Introduction

Coronavirus disease 2019 (COVID-19) has proved to be one of the most disastrous pandemics ever in the history of mankind, devouring a huge number of lives. Although several treatment protocols have been evaluated for its management, systemic glucocorticoids serve to be a life saver in many cases by improving the survival rates (2.8%) in COVID-19.

Systemic corticosteroids serve as a double-edged sword by giving favorable results and unfavorable consequences of producing immunosuppression leading to opportunistic infections. The predominant fungal pathogens that cause co-infection in COVID-19 patients are White fungus (Candida), Yellow Fungus (Aspergillosis), and Black Fungus (Mucormycosis).

The Yellow Fungus or

Diagnosis and management of mucormycosis in the dental clinic: A guide for oral health professionals in India

Gunjan S. Aswal¹, Renu Rawat², Dhara Dwivedi³, Nitin Prabhakar⁴, K. R Vinod Kumar⁵

¹School of Dentistry, Faculty of Medical Sciences, The University of West Indies, St Augustine, Trinidad and Tobago, ²Private Practitioner, Bangalore, Karnataka, India, ³Departments of Dental Medicine and ⁴Oral and Maxillofacial Surgery, College of Medicine and Health Sciences, Hawassa University, Hawassa, Ethiopia, ⁵Department of Periodontics, Jimma University, Jimma, Ethiopia

ABSTRACT

With the current pandemic raging over the world, science and medicine is faced with hereto with unfought enemies or less fought opponent in the form of viruses and consequently, other biotic entities. While researchers are striving to identify and conquer the variants of COVID-19, other innocuous organisms are raising their ugly heads in the form of opportunistic fungal infections. Mucormycosis/Black Fungus is an invasive opportunistic fungal infection caused by mucorale species. It spreads through blood vessels causing thrombosis, ischemia, and necrosis. Population with pre-existing immunocompromised conditions such as Diabetes Mellitus, Malignancy, Long-term immunosuppressant therapy are more susceptible. Mucormycosis associated with Corona Virus Disease-2019 (COVID-19) proved to be catastrophic due to its high mortality rates. Rhino orbital Mucormycosis is the most common form. The primary care physician, being the first and often, (more so in developing countries) and being the only point of contact with a healthcare professional, plays a pivotal role in the diagnosis and management of this condition. The keystone to decreasing mortality is early detection and diagnosis followed by preventive measures to control progression to the brain. A multidisciplinary approach by various specialties is a prerequisite for effective diagnosis and management. Antifungal therapy, surgical debridement, and resection of the affected areas are protocols to be followed. Post-operative defects cause impairment of function, phonetics, and esthetics. Prosthetic rehabilitation of these defects has shown favorable results, especially in the aged and immunocompromised individuals.

Keywords: COVID-19, dentists, maxillary sinus, mucormycosis, opportunistic infections

How to cite this article: Aswal GS, Rawat R, Dwivedi D, Prabhakar N, Kumar KR. Diagnosis and management of mucormycosis in the dental clinic: A guide for oral health professionals in India. J Family Med Prim Care 2022;11:4293-8.
Aspergillosis is an invasive fungal infection, the prevalence of which is documented to be 5–10 folds more common than Mucormycosis.[3] However, spike in the incidence of Mucormycosis is seen in COVID-19 affected individuals recently in India.[4] Mucormycosis is an aggressive, invasive, and potentially devastating opportunistic fungal infection first described by Pautlauf in 1885.[2] It is crucial to pay attention to Mucormycosis among COVID-19 patients due to the increase in mortality rate (as high as 90%).[8] Globally, the prevalence of Mucormycosis varies from 0.005 to 1.7 per million population, whereas its prevalence is nearly 80 times higher (0.14 per 1000) in India as compared to developed countries, in a 2019–2020 estimate.[3] Oral Mucormycosis is usually caused by inhalation of spores or direct contamination of open oral wound.[4] Fungal spores by angioinvasion causes thrombosis leading to tissue necrosis, which is a classic feature of this disease. The family physician is often the first (and often the only healthcare provider) clinician to be approached for almost all ailments, thus placing the onus of either apt diagnosis or timely referral of this possibly lethal condition on their shoulders. The role of Oral Clinicians is of relevance as the condition primarily occurs around the rhinomaxillary or rhinocerebral areas involving facial tissues, palate, alveolar bone, and mandibular bone. Inhalation through nasal passage or infection of extraction sockets with sporangiospores in immunocompromised patients causes larger areas of necrosis along with systemic dissemination.[3] Treatment of deep fungal infections like Mucormycosis is arduous as the drug target sites of eukaryotic pathogens closely resembling those of the human host, which limits therapeutic options.[3]

