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Oral Mucormycosis: Post Complication of COVID Era

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Mucormycosis is an invasive and potentially lethal fungal infection and a rare terminal complication of uncontrolled diabetes and other chronic debilitating diseases. The incidence of disease has increased considerably due to widespread use of antibiotics, steroids and longterm use of humidifiers in corona positive patients. Despite surgical and antifungal treatments the mortality rate is higher than 50% and even higher in immunocompromised patients. The role of dentist is of immense importance because mucormycosis primarily occurs around rhinomaxillary or rhino cerebral areas involving facial tissues, palate, alveolar bone and mandibular bone. The present article briefly reviews pathogenesis, signs and symptoms, risks and complications, diagnosis and the management of the mucormycosis.

Keywords: Oral Mucormycosis; Covid-19; Diabetes; Antifungal therapy.

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1. INTRODUCTION

Mucormycosis is an opportunistic fungal infection caused by phycomycetes mainly by species of Rhizopus and Mucor. It is a rare terminal complication of uncontrolled diabetes and other chronic debilitating diseases. The incidence of disease has increased considerably due to widespread use of antibiotics, steroids and long term use of humidifiers in COVID-19 patients. This fungal infection is an aggressive angio invasive infection caused by inhalation of environmental sporangiospores in immuno-compromised hosts. Thrombosis and necrosis further leads to blackish discoloration of tissues and gives it a label “the black fungi”.

There are six clinical types of mucormycosis, Rhino cerebral mucormycosis, Pulmonary mucormycosis, GI mucormycosis, Renal mucormycosis, Cutaneous mucormycosis, Disseminated mucormycosis. The most common form is rhino cerebral mucormycosis which is of greatest interest to the dental profession. An ulcer or extraction wound in the mouth can be a port of entry for fungal invasion of the hard palate, maxillary bone, paranasal sinus, orbit, intracranial cavity and brain and rarely in the mandible. Other sites of infection include the nose, lungs, gastrointestinal tract, skin, kidneys, and central nervous system. Clinical features may range from nasal obstruction, bloody nasal discharge, facial pain or headache, facial swelling or cellulitis, visual disturbances with concurrent proptosis, facial paralysis in case of facial nerve involvement. As the disease progresses into cranial vault it may lead to blindness, lethargy, seizures, and death [1].

2. HISTORY

In 1885, German pathologist Paltauf, reported the first case of mucormycosis in humans. In 1943, Gregory et al described the first case of rhino orbital cerebral mucormycosis associated with diabetes.[2] Harris in 1955 reported the first known survivor. The term “mucormycosis” was coined by an American pathologist R.D. Baker. [Fig. 1.]

3. PREDISPOSING FACTORS

Immunosuppression and breakdown of anatomical barriers such as the skin are the major risk factors for fungal infections. The risk factor for Mucormycosis includes any debilitating diseases especially diseases that can yield compromised blood flow to tissue. Almost all patients with invasive mucormycosis have some underlying disease that both predisposes to the infection and influences the clinical presentation.

- Case of concurrent or recently (≤ 6 weeks) treated severe Covid -19 as mucormycosis develops as secondary infections.
- Uncontrolled diabetes mellitus specially with ketoacidosis are at high risk. Diabetic ketoacidosis patients have high levels of serum iron and the pH ranging from 7.3 to 6.88, which is ideal environment for growth of *Rhizopus* [3].
- Immunosuppression by steroids (usage ≥ 3 weeks or high dose ≥1 week) including oral or intravenous steroids.
- Prolonged ICU stay and unhygienic humidifiers.
- Trauma and burns
- Post transplant and malignancy
- Voriconazole therapy [4].

4. PATHOGENESIS

When the immune system is breached, the fungi take advantage and invade human tissues. This infection is characterized by extensive angioinvasion that results in vessel thrombosis and subsequent tissue necrosis. COVID-19 patients who are on steroid therapy have suppressed immune system and hence they are more prone to develop mucormycosis. Fungal spores when inhaled or ingested get trapped in paranasal sinuses, phagocytic cells when unable to remove them, the fungal spores start germinating and colonization starts. Occlusion of blood vessels start due to increased affinity to blood vessels. This is also termed as angioinvasion that further leads to tissue ischemia and finally avascular necrosis of the involved area [Fig. 2.] The involved area turns black in color that is why this is also termed as black fungal infection [5,6]. Pathogenesis and mechanism of bone destruction is attributed to the reduced vascularity by thrombi formation and inhibition of angiogenesis due to elevated levels of GRP 78 [7].

