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Original Research Article

Incidence of Mucormycosis in the Midfacial Region during the COVID Pandemic: A Tertiary Care Hospital Study

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Abstract:

Aim and Objective: An unparalleled mucormycosis outbreak occurred following the second wave of COVID-19 in 2021. In particular, among individuals with uncontrolled Diabetes Mellitus (DM), the Rhino-Orbital-Cerebral Mucormycosis (ROCM) has evolved into a critical medical issue. ROCM is a rare infection associated with the angiotropic fungus, resulting in significant morbidity and mortality regardless of medical care. The aim of the study is to determine the incidence of ROCM and its contributing factors in the midfacial region.

Materials and Methods: A descriptive study was conducted in the Department of Dental Surgery, CMCH, Coimbatore, from May 2021 to May 2022. 154 cases of mucormycosis with midface involvement were included in the study, and various clinical, radiographical, and demographic analyses were carried out. The COVID status, vaccination status, and co-morbidities of COVID infection with mucormycosis were also assessed.

Results: The findings revealed that mucormycosis was prevalent in male patients with positive COVID status. Diabetic individuals exhibited a higher incidence of mucormycosis, with ROCM affecting mostly the left-side sinuses of the face. There was no significant difference in data on place of residence, steam inhalation, and oxygen usage throughout the illness. Co-morbidities besides Diabetes Mellitus showed no significant effect on individuals with mucormycosis.

Conclusion: Mucormycosis is a devastating opportunistic illness that necessitates prompt detection and treatment. Compared to those who are non-diabetic and were recently diagnosed with DM, COVID patients with DM showed a greater incidence of ROCM. Despite extensive medical management and surgical interventions, poor glycemic levels are associated with unfavorable outcomes.

Keywords: COVID-19 associated mucormycosis, Rhino-orbital-cerebral mucormycosis, uncontrolled diabetes, COVID vaccine.

Introduction

The COVID-19 pandemic has created significant hurdles to the worldwide healthcare sector. As we cope with COVID-19, there are new challenges and complications that require our immediate attention. [1] A wide range of bacterial and fungal co-infections may exist and are associated with preexisting morbidities. [2] One such is Mucormycosis, an uncommon opportunistic infection caused by a filamentous fungus from the Mucorales order, which is ubiquitous in nature, especially in soil and decaying vegetation. It usually affects people with impaired immune systems. [3,4] The alarming increase in mucormycosis cases has raised concerns among healthcare professionals worldwide. Relatively rarer than bacterial infections, the mortality rate

linked with fungal infections is quite significant. [5] Mucormycosis is predisposed by several factors such as immunosuppressive drugs, corticosteroids, diabetes, chronic kidney disease, HIV, stem cell transplantation, hematological and solid organ malignancies and immunodeficiencies.[6]

According to researches, diabetic patients are more prone to have serious complications from mucormycosis and the related factors such as reduced number of T cells, leukocyte apoptosis, altered dendritic cell activity, and neutrophilic dysfunction.[7] As a result, hyperglycemia promotes fungal development by lowering chemotaxis and phagocytic efficiency, creating an ideal environment for the fungus to spread and invade.[8]

Despite numerous treatment strategies, systemic glucocorticoids act as lifesaving agents in several instances, enhancing the survival rate in COVID-19. Systemic corticosteroids have positive as well as negative consequences, including immunosuppression, which can lead to opportunistic infections. [9] Systemic corticosteroid treatment can also predispose patients to secondary fungal disease such as pulmonary aspergillosis, uncommon mold infections (fusariosis), Candida infections, and COVID-19-related mucormycosis.[10]

COVID-19-associated mucormycosis (CAMCR) was reported to be high in patients with uncontrolled diabetes (94%), and they were generally presented with rhino-orbital and rhino-orbital-cerebral presentations (ROCM) [11]. The fungi frequently reside on the mucous membranes of the nose and become detrimental in an immunosuppressive state. Mucormycosis is established by spore inhalation and/or growing into the airways or any sensitive epithelium sprouting into angioinvasive hyphae. They utilize host conditions such as iron overload, neutrophilia, and hyperglycemia to cause a variety of destroying processes such as haemorrhage, thrombosis, and necrosis, resulting in widespread organ damage. [12,13]

Early identification and prompt treatment are crucial for treating ROCM. Considering the catastrophic effects indicated above, the purpose of this study is to establish the incidence and contributing factors of mucormycosis in the midfacial area. The study also identifies the association of demographic characteristics and epidemiology along with vaccination status, steroid therapy and co-morbidities associated with CAMCR.

