



COVID-19 and Mucormycosis in Dental Practice: Let's Decipher the Enigma!: A Review

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Abstract

The incidence of the opportunistic infections or the co-infections namely bacterial and fungal, is on the surge and is likely in consonance with the pandemic COVID-19. One of the culprit belonging to the category of such infections is known as "black fungus" or "mucormycosis", a very common opportunistic infection. Mucormycosis has definitely emerged as a new threat. An increase in number of COVID recovered patients have presented with symptoms of mucormycosis in the second peak. This review article portrays about the brief introduction, the association of COVID-19 with mucormycosis, various diagnosis and therapeutic modalities and the importance of oral health awareness and promotion in these turbulent times.

Keywords: Black Fungus; COVID-19; COVID; Coronavirus; Fungal Infection; Mucormycosis; Oral Hygiene; Pandemic; SARS-CoV-2

Introduction

Mucormycosis is an angioinvasive disease caused by mold fungi of the genus *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella* and *Absidia* of Order- Mucorales and Class- Zygomycetes. Mucormycosis also known as black fungus, zygomycosis or phycomycosis is an opportunistic infection of the fungi, affecting the patients with altered immunity. It is the 2nd most common group affecting the immunocompromised hosts after the invasive aspergillosis. It was first described in 1885 by Paltauf and later coined as Mucormycosis in 1957 by Baker for an aggressive infection caused by *Rhizopus*.

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with a broad range of opportunistic infections i.e. bacterial and fungal infections. This generally involves both Aspergillosis and *Candida* as the main fungal pathogens for co-infection in people with COVID-19. There has been a recent uprise of the cases

of mucormycosis in people with COVID-19 across the globe and in particular from India. This can be attributed to the fact related to the germination of the Mucorales spores in people with COVID-19 due to low oxygen (hypoxia), high glucose (hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization i.e. prolonged ICU (intensive care unit) stays.

Discussion

Organisms causing mucormycosis are omnipresent in the natural environment. Generally, the epidemiology of the disease is related to the inhalation of the spores into the upper and/or lower airways, inoculation in case of break in the continuity of the skin during trauma and rarely can be due to ingestion via the gastrointestinal tract.

Clinical manifestations of the disease generally depend on the site and extent of the involvement of mucormycosis. The disease can be categorized as pulmonary, rhinocerebral, cutaneous and may be associated with the other forms. The pulmonary mucormycosis is known to be associated with the "reverse halo sign" which includes ground glass opacities with a ring of consolidation. Moreover, the radiographic findings include nodules, consolidation, cavitary lesions, and/or wedge-shaped lung infarcts. The next form is the rhinocerebral mucormycosis, known by a number of names. Generally, this form involves the palate, the sinuses, the orbit and any adjacent structures, with or without extension via contiguous or hematogenous routes to the brain. The next form of the disease is the cutaneous mucormycosis, commonly occurs whenever there is a break in the continuity of the skin due to trauma. The other forms include the gastrointestinal tract, which is least commonly involved as the primary site of mucormycosis.

The oral manifestations of mucormycosis involves pain, tooth mobility, bad breath, nasal stuffiness and discharge (can be black purulent), epistaxis, pain in the para nasal sinuses, draining sinuses, nasal and facial erythema, ulcerations in the palate, blackish discoloured skin, erythema and edema of the peri orbital area, ptosis, diplopia, and pain in the orbit.

The diagnostic aspects of the disease involves primary and adjunctive diagnostic tests. Primary diagnostic tests generally involve the direct microscopy of clinical samples with an optical brightener such as calcofluor white. This helps to identify the hyphae of Mucorales, known to have the characteristic ribbon-like in appearance, and branched at an angle of 90-degrees. The adjunctive or the emerging diagnostic tests, as the name suggests, are the methods that supplement the primary diagnostic methods for mucormycosis. Immunohistochemistry on histopathology samples and molecular detection methods, including polymerase chain reaction-based strategies and matrix-assisted laser desorption ionization time-of-flight mass spectrometry are generally included in this category. In addition to this, radiographic diagnosis includes Gold Standard-Gadolinium Enhanced MRI and Adjuvant Imaging-CT PNS with contrast. Hence, imaging and diagnosis is helpful to determine the involvement and extent of the fungal infection.

Mucormycosis is an unusual disease thereby making it difficult to research the various therapeutic options for the same. Mucormycosis can prove to be life-threatening and rapidly progressive condition. Henceforth, swift and multidisciplinary approach to therapy is recommended. Based on this, the treatment approaches may include antifungal therapy, surgical therapy or a combination approach. The primary antifungal therapy includes Amphotericin

