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Review Article

Mucormycosis and its prosthodontic management: A review

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ABSTRACT

Coronavirus disease 2019 (COVID-19), during the second wave in early 2021, has created disastrous chaos. Adding more burdens to such a challenging situation, mucormycosis is an angioinvasive, fulminant fungal infection has seen a sudden raise in patients with COVID-19. Mucormycosis commonly affects the patients with compromised immunity. Early diagnosis, elimination of the predisposing factor, and antifungal therapy along with surgical debridement are the key factors responsible for successful treatment and patient survival. Mucormycosis is presented by various clinical forms. This paper reviews about the clinical presentation, diagnosis, and various treatment modalities for managing mucormycosis patients.

Keywords: Mucormycosis, Clinical forms, Antifungal therapy, Prosthodontic rehabilitation, Surgical obturator

INTRODUCTION

Mucormycosis is an aggressive and saprophytic fungal infection caused by aerobic fungi-Mucorales which belongs to the class phycomycetes.[1] Hence, it is also called as phycomycosis or black fungal disease. Nose and paranasal sinuses are the commonly involved sites.[2]

This fungal disease has been a widespread in COVID outbreak.[3] It is an opportunistic infection associated with immunocompromised condition and becomes noticable when the body defense mechanism becomes weaker.

Mucormycosis is an angioinvasive infection. Patients with low immunity are highly prone to develop this disease and its complications, where in the spores of the fungi colonizes the upper respiratory tract, develop hyphae, and invade blood vessels and surrounding tissues.[2] The devitalized tissue due to thrombosis and tissue necrosis which leads to continued fungal growth thus making it more as aggressive and fateful.

CLINICAL FORMS OF MUCORMYCOSIS

The various clinical forms of mucormycosis are – rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated.[4]

The population who are under risk involve diabetes, long-term corticosteroid use, excessive iron, organ transplants, and conditions that decrease immunity. The disease is developed due to the contact with the spores and compromised immune responses which can increase the widespread possibility of the disease.[4] These organisms proliferate rapidly, as they gain entry to the mucous membranes and invade the nearby blood vessels causing vascular thrombosis followed by necrosis, thereby leading to tissue destruction and non-healing necrotic ulcers with underlying bony destruction.[5]

Therefore, it demands maximum attention in patients who are previously infected with coronavirus disease 2019, for early diagnosis and surgical intervention to cease the propagation of infection to the vital organs of the body. Mucormycosis is diagnosed with the symptoms, history, examination, and laboratory investigations. The supportive investigations include computed tomography scan of sinus, tissue biopsy, and fungal culture. The treatment required the control of any metabolic diseases, antifungal medications, and surgical resection of affected tissues.

CLINICAL MANIFESTATIONS

Although, patients infected with mucormycosis are not encountered frequently in general dental practice, they may consult dentists during the initial stage of the disease when the symptoms overlap with that of dental origin such as dental pain, periorbital cellulitis, or mucosal sloughing.[6] Sometimes, palatal ulceration alone may be the pathognomonic sign that leads to the diagnosis of mucormycosis.[7]

Therefore, it demands consideration of mucormycosis as a distinctive diagnosis, when a patient shown with swelling of the perinasal and periorbital tissue, unilateral proptosis,

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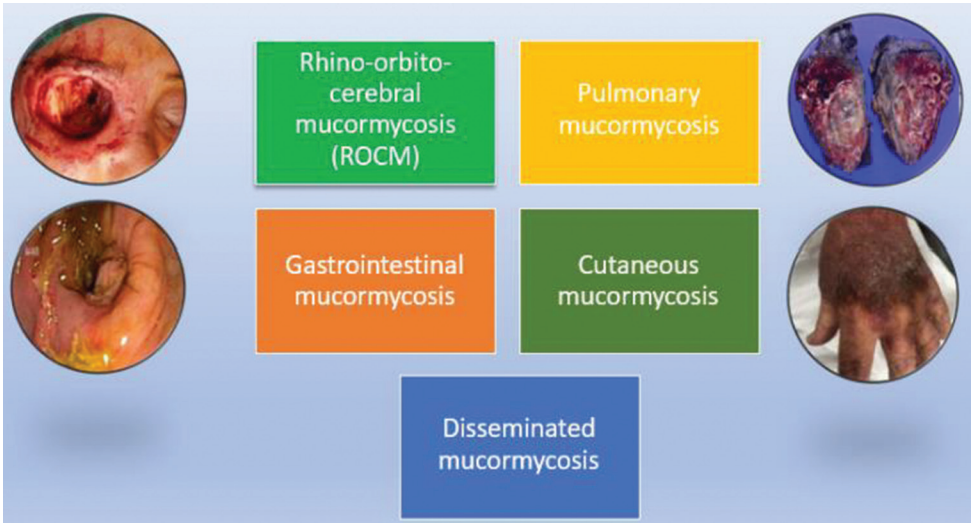