Materials and Methods

A cross-sectional descriptive study was conducted in the Department of Dental Surgery, Coimbatore Medical College and Hospital, Coimbatore, a tertiary care center, from May 2021 to May 2022. The research included 153 individuals with mucormycosis of the midface who had been diagnosed clinically, histopathologically, and radiographically. The goal of this study is to emphasize the distribution of different phases of rhino-orbital cerebral mucormycosis based on their incidence, demographic factors, clinical presentation, disease course, and contributing risk factors.

A complete history of the patient, including demographic information such as age, gender, and place of residence, was recorded. The history of COVID, oxygen dependence and steroid use, immunization status, and steam inhalation therapy were all documented. Systemic risk factors such as DM, Hypertension, Coronary Artery Disease, and other co-morbidities were identified. Extensive ophthalmic, neurological, and dental examinations were performed. Individuals diagnosed with midfacial mucormycosis based on radiological and clinical findings were included in the study.

Diagnostic nasal endoscopy (DNE) is performed to determine C-ROCM. Patients were classified according to the proposed staging of rhino-orbital-cerebral-mucormycosis based on the location and extent of the illness. [14] A computed tomography (CT) scan of the orbit and paranasal sinuses was obtained to determine the extension and severity of the lesion. Nasal swabs were obtained and submitted for fungal culture and histological evaluation. Patients who met the inclusion criteria were included in the study after providing complete written and informed consent.

In this study, 154 patients with proven ROCM based on clinical features, radiological findings, and histopathological evidence and history of COVID 19 were studied to determine the incidence and contributing factors of mucormycosis in the midfacial region.

Results

Demographical data: The research included 153 individuals, and the mean age of patients was 52.3 years, with a range from 21 to 75 years. [Table 1] Out of the total population, 64.7% were male and 35.3% were female, with men being significantly affected. The place of residence was taken into consideration and as a result, 52.3% of the people lived in urban areas, while 47.7% lived in rural areas. Though there was no significant difference, most people from rural areas were farmers, who were actively involved in agriculture. [Figure 1]

COVID and Vaccination status: At the point of examination, 103 of the 153 patients had a history of COVID infection, whereas the COVID status of 50 patients was unknown. In terms of vaccination

status, 121 of them were unvaccinated, while 17 of them received their first dose of vaccine and 15 received their second dosage as well.

Usage of Oxygen and Steroid along with steam Inhalation: In cases of moderate COVID infection, the oxygen levels may drop, and in such a scenario, oxygen therapy is recommended. In our study, a total of 52 (44%) of the participants had a history of oxygen therapy, whereas the remaining 101 (66%) participants had no history of oxygen therapy.

In our study, the data received shows that 92 (62.1%) of them received steroid treatment for COVID-19, but 61 (39.9%) participants did not receive steroids. The case history also reveals that of the 153 participants, 81 (52.9%) had steam inhalation throughout therapy, while 72 (47.1%) did not undergo steam inhalation.

Diabetes Mellitus and other co-morbidities: Among the 153 study population, 62.7% (96) were known Type II DM and under medications, and 26.8% (41) were recently identified as diabetics during their COVID-19/ Mucormycosis. At the point of investigation, just 10.5% (16) of the population was non-diabetic. [Figure 2] When assessing for any co-morbidities, most of the subjects had no other ailments, with a small population of people having hypertension (13), coronary artery disease (3), and hypertension with coronary artery disease (2), Tuberculosis (1), and HIV (1).

