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Review Article

Review on mucormycosis in the oro-facial region: an overview

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ABSTRACT

The study aims to identify the clinical manifestation of mucormycosis in the oro-facial region to distinguish the role of meticulous intraoral examination for early and timely diagnosis based on the review of reported cases, to propose the role of diabetes mellitus as a predisposing risk factor for mucormycosis in the oro-facial region, to propose the association of traumatic incidents like tooth extraction as a risk factor for mucormycosis in immune-compromised individuals and to perceive the use of amphotericin-B in its treatment. A systematic review was conducted on an electronic database, Google Scholar to analyze the existing data for the clinical manifestation of mucormycosis in the orofacial region. Out of the existing literature on this topic for various timelines, a period of 10 years from 2011 to 2021 was selected for the study. The sample size was calculated taking into consideration the 99.99% confidence interval. The data was extracted from these relevant articles in Microsoft Excel, showing remarkable conclusions. Mucormycosis does not show stereotypical clinical manifestations and thus the diagnosis of mucormycosis has to be confirmed through culture studies and histopathological or radiological ways. Diabetes Mellitus serves as a predisposing factor for mucormycosis in the oro-facial region other than the COVID-19 infection and immune-compromised conditions. Amphotericin-B was a drug of choice for the treatment of mucormycosis by many practitioners. The only hindrance to its usage being its nephrotoxicity.

Keywords: Mucormycosis, Diabetes mellitus, Amphotericin-B

INTRODUCTION

Mucormycosis (Zygomycosis) is an invasive, opportunistic, rare, but lethal fungal infection caused by a stream of saprophytic fungi in the Mucorales family.[1] These are molds, ubiquitous in the environment and generally seen to affect those with lower bodily immune responses than normal.[2] It has six most prevalent primary clinical forms based on anatomic localization, namely: rhino cerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous.[3] The mandibular involvement is comparably found to be a rarer finding and is subsequently reported lesser in the available literature on the oral implications of mucormycosis.[4] The most common form being, the rhino-orbital-cerebral type.[5] Considering its angioinvasive and fatal nature, rapid diagnosis of this disease has become necessary for providing early treatment and reaping a better prognosis. If delayed in getting diagnosed, mucormycosis can lead to fatalities, thus emphasizing a greater need to study its clinical manifestations to better understand its pathophysiology and the available treatment options.[6] Since, there is a strong correlation between Mucormycosis and immune-compromised conditions of the patient, the patient's past clinical history holds prime importance.[7] This article emphasizes the need for the further perception of this disease, early diagnosis, and

treatment preferences considered to encounter this opportunistic infection.

To identify the predisposing factors, clinical manifestation and treatment protocols for mucormycosis of the oro-facial region, a literature search was performed for English literature on the search engine, Google Scholar. The Google search lines used were "dental symptoms of mucormycosis", and "dental extractions mucormycosis". A database of about 4090 articles was recovered from the searches. This included data of global origin for various periods. Out of the available literature on Google Scholar, the literature reported for the time interval of 2011 to 2021 was considered for the study. This included case reports that exhibited complete information for the selected period of 10 years, accounting for about 2406 articles. The pieces of literature in the English language were considered. Case reports with complete preview available/ open access were preferred. Data restricted to the oro-facial region in humans were considered for the study. The sample size was calculated taking into consideration the 99.99% confidence intervals through the software EpiInfo, which came to about 930 articles (Table 1).

Table 1: Sample size (n) for various confidence levels.

Confidence levels (%)	Sample size
95	332
80	154
90	244
97	394
99	521
99.9	747
99.99	930

These articles were reviewed starting from the first page till the 47th page in chronological order for both the search lines. Data from these review articles were extracted in Microsoft Excel for analysis. Incomplete articles, articles not relevant or not related to the oro-facial region, articles in regional language and not English literature, articles not pertaining to or including human case reports were excluded from the study. Duplicates were tagged and excluded from the survey using Microsoft Excel.

Table 2: Clinical manifestations of mucormycosis.

Clinical manifestation of disease (n=258)	N	%
Halitosis	48	18.60465
Tenderness	33	12.7907
Pus discharge	81	31.39535
Pain	128	49.6124
Swelling	131	50.77519
Involvement of nerve	49	18.99225
Discoloration/necrosis	87	33.72093
Lymph node involvement	9	3.488372
Ulceration	49	18.99225
Oroantral fistula/communication/palatal perforation	37	14.34109
Gingival and periodontal features	49	18.99225
Exposed bone	52	20.15504
Erythematous appearance	20	7.751938

Out of the 930 articles reviewed, articles not matching up the inclusive standards, not relevant to the purpose of the study were removed. Duplicates were scanned and removed. Eventually, the total number of articles for the study purpose narrowed down to 172 including case reports of about 258 patients.