Rhinocerebral	Pulmonary	Gastrointestinal	Cutaneous	Disseminated
In rhinocerebral mucormycosis the infections spread from sinus to the brain It is seen in patients with renal transplants or uncontrolled diabetic patients.	The lung or pulmonary mucormycosis is observed in cancer patients or the organ transplant	The gastrointestinal mucormycosis is affected more commonly in children than adults. The clinical situations that compromise the immune response of children by the extensive use of antibiotics or surgeries are affected by gastrointestinal mucormycosis.	The skin or cutaneous mucormycosis occurs due to the outbreak in cutaneous tissue or skin	The disseminated mucormycosis the infection spreading through the bloodstream. The brain and the other vital organs such as heart and spleen are the primary organs affected by this variant

paranasal sinusitis, dilation and fixation of the pupil, and cranial nerve involvement.

Considering the various clinical forms of mucormycosis, rhinocerebral is the most predominant one. It accounts for the one-third to half of the reported cases. It is again divided as rhinoorbitalcerebral (Type 1) (more fatal) and rhinomaxillary form (Type 2) (less fatal), involving ophthalmic with internal carotid arteries and sphenopalatine with greater palatine arteries, respectively.[8]

In 1950, Smith and Krichner have introduced certain criteria for the clinical diagnosis of mucormycosis that are yet found to be the gold standard and are as follows: [9]

1. Dark colored, blood-tinged, and nasal discharge on the side where facial pain is elicited, of brief duration
2. Soft periorbital or perinasal swelling that progresses to induration and discoloration. (With progressive vascular occlusion)
3. Proptosis of the globe and ptosis of the lid, fixation and dilation of the pupil, and limitation of global mobility
4. Progressive lethargy, in spite of good response to diabetic therapy
5. Black necrotic turbinates and easily mistaken for dried blood
6. Loss of corneal reflex and onset of facial weakness, usually observed, late in the course of invasion.

Nithyanandam *et al.*, in 2003, put up three distinct clinical stages based on the signs and symptoms and degree of disease progression. Those clinical stages are as follows.[10]

- Clinical Stage 1: Signs and symptoms of sinonasal disease
- Clinical Stage 2: Signs and symptoms of rhino-orbital disease
- Clinical Stage 3: Signs and symptoms of rhino-orbito-cerebral disease.[10]

Clinical classifications aid in suitable surgical as well as prosthetic rehabilitative treatment planning to provide comprehensive medical care to the patient.[11]

Clinical stage	Nomenclature	Symptoms	Signs
Stage 1	Sino-nasal	a. Headache b. Nasal discharge c. Facial pain and swelling d. Fever	a. Nasal crusting b. Necrosis of turbinates c. Palatal necrosis and perforation
Stage 2	Rhino-orbital	a. Loss of vision b. Diplopia	a. Conjuntival chemosis b. Proptosis, ptosis and opthalmoplagia
Stage 3	Rhino-orbito-cerebral	a. Facial and other palsy b. Altered sensorium	a. Cavernous sinus thrombosis b. Altered mental functions c. Hemiplegia

RADIOGRAPHIC EXAMINATION

Radiographic examination discloses a wide range of uncovering, from cloudiness of the sinuses and thickening of the mucosal lining to extensive destruction of bone. Sinus mucosa nodular thickening, focal bone destruction, and absence of fluid in radiographs are considered to be the diagnostic features in mucormycosis.[11] The ethmoid and maxillary sinuses are always involved, but sphenoid and frontal sinuses are rarely involved in the disease process. Mucormycosis can be distinguished from the carcinoma by the involvement of multiple sinuses. The disease is mostly involves only one side of the face but sometimes, it can involve both ethmoid sinuses. Although radiography can sometimes be suggestive, the definitive diagnosis can be given only after biopsy of the infected tissues and by the identification of the organism.[12]

DIAGNOSIS

Early diagnosis of mucormycosis is considered very important for providing appropriate treatment for the patient. Histological examination of specimens can confirm the clinical diagnosis by the presence of the right-branching aseptate hyphae, which are observed typical for mucor species, along with tissue necrosis and angioinvasion. Cultures of fungi can also provide further confirmation.