B-based therapy, which is recommended as the first-line treatment of mucormycosis in all age groups. Due to the poor tolerance and adverse effects, the lipid formulations of amphotericin B, liposomal amphotericin B (L-AmB) were more encouraged in the patients. Another option is the Amphotericin B lipid complex (ABLC), an important therapy to be initiated upon suspicion of mucormycosis. The triazole monotherapy includes triazole antifungals namely Isavuconazole i.e. broad spectrum triazole antifungal indicated as a primary therapy of mucormycosis in adults. A combination antifungal therapy involving the use of a combination of L-AmB and an echinocandin as primary therapy for mucormycosis has also been recommended. In addition to this, the benefits of posaconazole when added to lipid-formulated amphotericin B for primary treatment of mucormycosis have been evaluated. Unfortunately, poor response and intolerance to the primary antifungal therapy were seen in the individuals. This gave birth to another therapy known as the salvage antifungal therapy. Posaconazole and isavuconazole have demonstrated efficacy as the salvage antifungal therapy. Moreover, their intravenous formulations have been used effectively in cases of severe disease. Salvage therapy has also proved its worth in cases with refractory or progressive disease. Another treatment modality includes the step-down therapy and duration, in which the response to the therapy is evaluated clinically and on repeated imaging of the affected site(s). The recommended guidelines for treatment of mucormycosis includes the continuation of antifungal therapy until complete resolution of clinical and radiographic findings, and reconstruction of the immune function. Surgical debridement in combination with antifungal therapy as a surgical modality improves survival and is strongly recommended for patients with the rhinocerebral and cutaneous forms of mucormycosis. Reversal of the etiological or the predisposing factors are recommended in patients with mucormycosis. In patients with COVID, the overzealous use of steroids has led to the immune system dysfunction and altered immunity, a common predisposing factor for mucormycosis. Moreover, during prolonged ICU stays and related poor hygiene standards in response to oxygen pipes for administration of oxygen through oxygen cylinder, led to a big surge in the number of mucormycosis cases. Control of hyperglycemia and acidosis is important for patients with uncontrolled diabetes mellitus. Deferoxamine serves as a siderophore and makes iron available for fungi to use metabolically is another risk factor. It has also been studied that repeated use of the same mask for 2 - 3 weeks may lead to the development of mucormycosis.

Keeping in view such harsh times, it is important to follow various guidelines related to the oral health. These include: regular brushing at least twice daily along with flossing and mouthwash with 1% povidone iodine in a COVID positive patient, monitor-

ing blood glucose levels for glycaemic control in diabetics, monitoring of the mucosal changes in patients wearing removable or fixed prosthesis, inhalation of steam, high protein and low sugar diet with multivitamins are advised. In addition to this, meticulous oral hygiene using tooth brush for oral hygiene and gauze piece for soft tissue hygiene is preferred in intubated patients. Dentures in such patients are to be cleaned properly with tooth brush (single use) and gauze pieces. Moreover, it is recommended to change the toothbrush in patients recovered from COVID-19. Conclusively, mass awareness should be created in response to the oral hygiene practices to stop the menace of the pandemic COVID-19 and mucormycosis [1-15].

Conclusion

The association of COVID-19 along with surge in the mucormycosis cases in Indian appears to be an ungodly triad of overzealous use of corticosteroids, diabetes, and poor hygiene standards related to the delivery of oxygen through the oxygen pipes in hospitals. Henceforth, it is recommended to make the patients aware of the judicious use of steroids, glycaemic control and regular monitoring and maintaining the appropriate hygiene standards for delivering the oxygen through the pipes. Henceforth, let us take a pledge as dental surgeons to create mass awareness for oral health promotion and its significance in avoiding the menace of COVID-19 along with mucormycosis.

Bibliography

- Vallabhaneni S, Benedict K, Derado G, Mody RK. Trends in hospitalizations related to invasive aspergillosis and mucormycosis in the United States, 2000-2013. *Open Forum Infect Dis*. 2017;4(1):ofw268.
- Wattier RL, Dvorak CC, Hoffman JA, et al. A prospective, international cohort study of invasive mold infections in children. *J Pediatric Infect Dis Soc*. 2015;4(4):313-322.
- Lionakis MS, Lewis RE, Kontoyiannis DP. Breakthrough invasive mold infections in the hematology patient: current concepts and future directions. *Clin Infect Dis*. 2018;67(10):1621-1630.
- Abidi MZ, Sohail MR, Cummins N, et al. Stability in the cumulative incidence, severity and mortality of 101 cases of invasive mucormycosis in high-risk patients from 1995 to 2011: a comparison of eras immediately before and after the availability of voriconazole and echinocandin-amphotericin combination therapies. *Mycoses*. 2014;57(11):687-698.
- Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ trans-plant recipients: a prospective, matched case-control study to assess risks for disease and outcome. *J Infect Dis*. 2009;200(6):1002-1011.
- Skiada A, Pagano L, Groll A, 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(12):1859-1867.
- Lanternier F, Dannaoui E, Morizot G, et al. A global analysis of mucormycosis in France: the RetroZygo Study (2005-2007). *Clin Infect Dis*. 2012;54(1):S35-S43.
- Pana ZD, Seidel D, Skiada A, et al. Invasive mucormycosis in children: an epidemiologic study in European and non-European countries based on two registries. *BMC Infect Dis*. 2016;16(1):667.
- Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. *Clin Infect Dis*. 2008;47(4):503-509.
- Lewis RE, Georgiadiou SP, Sampsonas F, Chamilos G, Kontoyiannis DP. Risk factors for early mortality in haematological malignancy patients with pulmonary mucormycosis. *Mycoses*. 2014;57(1):49-55.
- Bellanger AP, Navellou JC, Lepiller Q, et al. Mixed mold infection with *Aspergillus fumigatus* and *Rhizopus microsporus* in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient. *Infect Dis Now*. 2021:S2666-9919(21)00030-0.
- Karimi-Galougahi M, Arastou S, Haseli S. Fulminant mucormycosis complicating coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol*. 2021.
- Veisi A, Bagheri A, Eshaghi M, Rikhtehgar MH, Rezaei Kanavi M, Farjad R. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: A case report. *Eur J Ophthalmol*. 2021;10:11206721211009450.
- Sargin F, Akbulut M, Karaduman S, Sungurtekin H. Severe Rhinocerebral Mucormycosis Case Developed After COVID 19. *J Bacteriol Parasitol*. 2021;12:386.

15. Waizel-Haiat S, Guerrero-Paz JA, Sanchez-Hurtado L, et al. A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19. *Cureus* 2021;13:e13163.

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