Rhinocerebral mucormycosis variant, which is commonly associated with COVID-19, is a challenge to diagnose and manage. Early diagnosis is crucial, as a delay of 12 hours in diagnosis could turn out to be lethal for the patient.[3]

The Black Fungus: Etiology and Predisposing Factors

Mucormycosis also known as Zygomycosis or Phycomycosis is an insidious fungal infection caused by members of Mucorales and zygomycotic species.[8] It is frequently found in soil, residue of plants, spoiled food, and upper respiratory tract of healthy individuals.[7]

*Rhizopus arrhizus (oryzae)* is considered to be the most common organism associated with mucormycosis, which becomes pathogenic in susceptible individuals who are immunocompromised due to underlying diseases like Diabetes Mellitus, Malignancy, Renal failure, Liver diseases, Acquired immune deficiency syndrome, organ transplant patients under long-term immunosuppressant therapy, and other metabolic diseases. Among these, Mucormycosis was found to be more prevalent in patients with Diabetes Mellitus (60-81%).[7,8] Pathophysiology of this infection is presented in Figure 1.[9,10]

Aspergillosis is an invasive fungal infection, the prevalence of which is documented to be 5–10 folds more common than Mucormycosis.[3] However, spike in the incidence of Mucormycosis is seen in COVID-19 affected individuals recently in India.[4] Mucormycosis is an aggressive, invasive, and potentially devastating opportunistic fungal infection first described by Pautlauf in 1885.[2] It is crucial to pay attention to Mucormycosis among COVID-19 patients due to the increase in mortality rate (as high as 90%).[8] Globally, the prevalence of Mucormycosis varies from 0.005 to 1.7 per million population, whereas its prevalence is nearly 80 times higher (0.14 per 1000) in India as compared to developed countries, in a 2019–2020 estimate.[3] Oral Mucormycosis is usually caused by inhalation of spores or direct contamination of open oral wound.[4] Fungal spores by angioinvasion causes thrombosis leading to tissue necrosis, which is a classic feature of this disease. The family physician is often the first (and often the only healthcare provider) clinician to be approached for almost all ailments, thus placing the onus of either apt diagnosis or timely referral of this possibly lethal condition on their shoulders. The role of Oral Clinicians is of relevance as the condition primarily occurs around the rhinomaxillary or rhinocerebral areas involving facial tissues, palate, alveolar bone, and mandibular bone. Inhalation through nasal passage or infection of extraction sockets with sporangiospores in immunocompromised patients causes larger areas of necrosis along with systemic dissemination.[3] Treatment of deep fungal infections like Mucormycosis is arduous as the drug target sites of eukaryotic pathogens closely resembling those of the human host, which limits therapeutic options.[3]

Rhinocerebral mucormycosis variant, which is commonly associated with COVID-19, is a challenge to diagnose and manage. Early diagnosis is crucial, as a delay of 12 hours in diagnosis could turn out to be lethal for the patient.[3]

The Black Fungus: Etiology and Predisposing Factors

Mucormycosis also known as Zygomycosis or Phycomycosis is an insidious fungal infection caused by members of Mucorales and zygomycotic species.[8] It is frequently found in soil, residue of plants, spoiled food, and upper respiratory tract of healthy individuals.[7]

Rhi*zopus arrhizus (oryzae)* is considered to be the most common organism associated with mucormycosis, which becomes pathogenic in susceptible individuals who are immunocompromised due to underlying diseases like Diabetes Mellitus, Malignancy, Renal failure, Liver diseases, Acquired immune deficiency syndrome, organ transplant patients under long-term immunosuppressant therapy, and other metabolic diseases. Among these, Mucormycosis was found to be more prevalent in patients with Diabetes Mellitus (60-81%).[7,8] Pathophysiology of this infection is presented in Figure 1.[9,10]
Predisposing Factors in COVID-19