5. SIGNS AND SYMPTOMS

Mucormycosis presents itself as respiratory infection or skin infection, The infection usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache,

and sinus pain.[8] All of the sinuses become involved, and spread to adjacent structures, such as the palate, orbit, and brain, usually progresses rapidly over the course of a few days. However, there have been some reports of rhino-orbital-cerebral mucormycosis that progresses over the course of weeks. The hallmarks of spread beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars [Fig. 5]. destruction of the turbinates, perinasal swelling, and erythema and cyanosis of the facial skin overlying the involved sinuses and/or orbit.

Toothache or loosening of teeth and involvement of jaws and multiple periodontal abscess [Figs. 3, 4] can also be seen in oral cavity. Signs of orbital involvement include periorbital edema, proptosis, and blindness. Facial numbness is frequent because of infarction of trigeminal nerve. Spread of the infection from the ethmoid sinus to the frontal lobe results in obtundation. Spread from the sphenoid sinuses to the adjacent cavernous sinus can result in cranial nerve palsies, thrombosis of the sinus, and involvement of the carotid artery. Hematogenous spread to other organs is rare unless the patient has an underlying hematologic malignancy with neutropenia.[1,9]

6. RISKS AND COMPLICATIONS

If not properly diagnosed Mucormycosis can lead to some serious complications as infection spreads quickly throughout the body and usually starts from nose, cheek bones, palate, eyes and if not treated timely the infection can spread to the brain. Some serious complications may occur such as

- Blindness
- Brain abscess
- Meningitis
- Pulmonary hemorrhage
- Gastrointestinal hemorrhage
- Secondary bacterial infections, sepsis and death

To avoid such life-threatening situations proper diagnosis at the right time plays a very important role so that patient can receive treatment as early as possible [10,11].

7. PROGNOSIS

The prognosis of mucormycosis is usually fair to poor. The fatality rate in mucormycosis cases is very high. If goes untreated 80% of mortality but if treated timely mortality could be reduced to 40-50%. If the infection is detected at the sinus stage, patient recovers easily.

The prognosis depends on the early diagnosis and treatment plan. It also depends on overall health status of the patient or patient's ability to respond to the treatment.

Due to surgical debridement and tissue patients who survive often have some disabilities as limb loss, organ dysfunction, blood loss [10].

