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Periodontology

TAKE DIVERSION ! - A PERIODONTIST POINT OF VIEW ON MUCORRMYCOSIS.

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ABSTRACT A new recently emerged complication of COVID-19 is a rare fungal infection also called the black fungus caused by a group of fungi called mucormycetes. These group of fungi commonly appear throughout the environment, particularly in association with decaying organic matter and in the soil. Oral health is essential to general health and greatly influences the quality of life. Mucormycosis is a rapidly progressive fungal infection characterized by endothelium invasion and the development of thrombi in blood vessels resulting in necrosis. Mucormycosis localized to the periodontal tissues (i.e., gingiva and alveolar bone) is exceedingly rare.

The clinical manifestation of mucormycosis also overlaps with the dental findings of periodontal abscess, due to which it is misdiagnosed as lesion of periodontal origin. Early diagnosis is crucial in order to promptly initiate therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae and improving outcome and survival.

Diagnosis of mucormycosis remains challenging. Clinical approach to diagnosis has a low sensitivity and specificity, it helps however in raising suspicion and prompting the initiation of laboratory testing. Successful management of mucormycosis is based on a multimodal approach, including reversal or discontinuation of underlying predisposing factors, early administration of active antifungal agents at optimal doses, complete removal of all infected tissues, and use of various adjunctive therapies. Another emerging imaging technique, which may eventually aid in the diagnosis and management of mucormycosis is the Cone Beam computed tomography(CBCT). Periodontal disease is not a fatal disease, but it can lead to any systemic or life threatening complications, which can be avoided by accurate diagnosis.

KEYWORDS :

INTRODUCTION:

Mucormycosis is an infection caused by a group of filamentous molds within the orders Mucorales and Entomophthorales. Mucorales occupy environmental niches including soil, decaying vegetable matter, bread, and dust. Infections due to Mucorales may result from inhalation of spores into the respiratory tract, ingestion of contaminated foods, or inoculation of disrupted skin or wounds. In developed countries, mucormycosis occurs primarily in severely immunocompromised hosts. In contrast, in developing countries, a substantial number of cases of mucormycosis occur in patients with poorly controlled diabetes mellitus (DM) or persons who have sustained trauma (1).

Despite the widespread distribution of these organisms, infection due to mucormycosis is essentially limited to patients with poorly controlled diabetes mellitus and immunocompromised patients. Because neutrophils play a crucial role in the protective host response, it follows that the immune impairments associated with hematologic malignancy may increase the risk for this opportunistic fungal infection (2). Mucormycosis usually develops as an acute infection and presents itself in rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated clinical types. Oral mucormycosis is rarely seen in clinical practice and reported cases are scarce (3).

Pathogenesis Of Mucormycosis

The pathogenesis of mucormycosis initiates with inhalation or ingestion of sporangiospores, or inoculation of conidia via puncture wounds or trauma (4). In healthy individuals, mononuclear and polymorphonuclear phagocytes (PMNs) eliminate fungal spores and hyphae by oxidative and nonoxidative killing mechanisms. Persistence or growth of the organism is facilitated by defects in phagocytic activity (e.g., neutropenia or defects in phagocyte function). Importantly, hyperglycemia and acidosis impair chemotaxis and phagocytic killing. In addition, Rhizopus produces the enzyme ketone reductase that enables growth in acidic and glucose-rich environments such as ketoacidosis. Mucorales display inherent resistance to killing by human phagocytes, which may account for increased virulence.

Iron metabolism plays a central role in the pathogenesis of mucormycosis. Patients with iron overload states (including those receiving deferoxamine chelation therapy) are predisposed to mucormycosis (5). Deferoxamine increases in vitro fungal growth by acting as a siderophore for Mucorales. In addition, increased availability of serum iron in persons with acidosis, in part due to diminished affinity of transferrin for free iron at pH below may enhance susceptibility to mucormycosis. Mucormycosis has an affinity for invading blood vessels, with resultant thrombosis and tissue necrosis (6). Interaction of the fungal spores with endothelial cells may facilitate angioinvasion. Further, interaction with host endothelial cell receptors may promote endothelial cell damage and fungal spread.

Risk Factors Of Mucormycosis

Several conditions have been associated with the development of mucormycosis including: poorly controlled DM 1, neutropenia , immunosuppression or chemotherapy, autoimmune or rheumatic disorders; human immunodeficiency virus infection, peritoneal dialysis, iron overload states , malnutrition, trauma and burns(1).