Pulmonary mucormycosis typically develops in patients with profound neutropenia and graft-versus-host disease, whereas diabetic patients typically present with rhino-orbital disease.\[14\] Singh et al. conducted a systematic review that reported the findings of 101 confirmed mucormycosis cases in individuals with COVID-19; Diabetes Mellitus was reported in 80% of the cases, whereas 76.3% were receiving corticosteroids. Diabetic ketoacidosis is often observed due to corticosteroid intake. The acidic environment is a fertile media for mucor spores to germinate. Endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in CD4+ and CD8+ level are other effects of COVID-19 affected individuals that predisposes to mucormycosis.\[10\]

Investigations

Although mucormycosis presents with necrosis and specific signs and symptoms, clinically they mimic various other diseases. Hence, it is essential to run the gamut of investigations to arrive at a confirmatory diagnosis [Table 1].

Staging of Mucormycosis

Staging is important to read the extent of invasion for precise treatment and management of the infection.

| Investigations | Diagnostic features |
|----------------|---------------------|
| Imaging Techniques | Opacification is seen in case of mucormycosis. Aspergillosis shows radiological concretions in radiograph.\[19\] Mucormycosis shows reverse halo sign (RHS) - an area of ground glass opacity surrounded by a ring of consolidation on thoracic CT, or vessel occlusion on CT pulmonary angiography.\[9,14\] Involvement of sinuses and extent of bone destruction can be examined.\[14\] Foci of hyperdensity in the affected sinuses on CT scans are highly suggestive of fungal disease. CT is 100% sensitive and 78% specific in the diagnosis of sinonasal mucormycosis.\[9\] In CBCT the mucormycosis is depicted as erosion due to osteolysis of bone, perforation of palate to the maxillary sinus and extent of mushrooming of the infection can be seen in three-dimensional view.\[16,17\] Mucorales in potato dextrose agar and Sabouraud grown up to 3–7 days when incubated at 25°C.\[18\] Impression: Cottony white or grayish black colony.\[14\] Galactomannan, 1,3-β-D-glucan is Positive for mucormycosis. ELISA assays immunoblots and immunodiffusion tests are invasive towards Mucorales and mucormycosis.\[9\] |
| Radiograph | CT Cranial | Magnetic Resonance Imaging (MRI) Cranial | Cone Beam Computed Tomography (CBCT) [Figure 2] | biopsy |
| Computed Tomography (CT) Lungs | CT Cranial | Magnetic Resonance Imaging (MRI) Cranial | Cone Beam Computed Tomography (CBCT) [Figure 2] | biopsy |
| Culture and Microscopy | Serology | Biopsy | Direct Microscopy | Histopathology |
| ELISA assays immunoblots and immunodiffusion tests are invasive towards Mucorales and mucormycosis.\[9\] |
| Molecular staining | Immuno-histochemical staining using specific antibodies to distinguish between Mucorales and Aspergillus. Polymerase Chain reaction on either fresh or formalin-fixed paraffin-embedded tissue shown to be highly specific, although a variation in sensitivity has been reported.\[18\] |

Table 1: Investigations techniques for the diagnosis of Mucormycosis

Based on the areas of involvement, Rhino Orbital cerebral Mucormycosis staging is as follows:

Stage 1: Involvement of nasal mucosa 1a: Limited to middle turbinate 1b: Involvement of inferior turbinate 1c: Involvement of nasal septum.

Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: Two ipsilateral sinuses and or palatal or oral cavity 2d: Bilateral paranasal sinuses/zygoma/mandible.

Stage 3: Involvement of orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement, vision unaffected 3c: Central retinal artery/ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement.

Stage 4: Involvement of CNS 4a: Focal or partial cavernous involvement and or involvement of cribiform plate 4b: Diffuse cavernous sinus involvement/cavernous sinus thrombosis 4c: 4b plus involvement of skull base, internal carotid occlusion, brain infarction 4d: Multifocal/diffuse CNS disease.\[13\]
Sterilization is an imperative procedure to be followed in hospitals and clinical setups as the spores are found in contaminated air, water, and surfaces in hospitals. A study has observed that among 75 cases of mucormycosis in India, about 9% of the cases were due to nosocomial infection. Usage of non-sterile products, contaminated tongue depressant and instruments in the oral cavity, procedures like tooth extraction and surgeries using unsterile materials can make an immunocompromised patient more vulnerable to the disease.\(^7\) Hence, a sterile clinical or hospital setup is mandatory.