Another laboratory diagnostic tests include molecular detection of zygomycetes and cerebrospinal fluid analysis. However, the results so far have been less promising.

Imaging methods are also helpful during the initial stages of rhinocerebral mucormycosis with thickening of the sinus mucosa or extraocular muscles, which is considered as an early sign of the disease. CT scans used to assess the development of disease although correlation with the clinical findings may not always correct. MRI scans may be more accurate in evaluating the extent of disease due to fungal invasion of soft tissues.[13]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis involves sinusitis, carcinoma, and thrombosis of cavernous sinus. The symptoms are even complicated by predisposing conditions,[12] other entities for the differential diagnosis includes retro-orbital abscess, uremic frost, diabetic polyneuritis, gangrenous stomatitis, bacterial sepsis, and abscessed tooth.[12] Due to peak in the incidence reported in the literature has led to a raise degree of suspicion toward mucormycosis. Diagnosis and progression of treatment are based on the clinical findings and have resulted in a more favorable outcome.

SURGICAL CONSIDERATIONS

Therapy for rhinocerebral mucormycosis necessitates an integrated approach that includes,

1. Antifungal agents mainly intravenous amphotericin B
2. Surgical debridement, and
3. Control of the underlying disease that leads to infection.[14,15]

Early extensive surgical debridement of the infected tissues is of utmost importance for success of the treatment in rhinocerebral mucormycosis which includes resection of infected facial tissues, along with the skin, muscle, and mucosa of nasal and oral cavity, maxillary and palatal bones along with ethmoid and maxillary sinuses and tissues that are necrotic in the temporal and infratemporal region.

For an actively infected orbit with immobile and blind eye, orbital exenteration must be considered. It would be a life-saving decision if active fungal infection is present in the orbit.[16] The swift progression of the mucormycosis infection creates a high necessity of early aggressive surgical intervention. Furthermore, the fact that a clear-cut extent of excision cannot be decided before surgery based on radiological imaging unlike in tumor cases of benign and malignant origin.

Pre-surgical prosthodontic planning may not be possible in all the cases. After the surgical debridement, the patient is left with large bony and soft-tissue defects. This entails reconstruction to protect the remaining vital structures, restore as much function, and provide a socially acceptable appearance.

In the literature review conducted by Palacios *et al.*, in 2019 to evaluate the feasibility of immediate reconstruction after surgical debridement, inferred that, as secondary reconstruction leads to tissue atrophy and retraction resulting in higher patient disfigurement, immediate reconstruction may be enforced, on the basis of clinical criteria, after an

intraoperative study of wound edges and recipient's vessels and by histologic confirmation of absence of hyphae invasion. However, delayed reconstruction is recommended when there is hemodynamic instability, evidence of cellulitis, or aggregated infections, when a complete resection cannot be accomplished, or intraoperatory biopsy of wound margins is unavailable.[17] Although the existing literature discloses contradictory outlook regarding patient management, it is better that the reconstruction be delayed to be sure that the patient survives after surgical intervention, considering the high mortality rate of 85%.[18,19]

PROSTHODONTIC CONSIDERATIONS

The post-surgical defects of mucormycosis are remarkably different from the defects that are resulted from resection of the due to the indefinable, unpredictable fungus advancement, and the probable requirement of additional debridement procedure. The surgical modifications that are done in favor of prosthetic rehabilitation in tumor cases cannot be accomplished in case of mucormycosis.