Mucormycosis staging and Sinus Involved: C-ROCM has been determined by diagnostic nasal endoscopy (DNE), and the biopsy results were used to confirm the mucormycosis infection. The following phases of rhino orbital cerebral mucormycosis were identified based on clinical characteristics and imaging techniques. [Figure 3 – 7] Basically, the ROCM is divided into four stages, of which stage 1 involves the nasal mucosa, and stage 2 involves paranasal sinuses. Stage 2 was most common among the study population (n = 128), and it is further subdivided into four substages: 2a (involvement of one sinus (Maxillary/Ethmoidal/ Frontal/Sphenoidal) = 59), 2b (involvement of ipsilateral sinuses (Maxillary/Ethmoidal/ Frontal/ Sphenoidal) = 5), 2c (>2 ipsilateral sinuses, (Maxillary/Ethmoidal/Frontal/ Sphenoidal) and/or palate/alveolar bone/oral cavity = 56), and 2d (bilateral paranasal sinus involvement (Maxillary/Ethmoidal/Frontal/Sphenoidal) or involvement of zygoma or mandible = 5).

Subjects with involvement of the Pterygopalatine fossa (2cP–2) and (2dP–1)) were also reported. Stage 3 with orbital involvement (n = 20) and stage 4 (n = 4) with intracranial structure involvement were also noticed. Cutaneous extension of local disease was marked with suffix C. 1 participant had mucormycosis isolated from non-ROCM areas, such as the lungs, gastrointestinal tract, kidneys, and skin, which was marked as D. [Table 2, Figure 8]

Of the 153 participants in the research, the majority (54.9%) had sinus involvement on the left side, followed by the right-side (23.5%) and bilateral sides (21.6%). [Figure 9]

Table 1: Showing Age distribution

Total Population	Minimum Age	Maximum Age	Mean Age	Standard Deviation
153	21	75	52.36	11.94

Table 2: Staging of Rhino-Orbito-Cerebral Mucormycosis

Stage	Anatomical correlate
Stage 1	Involvement of nasal mucosa
Stage 2	Involvement of paranasal sinuses **2a:** One sinus (Maxillary/Ethmoidal/Frontal/Sphenoidal) **2b:** Two ipsilateral sinuses (Maxillary/Ethmoidal/Frontal/Sphenoidal) **2c:** >2 ipsilateral sinuses (Maxillary/Ethmoidal/Frontal/Sphenoidal) and/or palate/alveolar bone/oral cavity **2d:** Bilateral paranasal sinus involvement (Maxillary/Ethmoidal/Frontal/Sphenoidal) or involvement of the zygoma or mandible
Stage 3	Involvement of the orbit
Stage 4	Involvement of the intracranial structures
Suffix P	Involvement of Pterygopalatine fossa
Suffix I	Involvement of Infratemporal fossa
Suffix D	Disseminated disease with isolation of mucormycosis from sites other than ROCM such as pulmonary, gastrointestinal, renal, cutaneous*
Suffix C	Cutaneous extension of local disease