**Role of Dentists in the Management of Mucormycosis**

Dentists play a crucial role as most COVID-19 associated mucormycosis primarily occurs around the rhinomaxillary or rhinocerebral areas involving facial tissues, palate, and alveolar bone.\(^7\) In particular, oral symptoms become evident at the initial stage of the infection, hence prompt diagnosis is crucial. As mentioned earlier, undiagnosed cases can progress to fatal effects such as spreading to the brain and associated structures due to its angio-invasive property.\(^18\) Survival rates among groups of patients with invasive sinus disease without cerebral involvement may be as high as 50–80\%; if infection spreads to the brain, case fatality ratios exceed 80\%.\(^18\) Four factors are critical in managing mucormycosis: rapidity of diagnosis, reversal of the underlying predisposing factors (if possible), appropriate surgical debridement of the infected tissue, and appropriate antifungal therapy.\(^18\) Following diagnosis, a multidisciplinary approach is required to restore the structure, function, and esthetics of the individual.

**Early Diagnosis: A Critical factor in managing Mucormycosis**

Before proceeding with clinical examination, a comprehensive history of the patient is required. Recent history of COVID-19 hospitalization and treatment for the same is another vital pointer in history owing to the existing pandemic. However, a few case
reports have proved that immunocompetent patients have also acquired Mucormycosis. Soni et al. have reported a case of parasnal mucormycosis in an immunocompetent individual, where the patient revealed a brief history of Chronic Sinusitis. This individual become susceptible to Mucormycosis due to mucociliary dysfunction and alteration in immune defence. Gupta et al. have reported a case of an immunocompetent individual who suffered from Mucormycosis due to dental manipulation and emphasized the importance of recording the history of patients who report with signs and symptoms of the condition.

There also exists reports of cases that posed a diagnostic dilemma. Rai et al. reported a case of maxillary mucormycosis, which was masquerading as osteomyelitis. Pereiro-Filho et al. have reported a case of mucormycosis, which was mistaken for maxillary sinusitis and has discussed the importance of investigations pertinent to arrive at a final diagnosis. Possible differential diagnosis for oral mucormycosis include tertiary syphilis, Wegener's granulomatosis, carcinoma of the palate (squamous cell carcinoma/mucoepidermoid carcinoma), midline lethal granuloma, osteomyelitis, tuberculosis, other deep fungal infections, and ulcer due to bisphosphonate therapy.

### Comprehensive Management of the Infection

#### [Table 2]

#### Conclusions

Mucormycosis is a fulminating disease with immense potential for rapid spread. A multidisciplinary approach by a team of clinicians with emphasis on recording a detailed history, clinical examination, early detection and diagnosis, preventive antifungal medication, surgical management, prosthetic rehabilitation, and correction of surgical defect has proved to decrease the mortality rate and improve the quality of life of individuals. Published research on posaconazole (injectable), a triazole, antifungal agent that considerably eases the pressure and offers patients much needed and timely therapy options and simple procedures such as saline nasal irrigations must be borne in mind while managing this condition. The primary care physician/healthcare worker is duty bound to evolve and upgrade their expertise in order to productively contribute towards the preservation and welfare of mankind when faced with adversities such as this pandemic and play their role as healthcare providers in society.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

#### References

1. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (Covid-19) associated mucormycosis (CAM): Case report and systematic review of literature. Mycopathologia 2021;186:289-98.

2. Challu S. Mucormycosis: Pathogenesis and pathology. Curr Fungal Infect Rep 2019;13:11-20.

3. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15. doi: 10.1016/j.dsx.2021.05.019.

4. R R, MR M, Kumar SP. Mucormycosis following tooth extraction in a diabetic patient: A case report. Cureus 2020;12:e9757. doi: 10.7759/cureus.9757.

5. Reddy SG, Kumar KK, Sekhar CP, Reddy RB. Oral mucormycosis: Need for early diagnosis!! J NTR Univ Health Sci 2014;3:145-7.

6. Nishanth G, Anitha N, Babu NA, Malathil L. Mucormycosis-A review. Eur J Mol Clin Med 2020;7:1786-91.

7. Pandey A, Kaur G. Mucormycosis revisited: Case report with review of literature. J Dent Spec 2020;8:39-44.

8. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis 2012;54:S16-22.