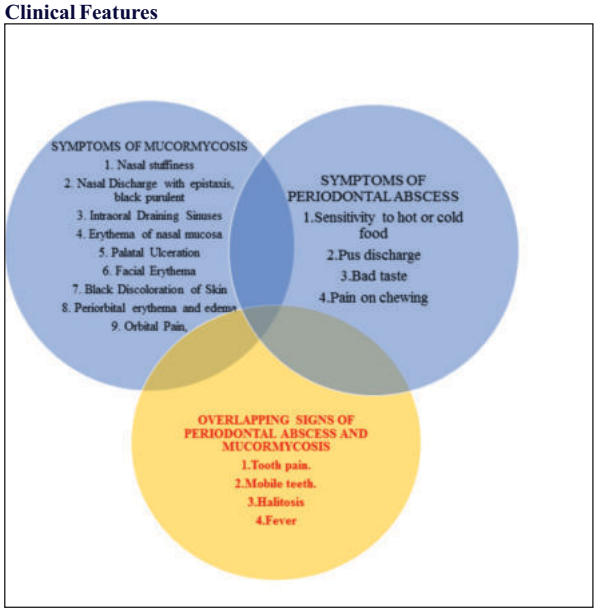
Mucormycosis rarely affects immunocompetent persons, but cutaneous, rhino-orbital, and (occasionally) disseminated infections have been reported following local cutaneous or soft tissue trauma. A recent meta-analysis of 600 publications from 851 cases of mucormycosis worldwide cited the following risk factors: DM (40%); trauma (33%); diabetic ketoacidosis (20%); neutropenia (20%); no underlying disease (18%); SOTR (14%); burns (11%); and natural disasters (5%).

Diabetes mellitus (poorly controlled, ketoacidosis)
Hematologic malignancy with neutropenia or graft vs. host disease
Organ transplantation
Autoimmune disorders
Immunosuppresive therapy
Human immunodeficiency virus
Iron overload.
Burns.
Trauma including surgery
Peritoneal dialysis
Malnutrition
Prior receipt of variconazole

In Asia, Diabetes Mellitus is the most common risk factor for mucormycosis. Diabetes was also the leading underlying condition in

the study by Stemler et al. in countries of the Middle East and North Africa(7). Mucormycosis has long been known for having a very poor prognosis, however, with aggressive medical and surgical management, survival rates are now thought to exceed 80%. Early detection has been correlated with less tissue destruction and a better overall outcome.

Clinical Features



Mucormycosis Mimicking A Periodontal Abscess

Clinicians face many challenges in diagnosing invasive fungal infections. Non specific symptoms present difficulties in definitive early diagnosis, and in such cases fungal infections like mucormycosis can be misdiagnosed as a periodontal abscess.

Most of the cases of mucormycosis represents the clinical appearance which resembles the clinical features of periodontally involved lesions. The characteristics of mucormycosis leads to diagnostic confusion . Mucormycosis produce the same clinical signs like **tooth pain, mobile teeth, halitosis, as of periodontal diseases.**

Figure.1 Represents A Case Of Periodontal Abscess In The Maxillary Right Premolar Region.

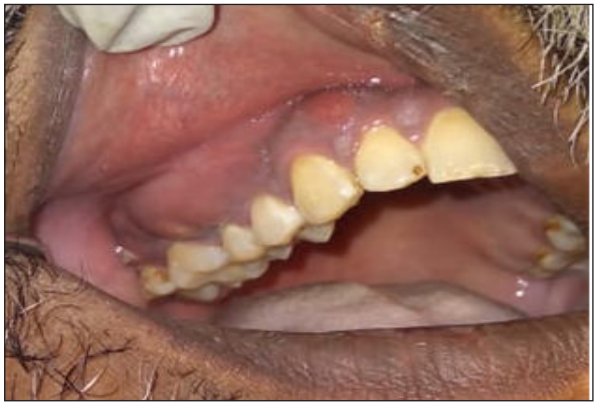


Figure.2 Represents The Clinical Sign Of Mucormycosis Which Is Misdiagnosed As Periodontal Abscess.

Mucormycosis : Need For Early Diagnosis!!

Tissue necrosis usually develops early in the course of mucormycosis.It leads to avascular necrosis which is known as "**bone death**", caused because of temporary or permanent loss of blood supply to bone.