On review of the case reports from the articles, rhino-orbital-cerebral was found to be a commonly documented form of mucormycosis majorly affecting the ethmoid, frontal, maxillary and sphenoid sinuses. The literature reported oral implications involving the maxillary, palatal region relatively more frequently, mandibular being rarer than any other oral form. The most common extra oral site reported was the orbital region. 154 male cases were documented, with female cases as 103 and gender was not mentioned in one of the cases. The average age was calculated to be 50.51 (in years). There were 10 cases below the age of 12 years. In the case reports reviewed, the patient mainly reached the clinician with a chief complaint of pain and swelling at the site of infection. On further clinical investigation, the disease either presented itself in the form of an ulcerated lesion, with an erythematous appearance or as a discolored necrotic patch. The most common site for ulceration was the palatal region. In most of the cases, palatal perforation, oro-antral fistulas, leading to oro-antral communication was observed. Pus discharge through the nasal route was a common finding. Many cases exhibited involvement of nerves, especially the facial and the trigeminal nerve. Features like numbness of the involved area, paresthesia, and hypoesthesia were exhibited. A very few patients complained of difficulty in mouth opening (trismus) (total of 3 cases). Many cases exhibited poor oral hygiene marked by exposed bone with gingival and periodontal involvement manifesting as mobility of tooth, recessed gingiva, bleeding on probing, etc. Maggot's infection was seen in a few cases (3 cases). The most common extra-oral feature documented for mucormycosis was related to the orbital region. Ptosis (drooping of upper eyelid), proptosis (abnormal protrusion of eye), cranial nerve palsy and orbital cellulitis were a few commoner extra-oral features. Since mucormycosis lacks stereotypical representations clinically, it may show resemblances to many other diseases affecting bones and the oral mucosa. Few of them considered by clinicians as a differential diagnosis while confirming the disease in the reviewed literature were: necrotizing ulcerative gingivitis,

osteomyelitis, granulomatous diseases like midline lethal granuloma, tuberculosis, syphilis (gumma), osteomyelitis and malignancies.

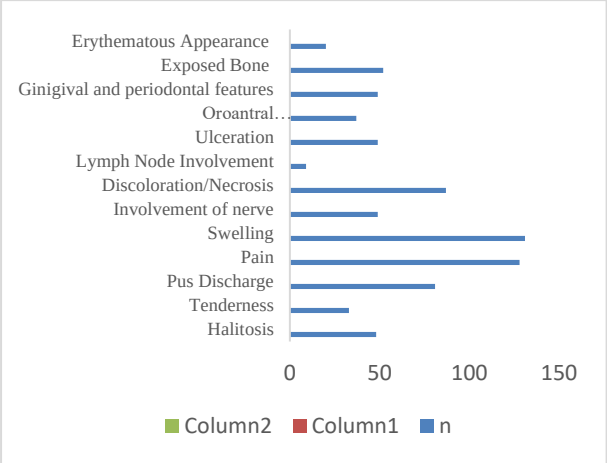

Figure 2: Clinical manifestations of mucormycosis.

On review of available literature, it was noticed that many patients exhibited the presence of unhealed intraoral tooth sockets with a history of either spontaneous exfoliation of teeth or a tooth extraction by a dental clinician (33.33% of cases). Few exhibited a history of trauma due to wearing dentures, fall, surgery or, blunt injury over the cheek/face area (101/258) (39.14% of cases). Considering these findings, the association of traumatic incidents like tooth extraction may be considered a risk factor for mucormycosis mainly in immune-compromised individuals, where delayed wound healing is exhibited. The following has also been highlighted in the article Balwan, et al where "trauma" is labelled as a "biggest risk factor" by the author.[8]

Diabetes mellitus was the most common underlying systemic illness reportedly seen in almost 63% of cases (163/258) exhibiting mucormycosis. Many manifested the presence of more than one systemic illness. For example, diabetes was seen along with the history of COVID-19 infections or diabetes with the presence of hypertension, etc. Only 7 cases of COVID infections (Without the presence of any other systemic illness) exhibiting mucormycosis were reported in the literature. This count is subject to increase in the coming years since the advent of COVID is rising. Leukemia was another disease of significance. Most leukemia patients suffered from mucormycosis infection. 42 otherwise healthy cases (n=258) (16.27%) were reported to suffer from mucormycosis as per the literature review findings.