9. KR Kumar P. Mucormycosis: A black fungus-post covid complications. J Regen Biol Med 2021;31-8. doi: 10.37191/Mapsci-2582-385X-3 (4)-078.

10. Riley TT, Muzny CA, Swiatlo E, Legendre DP. Breaking the mold: A review of mucormycosis and current pharmacological treatment options. Ann Pharmacother 2016;50:747-57.

11. Rajendra Santosh AB, Muddana K, Bakki SR. Fungal infections of oral cavity: Diagnosis, management, and association with COVID-19 [published online ahead of print, 2021 Mar 27]. SN Compr Clin Med 2021;1-12. doi: 10.1177/10600280216554252.

12. Pauli MA, Pereira LM, Monteiro ML, de Camargo AR, Rabelo GD. Painful palatal lesion in a patient with COVID-19 [published online ahead of print, 2021 Mar 28]. Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:620-5.

13. Gade V, Bajaj N, Sonarkar S, Radke S, Radke S, Kokane N, Rahul N. Mucormycosis: Tsunami of fungal infection after second wave of COVID 19. Ann RSCB 2021;25:7231-8.

14. Cornely AO, Aalbers‑Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: An initiative of the European cooperation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis 2019;12:e405-21.

15. Garlapati K, Chavva S, Vaddeswarupu RM, Surampudi J. Fulminant mucormycosis involving paranasal sinuses: A rare case report. Case Rep Dent 2014;465919. doi: 10.1155/2014/465919.

16. Pagare J, Johaley S. Diagnostic role of CBCT in fulminating mucormycosis of maxilla. Int J Res Rev 2019;6:575-9.

17. Shastry SP, Murthy PS, Jyotsna TR, Kumar NN. Cone beam computed tomography: A diagnostic aid in rhinomaxillary mucormycosis following tooth extraction in patient with diabetes mellitus. J Indian Acad Oral Med Radiol 2020;32:60.

18. Soni A. Paranasal mucormycosis in an immunocompetent individual: Importance of early diagnosis. Int J Oral Health Med Res 2017;4:52-6.

19. Gupta N, Kumar R, Soneja M, Singh G, Khot W, Mallu S, et al. Mucor menace in an immunocompetent young male after dental manipulation. J Family Med Prim Care 2019;8:757-9.

20. Rai S, Misra D, Misra A, Jain A, Jain P, Dhawan A. Palatal
mucormycosis masquerading as bacterial and fungal osteomyelitis: A rare case report. Contemp Clin Dent 2018;9:309-13.
21. Pereira-Filho VA, Cabrini Gabrielli MA, Hochulli-Vieira E, Real Gabrielli MF, Klüppel LE, et al. Misdiagnosed maxillary sinusitis: the case for further investigation. SOJ Surg 2015;2:1-5.
22. Nagarajan N, Jayachandran S, Vidya J. Clinical approach to palatal necrosis in an immunocompromised patient: A dental professional’s role. Indian J Case Rep 2020;6:625-8.
23. Prabhu S, Alqhtani M, Al Shehabi M. A fatal case of rhinocerebral mucormycosis of the jaw after dental extractions and review of literature. J Infect Public Health 2018;11:301-3.
24. McDermott NE, Barrett J, Hipp J, Merino MJ, Richard Lee CC, Waterman P, et al. Successful treatment of periodontal mucormycosis: Report of a case and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:64-9.
25. Gowda M, Shashidhar MP, Prakash P, Sahoo N. Rehabilitation of a defect secondary to sino-orbital mucormycosis- A prosthodontic challenge. IP Ann Prosthodont Restor Dent 2021;7:41-5.
26. Abrol K, Pandey S, Agarwal S, Siddhi T. Prosthodontic management of sub-total maxillectomy: A case report. Chron Dent Res 2019;8:61-5.
27. Rastogi S, Verma A. Jalaneti (saline nasal irrigation) as primary intervention in suspected rhino-orbito-cerebral mucormycosis helps improving the recovery: A case report. J Ayurveda Integr Med 2021;13:100516. doi: 10.1016/j.jaim.2021.08.009.
28. Asdaq SM, Rajan A, Damodaran A, Kamath SR, Nair KS, Zachariah SM, et al. Identifying mucormycosis severity in Indian COVID-19 patients: A nano-based diagnosis and the necessity for critical therapeutic intervention. Antibiotics 2021;10:1308. doi: 10.3390/antibiotics10111308.