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest, 1984; 74: 150–160.
4. Diamond RD, Haudenschild CC, Erickson NF 3rd. Monocyte-mediated damage to Rhizopus oryzae hyphae in vitro. Infect Immun, 1982; 38: 292–297.
5. Boelaert JR, de Locht M, Van Cutsem J et al. Mucormycosis during deferoxamine therapy is a siderophoremediated infection. In vitro and in vivo animal studies. J Clin Invest, 1993; 91: 1979–1986.
6. Abe F, Inaba H, Katoh T, Hotchi M. Effects of iron and desferrioxamine on Rhizopus infection. Mycopathologia, 1990; 110: 87–91.
7. Amin SB, Ryan RM, Metlay LA, Watson WJ. Absidia corymbifera infections in neonates. Clin Infect Dis., 1998; 26: 990–992.
8. Van Cutsem J, Boelaert JR. Effects of deferoxamine, feroxamine and iron on experimental mucormycosis (zygomycosis). Kidney Int, 1989; 36: 1061–1068
9. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes, 1982; 31: 1109–1114.
10. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosisexternal icon. Clin Infect Dis., 2012; 54(1): S23-34.

11. Lewis RE, Kontoyiannis DP. Epidemiology and treatment of mucormycosisexternal icon. Future Microbiol., Sep, 2013; 8(9): 1163-75.
12. Spellberg B, Edwards Jr. J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and managementexternal icon. Clin Microbiol Rev., Jul, 2005; 18(3): 556-69.
13. Song Y, Qiao J, Giovanni G, Liu G, Yang H, Wu J, Chen J. Mucormycosis in renal transplant recipients: review of 174 reported casesexternal icon. BMC Infect Dis., Apr, 2017; 17(1): 283.
14. Vallabhaneni S, Mody RK. Gastrointestinal mucormycosis in neonates: a reviewexternal icon. Current Fungal Infect Rep., 2015 Sept
15. Maertens J, Demuynck H, Verbeken EK et al. Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplant, 1999; 24: 307–312.
16. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis., 2000; 30: 851–856.
17. Lennette E, Balows A. Manual of Clinical Microbiology: American Society for Microbiology. Washington DC, 1985.
18. Nosari A, Oreste P, Montillo M et al. Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica, 2000; 85: 1068–1071.
19. Pagano L, Offidani M, Fianchi L et al. Mucormycosis in hematologic patients. Haematologica, 2004; 89: 207–214.
20. Ribes J16. A, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev., 2000; 13: 236-301.
21. Roberts GD. Clinical Mycology-Direct examination: zygomycetes. Mayo Foundation for Medical Education and Research, 2012.
22. Hata D. J, Buckwalter S P, Pritt BS, Roberts GD, Wengenack NL. Real-time PCR method for detection of zygomycetes. J Clin Microbiol, 2008; 46: 2353-2358.
23. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis., 2005; 41: 60–66.
24. Farnoosh G, Alishiri G, Hosseini Zijoud SR, Dorostkar R, Jalali Farahani A. Understanding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19) based on available evidence – A narrative review. J Mil Med., 2020; 22: 1-11.
25. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus, 2020; 12: e10726.
26. Cevik, M.; Bamford, C.; Ho, A. COVID-19 pandemic—A focused review for clinicians. Clin. Microbiol. Infect., 2020.
27. Werthman-Ehrenreich A Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med., S0735–6757(20): 30826–30833.
28. Tay M.Z, Poh, C.M, Rénia, L, MacAry, P.A. Ng LFP The trinity of COVID-19: Immunity, inflammation and intervention. Nat. Rev. Immunol., 2020; 20: 363–374.
29. Chuan, Q, Luoqi, Z, Ziwei, H, Shuoqi, Z, Sheng, Y, Yu, T, Cuihong, X, Ke, M, Ke, S, Wei, W. Dysregulated immune response in patients with COVID-19 in Wuhan China. Clin. Infect. Dis., 2020; 71(15): 762-768.
30. Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic fungal infections in the epidemic area of COVID-19: A clinical and diagnostic perspective from Iran. Mycopathologia, 2020; 185: 607-11.
31. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant Candida auris infections in critically Ill coronavirus disease patients, India, 2020. Emerg Infect Dis., 2020; 26: 2694-6.
32. Johnson AK, Ghazarian Z, Cendrowski KD, Persichino JG. Pulmonary aspergillosis and mucormycosis in a patient with COVID-19. *Med Mycol Case Rep*., 2021; 32: 64-67.
33. Pasero D, Sanna S, Liperi C, Piredda D, Branca GP, Casadio L, Simeo R, Buselli A, Rizzo D, Bussu F, Rubino S, Terragni P. A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. Infection., 2020; 17: 1–6.
34. Vijay Kumar Chennamchetty, Sowmya Adimulapu, Balaji Patel Kola, Michelle De Padua, Ambika C, Mahendra Kumar Verma, M. V. Raghavendra Rao. Post-COVID pulmonary mucormycosis - A case report. *IP Indian Journal of Immunology and Respiratory Medicine., 2021; 6(1): 62–66*
35. Sargin F, Akbulut M, Karaduman S, Sungaurtekin H. Severe Rhinocerebral Mucormycosis Case Developed After COVID 19. J Bacteriol Parasitol, 2021; 12(386): 1-3.
36. Verma A, Wüthrich M, Deepe G, Klein B. Adaptive immunity to fungi. Cold Spring Harb Perspect Med., Nov 6, 2014; 5(3): a019612.
37. Garg D, Muthu V, Sehgal IS, et al. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. *Mycopathologia*, 2021; 186(2): 289-298.
38. Hernández JL, Buckley CJ. Mucormycosis. [Updated 2020 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 Jan.
39. Bhandari J, Thada PK, Nagalli S. Rhinocerebral Mucormycosis. [Updated 2020 Nov 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 Jan.
40. S Sarvestani A, Pishdad G, Bolandparvaz S. Predisposing Factors for Mucormycosis in Patients with Diabetes Mellitus; An Experience of 21 Years in Southern Iran. *Bull Emerg Trauma*., 2013; 1(4): 164-170.

41. Agrawal R, Yeldandi A, Savas H, Parekh ND, Lombardi PJ, Hart EM. Pulmonary Mucormycosis: Risk Factors, Radiologic Findings, and Pathologic Correlation. Radiographics, 2020; 40(3): 656-666.