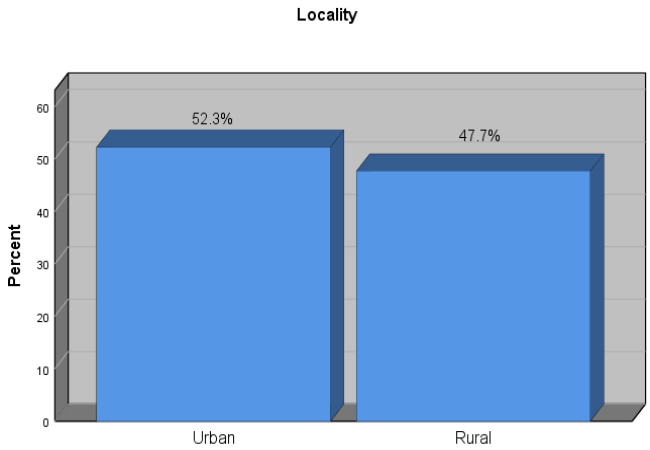

Figure 1: Place of residence

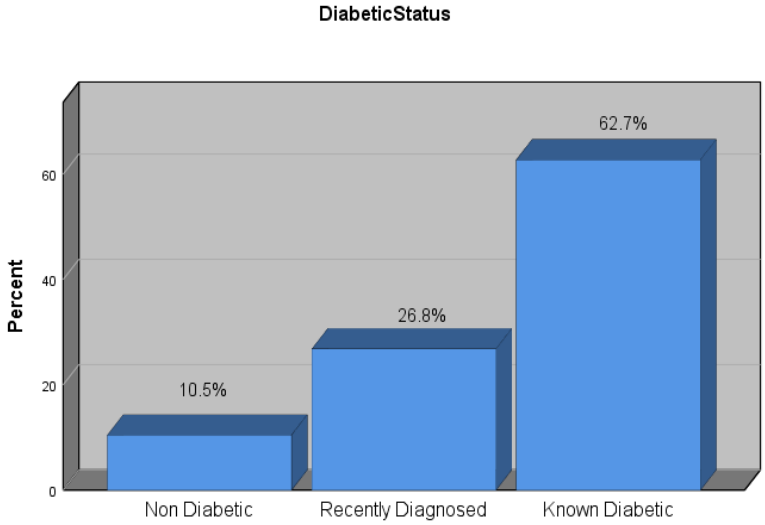

Figure 2: Diabetic status

Figure 3: Stage II Rhino-orbital cerebral mucormycosis with multiple buccal abscess

