Dental Perspective on Mucormycosis in COVID-19: a Literature Review

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Abstract
Purpose of Review The purpose of this paper is to gain an understanding of existing knowledge and attain familiarity on mucormycosis for early diagnosis and treatment. It highlights the systematic factors, signs and symptoms, diagnostic tests and treatment procedure for mucormycosis from dentistry point of view. PubMed/ Medline, Scopus, Web of Science were the search engine used. Study selection encompassed systematic reviews, critical reviews and case reports related to mucormycosis in COVID-19 patients and only mucormycosis. 19 articles were selected between Years 2001 to 2021. Analysis was done based on patient’s comorbidity, site of mucormycosis infection, use of steroids and its effect on people with COVID-19 infection.

Recent Findings Rhino-orbito-cerebral mucormycosis is the most common of all systemic manifestations of mucormycosis. Diabetes mellitus and long-term corticosteroid therapy are the leading risk factors with pre-existing diabetes mellitus accounting for almost 80% cases. Elements that facilitate the growth of mucor in COVID-19 patients are the presence of low oxygen levels, high blood glucose levels, acidic media, high levels of iron, immunosuppression, and episodes of prolonged hospitalization. Mucormycosis is heterogenic in nature. Its management requires an individualized plan that considers the immunity status of the host, stage of the infection, systemic disease, early diagnosis and susceptibility to anti-fungal agents. Supervised use of corticosteroids and betadine gargle prevent the occurrence of mucormycosis.

Summary The paper sheds some light on the warning signs and diagnostic tests that can help in early identification of infection by a dentist. This enables the timely implementation of therapy resulting in good prognosis of the treatment.

Keywords COVID-19 • Diabetes mellitus • Fungal infection • Mucormycosis • Obturator • Rhino-orbito-cranial mucormycosis

Introduction
COVID-19 has been associated with a wide range of opportunistic bacterial and fungal infections [1]. Among these infections, mucormycosis incidence, also known as the black fungus, has risen rapidly in India. [2] The primary reasons or ideal habitats facilitating the growth of mucor in COVID-19 patients are the presence of low oxygen levels (hypoxia), high blood glucose levels (diabetes, hyperglycemia), acidic media (diabetic ketoacidosis or metabolic acidosis), high levels of iron, immunosuppression, and episodes of prolonged hospitalization. [3] Other risk factors include underlying malignancy, burns, malnutrition, blood dyscrasias, and renal failure. [4] The disease progression is rapid in COVID-19 patients due to delay in IFN-ɤ response and decreased CD4 and CD8 cell count. In diabetic patients, this exacerbates the “cytokine storm,” thus increasing the severity of the condition. [5] The further reduction in phagocytic activity of the white blood cells and higher levels of accessible free iron in hyperglycemic conditions make a conducive resource for mucormycosis. [6] This paper elucidates the factors responsible for causing mucormycosis in a COVID-19–infected patient. As it is first manifested in the oral environment, it is important for a dentist to be aware of all the presenting signs and symptoms, the
diagnostic tests, and treatment procedure for better prognosis of the condition.

Methods

A total of 19 relevant articles were selected for the review. Most of them are recent articles, i.e., up to 5 to 10 years old, as the incidence of mucormycosis in COVID-19 patients has risen rapidly in recent times. Study selection encompassed systematic reviews, critical reviews, and case reports related to mucormycosis in COVID-19 patients and only mucormycosis. To ensure the originality of the topic, the focus was adjusted to literature search related to mucormycosis and infection of fungal origin. Articles related to infection from other sources were excluded. Keywords used include COVID-19, mucormycosis, obturator, diabetes mellitus, rhino-orbito-cranial mucormycosis, and fungal infection. When searching the literature, the keywords were combined with Boolean operators “AND,” “OR,” and “NOT.” To identify the relevant articles, search engines or electronic database like PubMed/Medline, Scopus, and Web of Science were used. Literature in languages other than English were excluded.

Discussion

Mucormycosis is an uncommon fatal fungal infection affecting patients with altered immunity. It is angioinvasive [7] and results in dissemination, tissue infarction, and necrosis. [8] Globally, the prevalence of mucormycosis in India was found to be 80 percent higher when compared with that of other developed countries. [9–11] The prime reason is India having the second largest population suffering from diabetes mellitus. [12] Diabetes mellitus is the leading risk factor for mucormycosis, with a mortality rate of 46%. [13] According to a systematic review, out of all the people affected by mucormycosis, 80% were diabetic, and 15% were suffering from diabetic ketoacidosis. Around 76.3% of patients reported a history of corticosteroid intake for the treatment of COVID-19 infection. [3] Among all systemic manifestations, rhino-orbital-cerebral mucormycosis occurs commonly, followed by cutaneous and pulmonary mucormycosis. [13] The nose and sinus are the most common organs involved (88.9%), followed by rhino-orbital (56.7%). [3]