Early evidence of the presence of disease could also be found on CBCT. Moreover during radiological assessment CBCT scans may be necessary to delineate the extend of disease.

Diagnosis of mucormycosis requires thorough clinical history and evaluation of underlying medical illness. CBCT shows bony erosion, involvement of sinus, and nasal cavity, mucosal thickening. These features may be seen in other diseases, but if CBCT shows bony erosion and sinus involvement in an immunocompromised patient, invasive fungal sinusitis should be one of the differential diagnosis. However, invasive fungal infections with intracranial and orbital extensions are incompletely evaluated in CBCT.

Therefore, CBCT may have a role in the early stages of mucormycosis, providing detailed information about extensions into all the sinuses; but if there orbital and intracranial extensions. CBCT also revealed irregular socket healing with disrupted cortical outline, which was otherwise not apparent in panoramic radiograph. Moreover, intact sinus walls in the CBCT and absence of clinical symptoms ruled out intracranial or orbital extension of the disease.

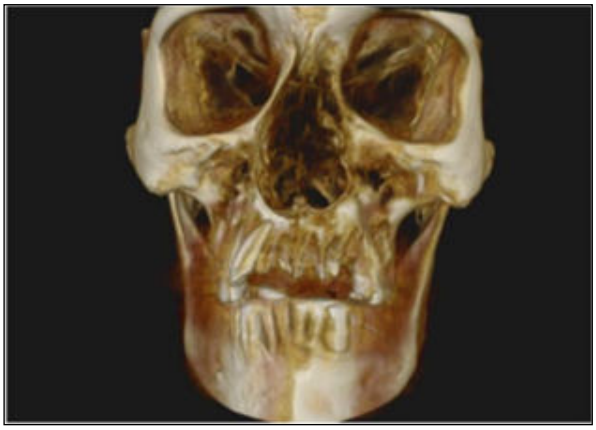


Fig.3. CBCT Revealed Erosion Of The Maxillary Bone With "**moth Eaten"** Appearance In Three Dimensional View (14).

Periodontitis A Risk Factor Of Mucormycosis

Chronic periodontitis, a progressive disease affecting gingiva, periodontal ligament and alveolar bone results when gingival inflammation subsequently affects the supporting apparatus of the tooth structure resulting in alveolar bone resorbtion(9).

The two primary forms of periodontal disease are gingivitis and periodontitis . Gingivitis the early form disease where inflammatory changes are restricted to marginal gingiva and surrounding connective tissue without loss of attachment is a mild and reversible condition. Periodontitis occurs when inflammatory changes reach the periodontal ligament and alveolar bone and changes are irreversible and destructive ultimately leading to tooth loss.

Mucormycosis of the oral cavity is usually due to transpalatal extension of rhinocerebral infection, and mucormycosis localized to the periodontal tissues (i.e., gingiva and alveolar bone) is exceedingly rare; to our knowledge, only 6 cases have been reported in the English-language literature in the past 25 years. The clinical features of these cases are summarized in Table I. Of note, all of the patients were neutropenic as a result of chemotherapy for hematologic malignancy or carried a diagnosis of diabetes mellitus. In three patients, mucormycosis arose at the site of recent dental extraction. Treatment involved amphotericin B with or without local debridement(2).

Table I. Periodontal mucormycosis

Case source	*Age(yr)/gender*	*Underlying condition*	*Location*	*Treatment*	*Outcome*
Dogan et al. (2007)[16]	7/M	AML/neutropenia	Maxilla gingiva	Debridement, amphotericin B	Full recovery
	9/M	ALL/neutropenia	Maxilla gingiva	Amphotericin B	Full recovery
Aulack (2007)[17]	58/M	Diabetes	Maxilla extraction site	Debridement, amphotericin B	Full recovery
Salisbury et al. (1997)[18]	60/M	AML/neutropenia	Mandible extraction site	Debridement, amphotericin B	Full recovery
Jones et al. (1993)[19]	43/M	AML/neutropenia	Mandible gingiva	Debridement, amphotericin B	Full recovery
	68/M	Diabetes	Maxilla extraction site	Amphotericin B	Lost to follow-up

Clinical Manifestation

The most common oral sign of mucormycosis is ulceration of the palate. The differential diagnosis may include odontogenic or periodontal infection and maxillary sinusitis. Clinical manifestations were similar: the patients complained of gingival pain with fever. Physical examinations revealed bluish, grayish, or whitish edematous plaques as well as necrotic changes. Unlike rhinocerebral mucormycosis, the gingival type was observed without central nervous system involvement and with slower progression.