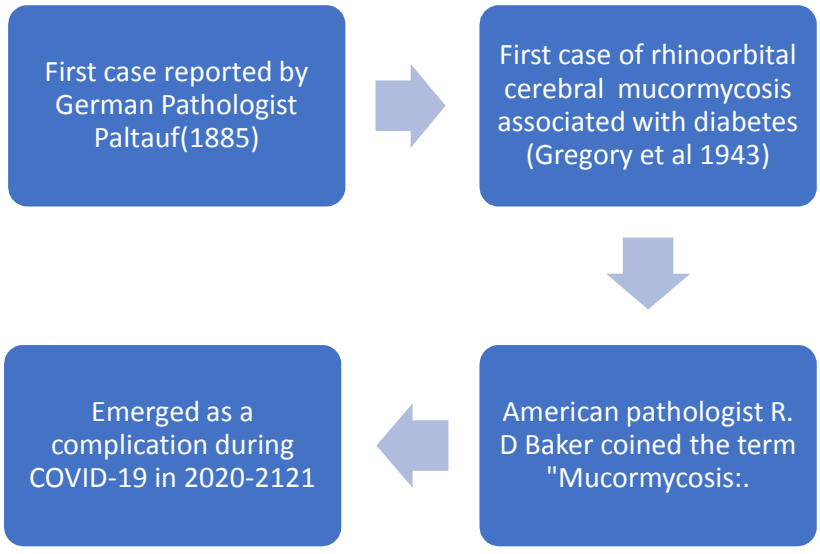

Fig. 1. Historic Description of the Mucormycosis

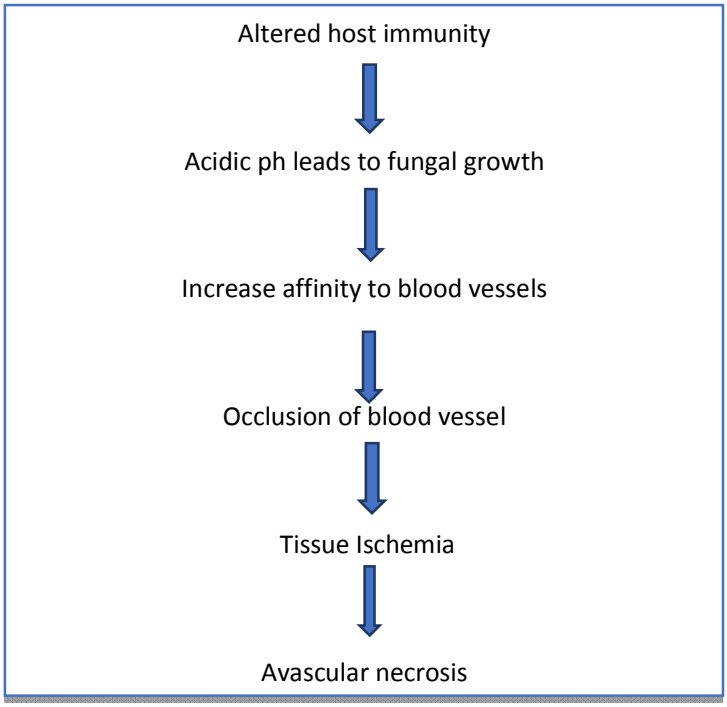

Fig. 2. Pathogenesis

Figs. 3,4. Multiple abscess

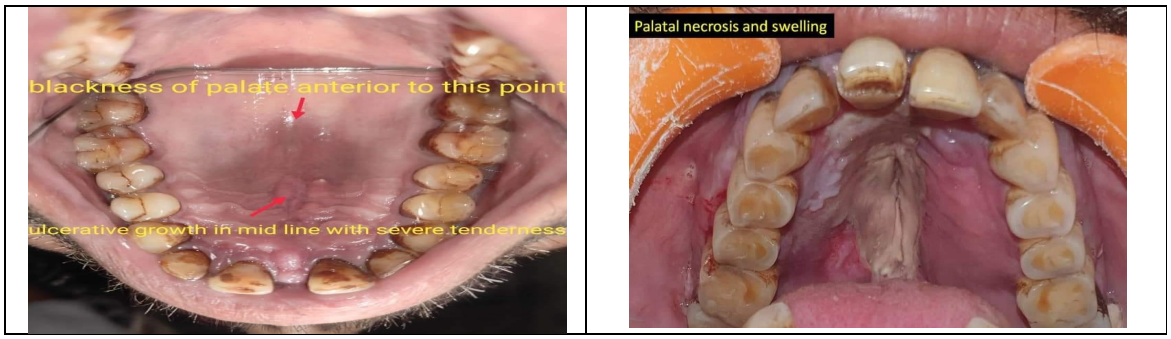

Fig.5.Palatal Necrosis

8. DIAGNOSIS

Good clinical examination with history and a sharp approach in treating without delay can reduce morbidity and mortality. A proper medical history, physical examinations and laboratory tests (CBC, blood sugars) should be done for presumptive diagnosis. The symptoms, signs and radiographic manifestations of mucormycosis are nonspecific, and in order to obtain a conclusive diagnosis, direct identification of the characteristic hyphae or retrieval of the organism in culture from the specimens obtained from the site of infection are required. Direct examination of sputum, paranasal sinus secretions or bronchoalveolar lavage fluid is the most rapid approach for a first orientation of diagnosis and has to be considered as evidence of infection in blood cultures are rarely positive. Laboratory diagnosis is based on conventional methods such as direct examination and culture. [12,13]

The role of dentists is to identify and diagnose infection of the oral and maxillofacial region as early as possible, and to provide effective local surgical, pharmacological, and restorative treatments, in cooperation with other medical specialists Nonhealing of extraction sockets and immunocompromised states should alert high suspicion, judicious approach by the dentist and early diagnosis and appropriate management helps to reduce the size of defect. [1,4,14]

9. INVESTIGATIONS

KOH mount and microscopy, histopathology of debrided tissue (presence of Ribbon like aseptate hyphae 5-15mu thick branch at right angles), cultures, imaging and tissue biopsy are different measures for diagnosis of mucormycosis. Tissue biopsy leads to definitive diagnosis for mucormycosis. Biopsy should be taken from lesion and confirmed by microbiological tests. (Fig. 6.)