Figure 4: Stage II Rhino-orbital cerebral mucormycosis with palatal necrosis

Figure 5: Stage III Rhino-orbital cerebral mucormycosis involving orbit

Figure 6: Stage IV (C) Rhino-orbital cerebral mucormycosis with skin involvement

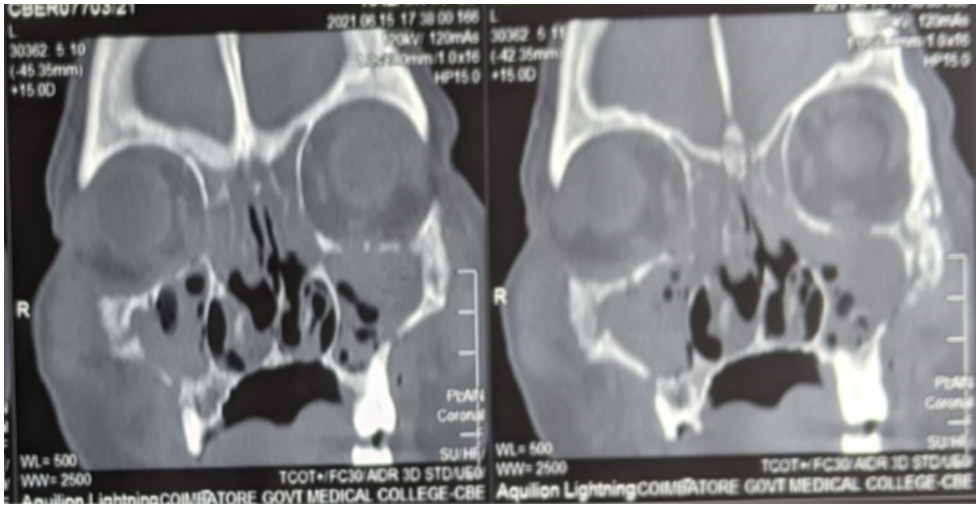

Figure 7a: Computed Tomography images showing ROCM involvement

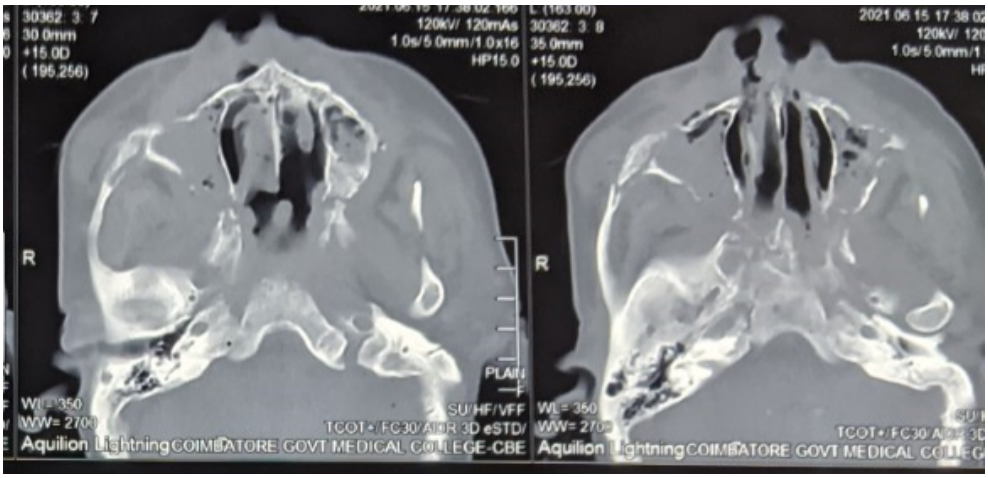

Figure 7b: Computed Tomography images showing ROCM involvement

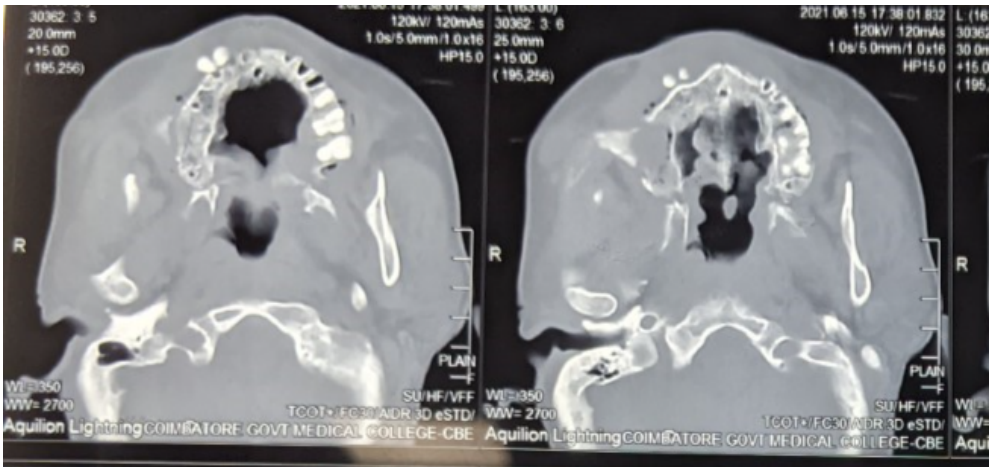

Figure 7 c: Computed Tomography images showing ROCM involvement

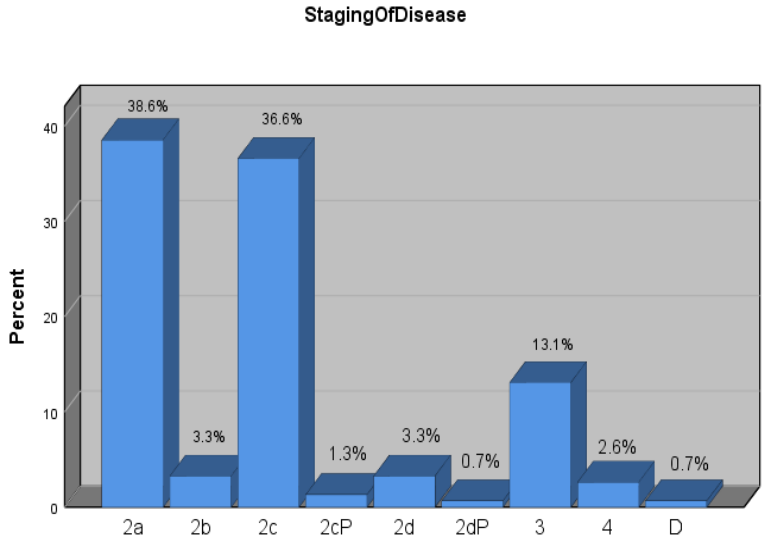

Figure 8: Staging of Mucormycosis

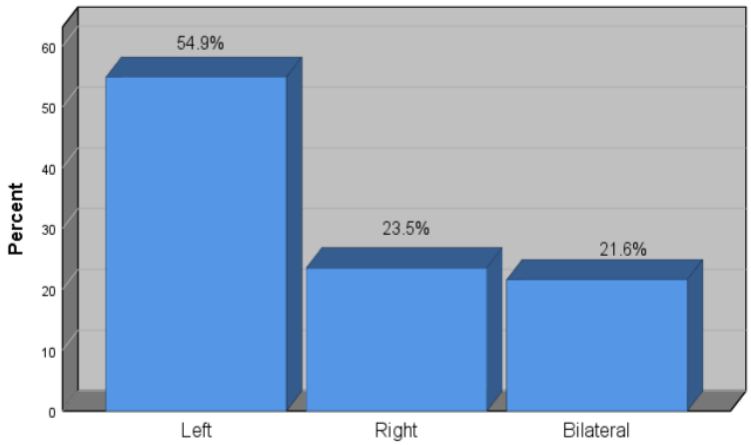

Figure 9: Sinus affected

Discussion

This descriptive study determines the incidence and contributing factors of mucormycosis in the midfacial region and aims to analyze the risk factors, disease severity, involvement of the facial structure, and various stages of mucormycosis. The study also evaluates the association of demographic characteristics (age, gender, place of residence) with mucormycosis. The study also investigates the COVID status, immunization history, and co-morbidities related to COVID infection and mucormycosis. The COVID-19 pandemic has had a profound impact on countries worldwide, and India's dense population, particularly in urban areas, poses a significant risk for rapid transmission. Since the COVID-19 pandemic began, concurrent opportunistic infections have also surfaced as an additional spectrum of diseases.