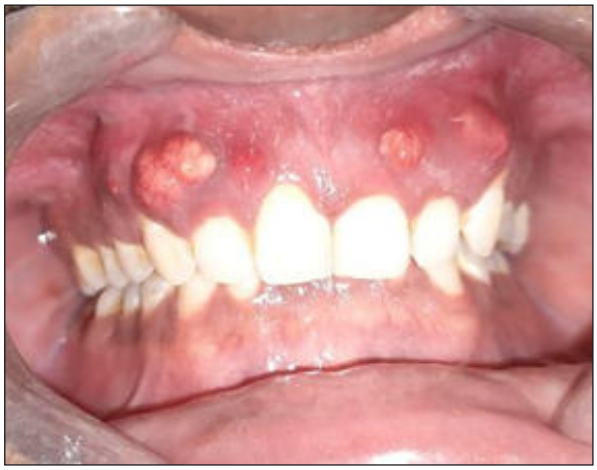


Fig.4

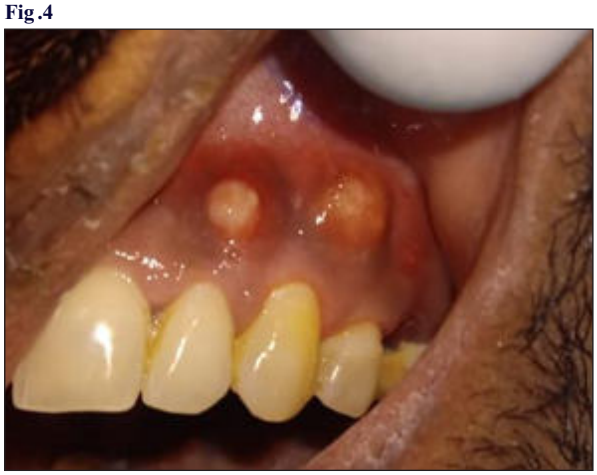


Fig.5. Gingival Ulceration In The Form Of Papules Limited To The Keratinized Gingiva With Diffuse Erythema Extending Into The Buccal Of Second Premolar

Case Report 1 (Diabetes With Mucormycosis)

A patient reported for evaluation of pain in the posterior palate region. Pain was moderate in nature, aggravated on bending the head and chewing food. The patient also complained of nasal congestion and headache. There was no history of fever, purulent discharge, paresthesia or foul odor. The patient was a known diabetic on treatment with oral hypoglycemics for the last 10 years. However, he continued the same medication.

On general examination vital signs were within normal limits. Intraoral examination showed a necrotic bone of about 1 cm diameter in palate region. Maxillary molars were missing and surrounding soft tissues were normal.

Biochemical investigations revealed an elevated blood sugar levels. Fasting blood sugar was 238 mg/dl & post prandial blood sugar level was 386 mg/dl. A biopsy was advised. Hard tissue specimen along with the adjacent soft tissue was excised under local anesthesia and sent for histopathological examination.

Histopathological examination identified non-septate mucormycotic hyphae. Grocott's modified special staining technique further identified these non-septate branching hyphae of mucormycosis. The patient was hospitalized and physicians controlled blood sugar levels with insulin.

The necrotic bone along with 1 cm of adjacent bone was excised under general anesthesia. The patient was administered Amphotericin-B 0.8mg/kg/day intravenously for two weeks. It was slowly infused over 4-6 hours and blood urea and creatinine levels were monitored as the drug can cause renal toxicity. Two weeks later the area started healing and subsequently after three months an obturator was made for the patient(11).