In suspected cases proper imaging including Computed Tomography and Magnetic resonance imaging of involved part should be done. Imaging tests includes CT of sinuses and CT chest for suspected pulmonary involvement and MRI brain to see the extent of systemic involvement which help in detection and extent of infected tissue and guide surgical debridement of tissue.[15] A reverse halo sign in CT chest findings is highly suggestive of mucormycosis. Currently, MRI with gadolinium contrast is investigation of choice in rhino orbital cerebral mucormycosis [4,16,17].

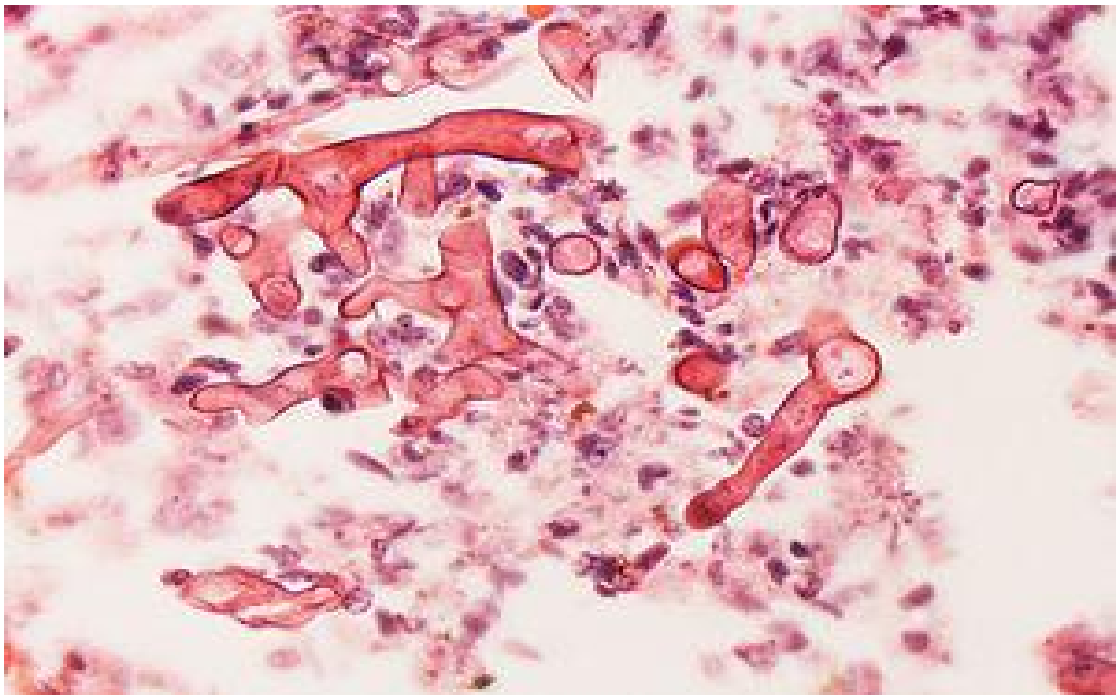

Fig. 6. Biopsy showing lesions

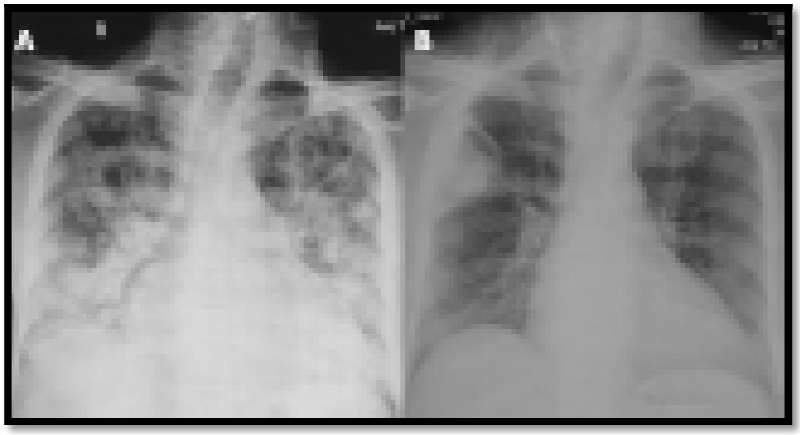

Fig. 7.Chest radiograph showing bilateral diffuse infiltrates

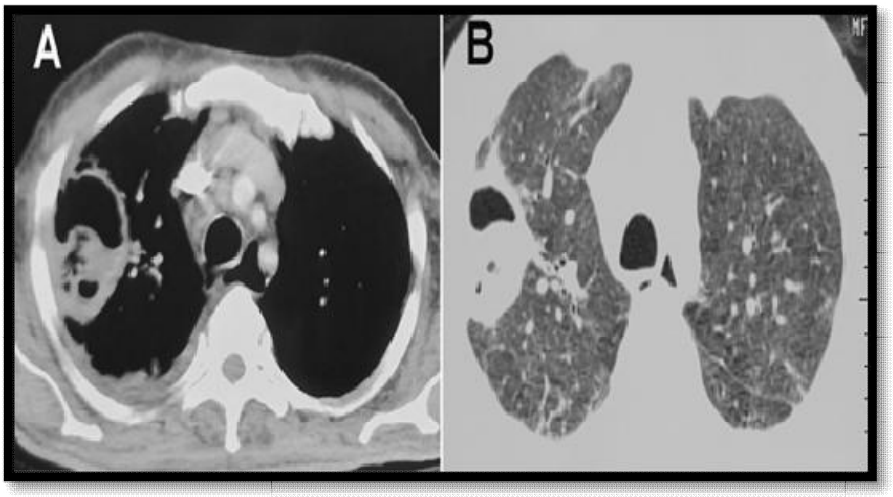

Fig. 8. Computed tomography showing thick-walled cavity in the right upper lobe of lung

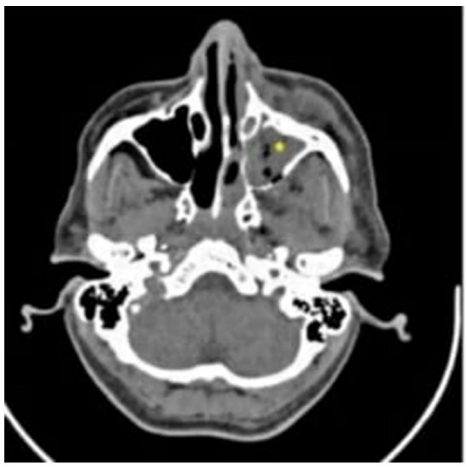

Fig. 9. MRI shows hyperintense signal intensity along peripheral left maxillary and frontal sinuses

10. PREVENTION

Simple tests like pupillary reaction, ocular motility, sinus tenderness and palatal examination should be a part of routine physical evaluation of a COVID-19 patient.

- Use masks if visiting dusty construction sites.
- Wear shoes, long trousers, long sleeve shirts, gloves while handling soil or manure.
- Maintain personal hygiene including thorough scrub bath.
- Adequate rest and proper hydration.