Significance of Dentistry in Treatment of Mucormycosis

The condition of mucormycosis is gaining interest in dentistry due to its first manifestation in the facial and oral tissue. Oral manifestation includes ischemic necrosis of the palatal mucoperiosteum with bony dehiscence. [14]

List of warning signs and symptoms include the following:

- Nasal stuffiness
- Foul smell
- Epistaxis
- Nasal discharge—mucoid, purulent, blood-tinged, or black
- Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
- Eyelid, periocular, or facial edema
- Eyelid, periocular, or facial discoloration
- Regional pain—orbit, paranasal sinus, or dental pain
- Facial pain
- Worsening headache
- Proptosis
- Sudden loss of vision
- Facial paresthesia, anesthesia
- Sudden ptosis
- Ocular motility restriction, diplopia
- Facial palsy
- Fever, altered sensorium, paralysis, and focal seizures

The COVID-19 care teams, patient, and family should be aware of these warning signs for early diagnosis of a possible case of mucormycosis. Any individual presenting these signs and symptoms <6 weeks from the treatment of COVID-19, diabetes mellitus, use of systemic corticosteroid, mechanical ventilation, or supplemental oxygen falls under the category of possible mucormycosis (ROCM). [15]

Establishing an early diagnosis of mucormycosis is critical to enable a reasonable prognosis of antifungal therapy. There is a need for the staging of ROCM to enable proper diagnostic modalities and treatment. Depending on the anatomical progression of the infection, staging of ROCM has been proposed as follows:

- Stage 1: Involvement of the nasal mucosa
- Stage 2: Involvement of the paranasal sinuses
- Stage 3: Involvement of the orbit
- Stage 4: Involvement of the CNS [15]
The preferred diagnostic tests to evaluate these stages include the following:

1. Direct microscopy of the swab using KOH mount and calcofluor white for rapid diagnosis.
2. Culture of infected swab or tissue. Brain heart infusion agar, potato dextrose agar, or preferably Sabouraud dextrose agar with gentamicin or chloramphenicol, and polymyxin-B, but without cycloheximide, are some incubation media used.
3. Use of commercially available molecular diagnostic kits for tissue or blood culture.
4. Histopathologically use of special stains like hematoxylin–eosin, periodic acid-Schiff, and Grocott-Gomori’s methenamine silver.
5. Imaging techniques include CT scan and contrast-enhanced MRI, the latter being more preferable. [8, 16]

After determining the stage and conclusive diagnosis, favorable treatment should be exhibited immediately. The first line of treatment comprises the use of antifungal drugs. Data suggests that lipid formulations of amphotericin B are more effective compared to the amphotericin B lipid complex. Also, it demonstrates significantly lesser nephrotoxicity. Posaconazole and deferasirox are the available options for salvage therapy of mucormycosis (cases of refractory mucormycosis). In non-neutropenic patients, GM-CSF (mobilized granulocyte transfusion) or IFN-γ has shown to augment the host response and antifungal effect. [17] In case of disease progression, surgical debridement of the infected tissue is indicated. Different surgeries like turbinectomy, orbital exenteration, debridement of paranasal sinuses, and palatal resection are carried out depending on the anatomical part involved. All the surgical procedures can be executed only if systemic conditions permit. In cases where surgery is not feasible, only supportive treatment is implemented. [15] Postsurgical reconstruction of the palate is done by fabrication of an obturator. Open and closed hollow obturators make the prosthesis light in weight, making it comfortable to the patient. Also, its extension into the defect increases retention and acts like a feeding plate. [18]

The incidence of mucormycosis can be reduced by undertaking specific preventive measures. These include careful monitoring of vision, ocular motility, and sinus tenderness, routine physical examination, aggressive monitoring of blood glucose levels, maintenance of personal hygiene, and strict aseptic precautions. Supervised use of corticosteroids and betadine mouth gargle can prevent the occurrence of mucormycosis. [15, 19]

There are certain limitations to this review based on the heterogeneity of reporting cases. Certain reports do not present minute details like the time duration of diabetes mellitus or corticosteroid therapy. The facts are related to onset of mucormycosis in active or recovered COVID-19 cases. The underrepresentation and subjective analysis may result in publication bias.

Summary

Awareness about mucormycosis infection by a dentist is necessary and critical as it is associated with a high mortality rate. Attention to the warning signs and symptoms with an early diagnosis can help implement a detailed treatment plan. As dental surgeons, we are often presented with the opportunity to come across this infection at a nascent stage. Conscious diagnosis and referral along with follow-up can lead to minimizing or optimizing the morbidity of mucormycosis infection.

Abbreviations

COVID-19: Coronavirus disease 2019; IFN-ɤ: Interferon gamma; CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8; ROCM: Rhino-orbital-cerebral mucormycosis; CNS: Central nervous system; KOH: Potassium hydroxide; CT: Computed tomography; MRI: Magnetic resonance imaging; GM-CSF: Granulocyte-macrophage colony-stimulating factor

Declarations

Competing Interests The authors declare no competing interests.

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