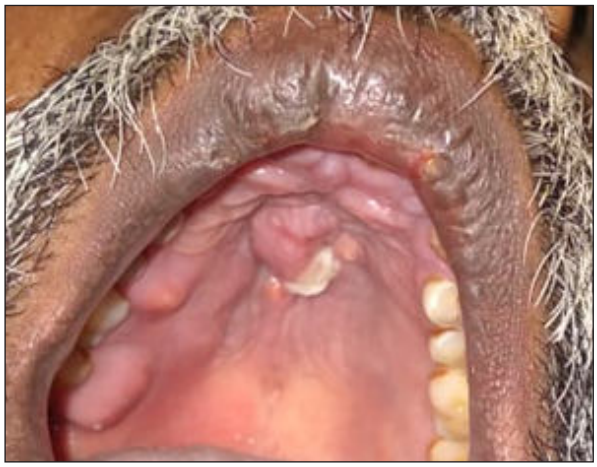


Fig.6

Case Report 2(Acute Myelogenous Leukemia With Mucormycosis)

A 60-year-old man was referred to the hematology/oncology service with laboratory values as follows: white blood cell count = 1200/µl, absolute neutrophil count = 200/µL hemoglobin = 8.6gm/ dl, hematocrit = 24.5%, platelets = 15,000/µL. He was afebrile but complained of dizziness. His medical history included prostate cancer, hypertension, and heavy use of alcohol and tobacco. A bone marrow biopsy diagnosed acute myelogenous leukemia.

A dental consultation was performed on the day of admission. The dental history included no regular care and recent pain and swelling associated with the mandibular right second molar.

Radiographs showed deep vertical bone defects involving the second molars and a periapical radiolucency of the mandibular right second molar. In addition, the mandibular left second molar had previous endodontic treatment and a failing restoration but no periapical radiolucency. Periodontal probings up to 7 mm were associated with all four of these teeth. After consultation with the oncologists, the decision was made to extract the four second molars. Before this procedure the patient empirically received broad-spectrum antibacterial agents. No prophylactic antifungal medication was given.

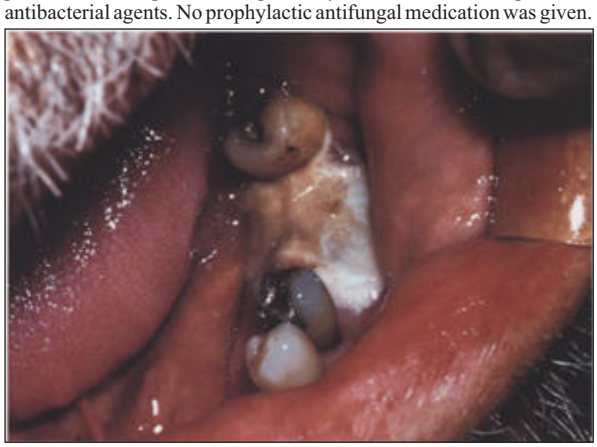


Fig.7

The four teeth were routinely extracted in the clinic with no apparent complications. Although the patient smoked postoperatively in spite of our warnings, his initial course was uneventful, and myelosuppressive chemotherapy was begun 3 days after the extractions. At 16 days postextraction, during the period of profound neutropenia, the mandibular left extraction site was encompassed by white necrotic-appearing tissue. Swelling was noted in the adjacent buccal vestibule.

A biopsy of the necrotic lesion showed fungal hyphae consistent with Mucorales invading the submucosal connective tissue and vasculature. The biopsy confirmed the diagnosis of mucormycosis, and tissue cultures were also positive for Mucorales.

Amphotericin B was immediately begun, and the patient was taken to the operating room for excision of the necrotic lesion. The resection included removal of the adjacent tooth, underlying bone, and a wide margin of normal appearing soft tissue. The neurovascular bundle was not disrupted, and the wound was closed primarily.

A soft diet was maintained and wound care included hydrogen peroxide irrigation of the surgical area and chlorhexidine rinses. With aggressive medical management the patient held a steady course, and a week after the resection his neutropenia had resolved. Antibiotics were gradually tapered as clinical conditions improved. One month after discharge, the oral cavity showed no tissue breakdown in the area of previous infection. There has not been any reappearance of mucormycosis(12).

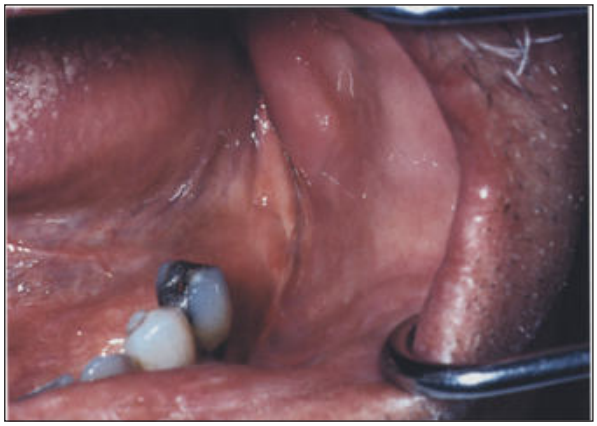


Fig.8. Left Posterior Mandible Area Of Resection Shows Well-healed Mucosal Tissue Without Evidence Of Recurrent Mucormycosis.