- Use of methylene blue in humidifiers.[8]

Dos

- Control hyperglycemia and blood sugar between 120-180 mg/dl.
- Monitor blood glucose levels post covid -19 discharge and in diabetics.
- Judicious use of steroids.
- Use sterile clean water for humidifiers during oxygen therapy.
- Use antibiotics and Anti-fungal judiciously.
- Saline nasal spray twice a day.
- ENT/OMFS evaluation on 3^{rd} ,7^{th} and before discharge (biopsy, nasal swab)

DONTs

- Do not miss warning signs and symptoms.
- Don't take blocked nose lightly mainly after recovered from covid-19.
- Don't hesitate for investigations related to fungal infection.
- Don't delay to initiate the treatment for mucormycosis [8].
-

11. MANAGEMENT

Treatment for mucormycosis require very fast treatment plans as disease spreads so rapidly resulting in irreversible significant tissue damage. Most of the patients will require both medical as well as surgical treatments. Indian council of medical research have published an evidence based medical advisory in the time of covid-19. According to guidelines

- Control diabetes and diabetic ketoacidosis.
- Reduce steroids
- No antifungal prophylaxis needed

Multidisciplinary team will facilitate steps for prevention and early diagnosis with rapid initiation of antifungal therapy as wells as medications to treat any debilitating underlying diseases and aggressive early surgical debridement with optimal correction of co-morbidities.