The most common treatment option sought for the treatment of mucormycosis along with medicaments was the surgical approach that included surgical debridement of the affected area. This involved major surgeries like sequestromy, partial maxillectomy, excisional removal of necrotic bone, orbital exenteration in case of orbital mucormycosis, endoscopic sinus surgery in case of sinus involvement, etc. In many of the cases, hyperbaric oxygen therapy was used as an adjunctive treatment option to treat patients (7 cases). Amphotericin B was the most common antifungal medication used. However, its nephrotoxic nature was one limitation for its usage. Posaconazole, a topical medicine, was considered as step-down therapy for discontinuation of amphotericin. It was used as salvage therapy in critical cases that did not respond well to amphotericin or patients in which the use of amphotericin was not permitted. Itraconazole was another widely used antifungal medicament. In addition to the treatment modalities, reversal of predisposing factors like control of underlying systemic illness was reported to bring good improvement in the condition of the patient. Patients were reportedly provided with post-surgical prosthetic rehabilitation whenever needed.

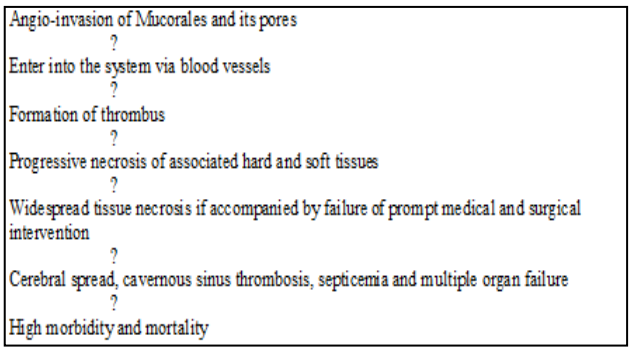

Figure 3: Probable pathophysiology.

Mucormycosis commonly known as black fungus has shown an increasing trend since the advent of COVID-19. However, these cases have been documented since the early years most commonly in immunocompromised patients.[9] Three common groups of mucorales cause mucormycosis in humans namely, rhizopus, rhizomucor and absidi, with rhizopus accounting for 90% of cases involving the head and neck region.[10] Mucorales are cultured from the oral cavity, nasal passage and pharynx of healthy individuals without any clinical signs of infection. Invariably mucormycosis manifests when the organisms affect the immunocompromised patients.[11]

The infection mainly routes through the nasal mucosa through airborne spores since the fungi are found everywhere in nature. Being angioinvasive, they are naturally inclined to germinate into the arterial system. Their hyphae grow within the arterial system forming a "fungus ball" that later occludes the artery causing thrombosis and infarcts.

The fungus is also known to invade nervous tissue and result in features like cranial nerve palsy.[12] Some of the causes highlighted in the literature for its predisposition to diseases like diabetes Mellitus include high blood glucose levels, impaired neutrophil and phagocytic response and increased available serum iron levels.[13] Diabetes ketoacidosis is an important predisposing factor for consideration as the mucor thrives in acidic pH.

Acidosis is also marked to decrease phagocytic response which in turn favors the growth of the fungus.[14]

Limitations

Limitation of current study was that the presented data is secondary data from available literature sources.

CONCLUSION

There have been several studies of mucormycosis in the oro-facial region that reveal the presence of traumatic incidents like tooth extraction, surgery, fall or blunt hurt in the oro-facial region. This can be attributed to the fact that the wound serves as an access point for implanting fungal spores in the body. Later, delayed wound healing, lack of proper blood supply, and conducive environment owing to the underlying systemic disease helps in the rapid proliferation of the mucor thus exhibiting the clinical manifestation of the disease. With almost 33.3% of cases of unhealed tooth sockets showing a strong correlation with mucormycosis, it is a crucial discovery that superimposes the role of oro-facial involvement leading to this fatal condition. Documentation of a patient's medical history is indispensable for the provision of effective leads for the diagnosis of diseases like mucormycosis. Also, the article fortifies the idea that a simple procedure like tooth extraction by a clinician can lead to fatal circumstances like mucormycosis in an immune-compromised individuals if due care is not taken. This highlights the role of dental clinicians in identifying the consequences that can be potentially hazardous if efforts for persistent postoperative follow up are not embarked upon. Therefore, it can be articulated that the patient's medical history is of utmost significance to understand and anticipate the potential prognosis of a case and its severity leading to mucormycosis and its associated complications. As the article highlights a considerably high number of cases which are relative as basic as tooth extraction but which lead to an unhealed socket that was further identified as potentially hazardous leading to a fatal condition like that of mucormycosis, the roles of dental clinicians for both preoperative case histories as also post-operative follow-ups can be thus concluded of extreme importance.

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