[12] Prior to COVID-19, ROCM was extremely uncommon, with immunocompromised individuals experiencing the highest degree of incidence. Infections caused by Mucorales are acquired by the inhalation of spores, consumption of contaminated food, or inoculation of injured or damaged surfaces. [15] Mucormycosis has a strong tendency to invade blood vessels, resulting in necrosis, thrombosis, and tissue rupturing. [16]

Most of the middle-aged and elderly patients who received treatment were men, and the incidence of mucormycosis in female was low, suggesting that estrogen may be able to prevent fungal infection. Another reason is that the immunological response

differs across sexes, with women exhibiting more potent humoral and cell-mediated proinflammatory responses than males. [17]

Mucorales and other saprophytic fungus are found in decaying plants, dirt, and dust, among other ecological niches. When compared to people living in urban areas, the incidence of mucormycosis was greater among those from rural regions, particularly those with a history in farming or agriculture. [18] Accordance with the study, the result of our study also supports the fact that people in dusty environment (47.7%) are prone to mucormycosis.

In research, it was concluded that the rate of infection would drop if vaccination rates were raised, and more people received vaccinations than the critical population threshold. This implies that an epidemic scenario may be averted, and the chain reaction of an infection can be prevented. [19] This was in accordance with our study where 103 of the 153 patients had a history of COVID infection, whereas the COVID status of 50 patients was unknown.