Antifungal therapy- Liposomal Amphotericin -B (initially intravenous) injection is the prime treatment for the treatment of this fungal infection.

- Inj. Liposomal amphotericin B 5-10mg/kg/day (intra cranial involvement-10 mg/kg /day)
  Or
- Inj. Amphotericin B lipid complex 5mg /kg/day
  Or
- Inj. Amphotericin B (1.0-1.5 mg/kg/day)

It should be diluted in 5% dextrose as it is incompatible with normal saline. It should be given over 2-3 hrs and should be started with full dose from the 1^{st} Day.

12. SECOND LINE OF TREATMENT AZOLE DERIVATIVES (STEP DOWN OR SALVAGE THERAPY)

After 14 days, patient can be shifted to oral therapy if clinically stable,

- Posaconazole is broad-spectrum azoles available in both parenteral and oral formulations.
- Dosage:

  1. 200 mg four times per day.

- Alternatively, Posaconazole delayed-release tablets (300 mg every 12 hours on first day, then 300 mg once daily) taken with food or Isavuconazole (200 mg 1 tablet thrice daily for 2 days followed by 200mg daily).

Patient may need additional surgeries and antifungal therapy for extended period of time (weeks to months)

12.1 Surgical Therapy

Depending upon the extent of lesion surgical debridement of necrotic tissue is done. Successful surgical treatment for mucormycosis

of the hard palate have been reported, and the operative procedures varied from simple resection of the hard palate to total maxillae/mandible resection.

i. Nasal and sinus involvement is present without bony erosion of maxilla/ zygoma and orbital floor: Procedure done is Endoscopy sinus surgery debridement

ii. Maxilla involvement

- Maxillectomy (partial/ total) with
- Zygoma debridement

iii. Maxilla + Minimal zygoma involvement—
- Maxillectomy (partial/ total), Zygoma debridement

iv. Maxilla+ Zygoma+ orbit

- Maxillectomy (partial/ total), Zygoma debridement
- Debridement of Orbital floor/ walls, Localised debridement of necrosed tissue in early localised orbital disease

I. Exenteration of eye in case of

1. Vision loss
2. Total ophthalmoplegia
3. Chemosis
4. Necrosis of orbital tissues

Although, loss of vision in not always the indication of exenteration

II. Frontal bone and skull base

- Anterior Table: Debridement
- Posterior Table: Cranialization
- Debridement of Osteomyelitis skull bone and involvement of the cerebral parenchyma (Safe maximum resection)

III. Prosthetic reconstruction should be planned after surgery, but interim solutions should be planned as feeding plate even before surgery of the jaws for better long-term outcomes [4].

Patient should be monitored and supportive treatment should be given post operatively

- Supportive care – kidney functions should be monitored.
- Postoperative respiratory care.
- Sepsis control
- Chest physiotherapy
- Nutritional care
- Psychological care [13]

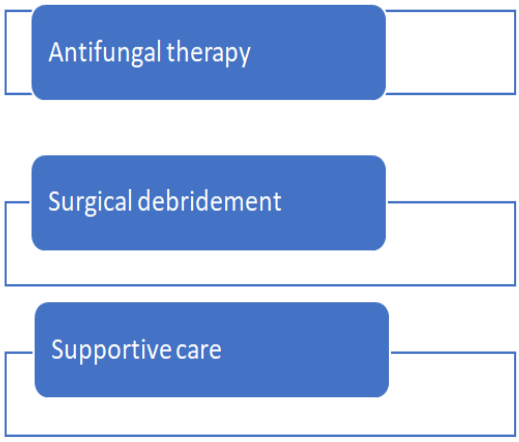

Fig. 10. Flow chart of prime treatment for the treatment

13. CONCLUSION

In conclusion, early diagnosis with biopsy, correction of the underlying disease that compromises the immune system, and appropriate pharmacological and surgical therapy is important for the management of mucormycosis. Multidisciplinary team treatment is often required. Appropriate surgical debridement with Anti-fungal therapy should be started at the right time so as to avoid life threatening complications of mucormycosis. Dentist should also keep a keen eye during dental examination and diagnosis of covid recovered patients and proper medical history including covid-19, diabetes and other patient's medical status should always be recorded so the treatment of patient can be started without any delay to avoid any life-threatening outcomes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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