Therefore, provision of prosthodontic rehabilitation is compounded in mucormycosis patients especially when they are no teeth remaining, as the resultant defect often cannot be used effectively to support, retain, or stabilize the obturator prosthesis and the fact that these defects are let to epithelialize, result in a non-keratinized membrane formation, aiding in poor stress-bearing surface. Definitive prosthetic treatment should only be given once the healing is completed since the presentation of the permanent defect is decided based on the healing process and scar contraction.[15]

The reconstructive and rehabilitative approach of the resultant defects differs widely. Therefore, classifications of maxillofacial defects that consider the functional and esthetic outcome and also indicate the most appropriate form of management are to be contemplated.

Prosthodontic therapy for patients with acquired surgical defect after maxillary resection is rehabilitated in three phases by an obturator prosthesis that supports the patients through different stages of healing. The phases of treatment are arbitrarily divided as follows:

1. Surgical obturation
2. Interim obturation
3. Definitive obturation.

Surgical obturation

Immediate surgical obturation grants the placement of prosthesis at surgery. It is defined as the temporary prosthesis used to restore the continuity of the hard palate immediately after surgery. It is retained for about 6 days post-surgery.

The obturator acts as an arrangement on which surgical dressing may be placed. It also decreases contamination of the raw wound, aids in deglutition, thereby permitting early removal of nasogastric tube. Altogether, it lessens the psychologic impact of surgery to some extent. Before surgery, impressions are made and the casts are mounted on the articulator.

Later, the outline of surgical margins is discussed by the operating surgeon and prosthodontist on the cast and accordingly, the maxillary cast is altered and the prosthesis is fabricated.[20] Explicit planning before surgery regarding the surgical margins may not be always possible especially in mucormycosis cases since it is rapidly progressive in nature.[21] Nevertheless, a delayed surgical obturator can be planned in situations where it necessitates emergency surgical debridement which would be a lifesaving action, and also in cases where a prosthodontist could not be consulted beforehand. It could also be considered in cases where there is requirement of additional debridement procedure due to indefinable advancement of the fungus.

Delayed surgical obturator is fabricated within few days of surgical resection. Since the impression procedure is carried out after the surgery, it is required to handle the fresh surgical site, and the patient, with utmost care as they tend to be apprehensive. It is advised to reduce the time duration between impression making and obturator delivery, as the time lag would result in tissue contraction and edema, making it uncomfortable to the patient during obturator insertion.

An additional advantage of delayed surgical obturator is that it can be readily converted to an interim obturator wherein the margins of the obturator are not compromised till the final prosthesis is fabricated.[22]

Interim obturation

Fabrication of definitive prosthesis cannot be considered till the surgical site is healed, dimensionally stable and most importantly, until the patient's systemic condition becomes stable, specifically in rhinocerebral mucormycosis, which has a high chance of recurrence and high mortality rate even after treatment.[15]

Interim obturator is advised in cases with large defects, where appropriate function and comfort cannot be maintained until fabrication of a new prosthesis. The surgical and definitive obturators are intervened by the interim obturator.[20]

Definitive obturation

A definitive obturator is usually indicated on an average, 3 months after the surgery. The factors such as the state of healing, dimension of the defect, and effectiveness of the previous obturator and the remaining teeth present must be considered to construct a definitive obturator. In addition, the prognosis of the fungal infection along with the systemic condition of the patient must be determined.

The dimensional changes occurring due to structuring of the wound and scar contracture are extended for at least 1 year and are fundamentally related to the lining soft tissues rather than the underlying bony area, thereby demanding periodic follow-up.[22]

In edentulous patients, the obturator prosthesis may exhibit varying degrees of movement depending on the outline and amount of the residual hard palate, the contour, size, and mucosal lining of the defect, the accessibility of undercuts, and the support areas that can be engaged within and peripheral to the defect.

Engaging the defect extensively maximizes stability support and retention of the obturator. In edentulous patients, the defect margin in the posterior region plays a crucial role in treatment planning since it demands implant placement if the margin extends beyond the junction of soft and hard palate. In dentulous patients, the status of remaining natural teeth should be carefully addressed as they play a decisive role in designing the obturator prosthesis. The diagnostic casts should be surveyed carefully for location of undercuts, location, and contour of potential guide planes. A compound path of insertion must be employed to use the undercuts available in the defect adequately. Furthermore, inclusion of multiple rests is suggested to improve support and stability for the prosthesis. In defects extending to or beyond the midline, additional bracing may be necessary to distribute lateral forces more widely among remaining dentitions.