Case Report 3 (Acute Myelogenous Leukemia With Mucormycosis)

A 43 year-old black man referred the oral and maxillofacial surgery clinic a for evaluation of pain in the mandibular right premolar region. Findings of a head and neck examinalion were within normal limits.

Intraoral examination revealed multiple missing teeth and moderate to-severe periodontal disease. The attached gingiva buccal to the mandibular right first and second premolars was grey fibrotic in appearance and demonstrated a well-delineated sloughing border .

A panoramic radiograph revealed moderate horizontal bone loss and a 3 mm vertical defect associated with the distal surface of the mandibular right second molar. The palate,floor of the mouth, tongue, nasal mucosa and nasal septum were unremarkable. Because the patient was pancytopenic, dental treatment was delayed . The patient's medical history was significant for AML, diagnosed by bone marrow biopsy . The patient's postinduction chemotherapeutic course was complicated by acute renal failure, upper gastrointestinal bleeding, hepatosplenic candidiasis. and pancytopenia.

The hepatosplenic candidiasis was treated initially with amphotericin B; however elevated serum creatinine levels developed, and the drug was withdrawn. The patient was subsequently placed on long-term fluconazole. The two premolars were extracted, and incisional biopsy specimens of the fibrotic gingiva and underlying bone were obtained for histopathologic evaluation.

Microscopic examination of the soft tissue specimen demonstrated necrotic stratified squamous epithelium and subjacent fibrous connective tissue. The fungal hyphae were noted within and adjacent to the necrotic blood vessels. The decalcified specimen revealed fragments of partially vital bone trabeculae and adjacent fibrous connective tissue. The fibrous connective tissue was composed of loosely and densely arranged collagen fibers interspersed with fibroblasts,were noted throughout the fibrous connective tissue. The fungal organisms were seen immediately adjacent to the bone trabeculae. The soft and hard tissue specimens were diagnosed as mucormycosis and candidiasis.

After the above diagnosis was rendered, the patient was placed on 80 mg of amphotericin B. And all remaining necrotic tissue in the right mandible was debrided. A follow-up examination revealed no oral soft tissue or bony abnormalities. The gingival tissue appeared normal in color and texture. The patient remains on fluconazole for treatment chronic hepatosplenic Candidiasis(13).

Treatment Of Periodontal Mucormycosis

Although vast majority of cases of oral mucormycosis have palatal ulceration and demonstrate extension into adjacent vital structures ,occasional examples have been reported that involve the buccal mucosa, maxillary alveolar ridges, upper lip,lower lip and mandible.

Early diagnosis and improved periodontal therapy in case of mucormycosis have resulted in decreased patient morbidity and mortality.

The recommended treatment protocol consists of controlling any underlying immunosupressive disease, wide surgical excision and Amphotericin B therapy.

CONCLUSION

Mucormycosis have been reported in the wake of COVID-19 cases, bringing worldwide attention to this deadly yet neglected disease. The infection can be deadly in patients with an impaired immune system, in those with uncontrolled diabetes mellitus or individuals receiving steroids. The global prevalence of periodontal disease is expected to increase in coming years due to growth in the aging population. Periodontitis is the sixth most common disease with a prevalence of 11.2%. The metastatic spread of microorganisms and and their products from dental plaque and inflammatory mediators from periodontal tissue to other organs of the body is believed to account for this periodontal and systemic disease condition. The mortality of mucormycosis remains high. Prompt diagnosis and early initiation of treatment can prevent mortality. Diagnosis of mucormycosis requires thorough clinical history and evaluation of underlying medical illness. Clinical approach to diagnose a mucormycosis can be misdiagnosed as periodontal abscess. The clinical manifestation of mucormycosis also overlaps with the dental findings of periodontal abscess. By taking diversion ,early CBCT diagnosis reveals the progression of bone necrosis in mucormycosis cases. Periodontal disease is not a fatal disease, but it can lead to any systemic or life threatening complications.

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