In the study we conducted, 52 subjects (44%) had a history of oxygen therapy, whereas 101 subjects (66%) had no history of oxygen therapy. Oxygen is used as an adjuvant therapy for COVID-19, and it has been advocated for the management of shock, hypoxemia, and respiratory distress. [20] An excellent, age-old method of treating respiratory infections is steam inhalation. Respiratory illnesses, including bronchiolitis, croup, and the rhinovirus-mediated common cold and influenza virus-mediated common flu are usually treated using steam inhalation as an additional treatment strategy in home settings. [21]

Corticosteroids are potent anti-inflammatory agents, and its early administration in illness has been demonstrated to decrease inflammation, which is associated with a dysregulated immune response and could potentially reduce mortality.[22]

The host factors such as corticosteroid usage, immunocompromised state, diabetes, malignancy, malnutrition, and high body mass index play a critical role in occurrence of Mucormycosis. [23] Though progression has been associated with several factors, in Asia, Diabetes Mellitus is the most prevalent risk factor. [24]

In our study population, 62.7% (96) were known DM and 26.8% (41) were recently identified as diabetic at the time of COVID illness/Mucormycosis. Patients' levels of severe hyperglycemia were correlated with the intensity of their COVID-19 infection. Rhizopus and Mucor are the co-offenders and spread their infection primarily by spore inhalation.[25] Mucormycosis is exacerbated by uncontrolled diabetes-related ketoacidosis through two different processes. It has been established that in diabetic ketoacidosis, the fungus is able to use the patient's ketone bodies as it produces the enzyme ketoreductase and interferes with transferrin's ability to bind iron, which destroys the key host defensive mechanism favoring fungal growth. [26] The cytokine storm is brought on by SARS-CoV-2, and a noteworthy rise in mortality was noted in COVID-19-infected individuals with age-related diseases such as cancer, Parkinson's condition, diabetes mellitus, and cardiovascular disease. [27] Individuals with compromised humoral or cellular immunity lack the ability to defend, which allows Mucorales to infiltrate the arteries, deeper tissues, and paranasal sinuses, resulting in ischemia, necrosis, and thrombosis. [28]

Malhotra HS et al., in their study proposed a revised and restructured staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM) with severity in each of these anatomical regions depends on the course of the disease, starting with the nasal mucosa and moving on to the paranasal sinuses, orbit, and brain. Apart from that the involvement of Pterygopalatine fossa, Infratemporal fossa, cutaneous extension of local disease, and disseminated disease sites were marked with suffix along with side involvement. [14] Our investigation used similar staging and our analysis revealed that most of our subjects were in stage II ROCM with dominantly having left involvement (54.9%), right side involvement (23.5%), and bilateral involvement (21.6%).

There are five distinct forms of mucormycosis based on the clinical manifestations, considering the oral symptoms, the rhinocerebral variant is the most prevalent and significant for Dentists. The infection starts in the sinus and perforates the hard palate, resulting in halitosis, gingival thickening, severe necrotic ulcerations, pus discharge, and tooth mobility.[29] Typically, this infection develops in the nose or mouth and passes via the eyes to the central nervous system. Clinical characteristics include fever, anosmia, runny or clogged nose, bloody nasal discharge, facial pain, numbness, unilateral eye discomfort or headache, and facial and trigeminal nerve paralysis.[30]

Identifying ROCM at an early stage of the illness is still difficult, and the diagnosis of mucormycosis will depend on the early identification of risk factors, clinical investigations, and radiological analysis as well as the confirmation of cultures and biopsy results. Alternative molecular diagnostic methods, such polymerase chain reaction (PCR) and in-situ hybridization, are crucial to identify and characterize fungus at the genus or family level for epidemiological, therapeutical, and prognostic considerations. [31]

Conclusion

Dental surgeons play a vital role in diagnosing COVID associated mucormycosis predominantly occurring around the midfacial areas affecting maxilla, alveolar bone and facial tissues.

Early identification is critical as oral symptoms become more noticeable during the early stages of the infection. While treating patients with COVID-19 infection, especially those with uncontrolled DM, we should be mindful of the risk of invasive secondary fungal infections.

Despite the fact that the ROCM is aggressive and potentially fatal, a multidisciplinary approach focusing on a thorough case history, detailed clinical examination, early diagnosis, prompt treatment involving using medications, surgical procedures, prosthetic rehabilitation, are essential to restore the individual's structure, function, and aesthetics.

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