IMPLANTS

Osseointegrated endosseous and maxillofacial implants such as zygomatic and pterygoid implants have dramatically raised the potential for reconstruction of the patients with varied soft- and hard-tissue maxillofacial defects. Implants contribute to the retention, support, and enhance the stability of the prosthesis. Moreover, placement of implants along with staged surgical reconstruction of the extensive hard-tissue defects facilitates prosthodontic rehabilitation with fixed prosthesis.

The decision whether to place implants or not should always be critically evaluated specifically in mucormycosis patients as they are systemically immunocompromised and may not be willing for another psychological burden due to surgical intervention. Patients suffering from chronic liver disease or in liver transplanted cases, it is estimated that approximately 30% patients suffer from osteoporosis which is a subject of concern.[23] Therefore, the decision-making should involve a team comprising of a general surgeon, a physician, a maxillofacial surgeon, and a prosthodontist along with the patient attendees.

RECENT ADVANCES

The introduction of 3D computer aided designing (CAD) and computer aided manufacturing (CAM) has transformed the field of maxillofacial prosthodontics. Ever since the digital technology has arrived, it has made it possible to record oral morphology devoid of traditional impression materials and methods.

CAD/CAM technologies are capable of palliating most of the limitations of conventional techniques such as risk of impression material dislodgement into the surgical site, loss of impression accuracy due to nasal mucosal secretion on impression material, difficulty caused by severe trismus, and the inconvenience caused to the patient.[24] Cone beam computed tomography (CBCT) grants volumetric data which is convertible to standard tessellation language files that further can be used for rapid prototyping procedures such as stereolithography 3D printing to fabricate accurate anatomic casts. By utilizing this model, maxillofacial prosthesis can be fabricated by conventional method.

Recently, intraoral scanning devices have also been developed and employed along with CAD/CAM technology in dentistry, with numerous advantages. Intraoral optical impression systems provide three dimensional datasets that are developed to obtain digital impressions of teeth, implants, and surrounding soft tissues. Today, the intraoral scanner data and 3D volumetric data of craniofacial tissues from the CBCT images can be fused using certain software to obtain a resin master model with clearly defined soft-tissue details to fabricate the prosthesis.[25]

The literature has also reported the use of combination of facial scanner and intraoral scanner to acquire the digital data for fabrication of extraoral prosthesis to obtain detailed skin textures.[26] However, the unavailability of equipment in the clinic and that it is high-priced limits their practical application. To overcome these constraints, the technology is stepped higher by introducing an in-house and also economical smartphone-integrated stereophotogrammetry (SPINS) 3D scanner. The palatal defects can be scanned using SPINS and the prosthesis can be designed and fabricated by utilizing the 3D models obtained with SPINS.[27]

Advances in tissue engineering have also privileged maxillofacial reconstruction at a preliminary level as it has been considered as a possible solution to replace complex reconstructive methods. It is based on accumulating stem cells that possess capability to form an organ. These harvested cells are then laid on laboratory manufactured scaffolds, to resemble the desired tissue to be replaced. Simple tissue regeneration has been successfully achieved so far to restore tissue defects, but complex tissue structures along with its functional restoration are yet to be carried out.[28] Adopting customized tissue-engineered biodegradable scaffolds, such as polycaprolactone, fabricated using the patient's computed tomography data, and an extrusion-based 3D printing system, have been documented and confirmed to promote regeneration of the deficient tissue for maxillofacial bone reconstruction in patients with complex maxillary defects.[29] Thus, the future developments in the field of tissue engineering will have a significant influence on managing post-surgical defects.

CONCLUSION

As mucormycosis is a fatal fungal infection, it necessitates early diagnosis and treatment planning through a collaborative approach, in which the maxillofacial

prosthodontist plays a key role to improve the patient's quality of life. The defects that occur after surgical debridement, in mucormycosis, are different from those that occur otherwise. Therefore, it demands thorough knowledge about the course and nature of the disease, to critically evaluate the anatomic structures and prostheses designs to obtain maximum retention, stability, and esthetics. Maxillofacial prosthesis not only rehabilitates the defect but also recreates the self-confidence of the patient, which lead life to the fullest.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Authors Dr. Usha Radke and Dr. Richa Sahai are on the Editorial Board of the journal.

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