Review Article

Mucormycosis of jaws – literature review and current treatment protocols

ABSTRACT

Mucormycosis is a modern-day lifestyle disease that has burst into the health-care scenario. It is an opportunistic fungal infection that proliferates into the immunocompromised host by invasion of the fungus into the paranasal sinuses, thereby invading the palate, maxilla, and orbit. Left untreated it invades the cranial components such as cavernous sinus, skull base, and brain. Mucormycosis invades blood vessels, making these infections highly angioinvasive. We reviewed 45 cases of mucormycois of the head-and-neck region from 2010 to 2020 on the basis of electronic search peer-reviewed journals in Medline (PubMed) database. Presenting symptoms, risk factors, history of extraction, and treatment were tabulated and the data were analyzed. The mean age of patients was 53.8 years. 73.93% of patients had diabetes mellitus, 13.63% of patients had no immunocompromised state, and 8.74% of patients had other medical disorders. About 34.78% of cases had a history of extraction prior to manifestation of symptoms. Mucormycosis remains difficult to treat disease with a high mortality rate. At present, the triad of clinician's awareness, appropriate antifungal therapy, and aggressive surgical intervention represents treatment protocols against the disease.

Keywords: Diabetes mellitus, maxilla, mucormycosis, orbit, *Rhizopus oryzae*

INTRODUCTION

The term "mucormycosis" was proposed by Baker and is a potentially life-threatening fungal invasion which is an aggressive, granulomatous, acutely infective, and opportunistic infection that occurs in immunocompromised patients. These infections are now more common with very poor survival rates.[1] It is related to very high morbidity and mortality. The aim of this article is to focus on the rapid emergence of mucormycosis in modern lifestyle and health-care scenario.

History

Meyer in 1855 recognized the pathogenicity of mucor organisms.[1] It was first described in humans by Paultaufi in 1885.[2] The first case of a patient with cerebro-rhino orbital mucormycosis who survived the disease was reported by Harris in 1995.[2]

LITERATURE REVIEW

An electronic search was conducted without time restriction in June 2020 from the following databases: PubMed/Medline, Science Direct, Cochrane, and Google Scholar. The term used for the search was Mucormycosis. Inclusion criteria comprised mucormycosis involving orofacial region; cases where presenting signs and symptoms, its duration, and treatment were mentioned, also reports published only between 2010 and 2020 were to be considered. Exclusion criteria included cases where presenting signs and symptoms are not mentioned or described vaguely. The titles, abstracts, and full reports (when required), of all reports identified through the electronic searches, were read independently by the authors.

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Thirty-six articles were obtained which fit our criteria [Table 1].[3-38] Data of 45 patients were noted. Male: female ratio found was 1.1 = 1. The mean age of patients was 53.8 years. 73.93% of patients had diabetes mellitus (DM), 13.63% of patients had no immunocompromised state, and 8.74% of patients had other medical disorders. 34.78% of cases had a history of extraction prior to manifestation of symptoms. Three mainstays of treatments used in all these cases were aggressive surgical debridement, antifungal therapy, and control of predisposing factors.

EPIDEMIOLOGY AND RISK FACTORS

It is potentially lethal, third-most typical angioinvasive infection after candidiasis and aspergillosis. In cases of DM, leukemia, malignancy, immunosuppressive therapies, and organ transplantations, mucormycosis has been commonly observed. DM is a predisposing factor for mucormycosis in 36%–88% of cases, particularly in uncontrolled ketoacidosis.[3,39-41] Mucormycosis has also been reported in victims of road traffic accidents and natural disasters in immunocompetent hosts.[39,42,43]

Data from a tertiary care center in India showed that 74% of patients with mucormycosis had uncontrolled DM. In 43% of these cases, it was diagnosed for the first time. In a meta-analysis of all mucormycosis cases reported from India, Reddy *et al*. stated that an overall prevalence of rhino-orbital-cerebral mucormycosis was 58%, cutaneous: 14%, pulmonary: 6%, disseminated: 7%, gastrointestinal: 7%, and isolated renal: 7%, which is consistent with the global trend. In India, a substantial number (16%–23%) of diabetics remain undiagnosed of their underlying disease before the presentation of mucormycosis.[3]

TAXONOMY

The most common etiological agents of mucormycosis in humans belong to two orders: Mucorales and Entomophthorales. It is caused by members of the Phycomycetes class of fungi belonging to the subphylum Mucoromycotina. The most common organisms causing mucormycosis are Rhizopus, Mucor, and Absidia. *Rhizopus oryzae* is the main causative organism in almost 70% of all cases.[1,44]

TYPES

Mucormycosis occurs in the following forms:

1. Rhino cerebral
2. Pulmonary
3. Gastrointestinal
4. Disseminated
5. Cutaneous
6. Miscellaneous.[45]

PATHOPHYSIOLOGY

Hyperglycemia, a typical feature in mucormycosis patients, causes excessive glycosylation of proteins like ferritin and transferrin. This adds to low pH strongly due to increased ketone bodies impairing their ability to chelate iron [Figure 1]. Hyperglycemia and low serum pH affect both the phagocytic effect of macrophages and the chemotactic and oxidative burst of neutrophils. Thus, it diminishes the main host defense against the invasion of mucormycetes.[46]

Rhizoferrin produced by fungal hyphae binds to serum iron. This rhizoferrin–iron complex is essential for fungal growth. Thus, diabetic ketoacidosis patients are more vulnerable to mucormycosis due to elevated levels of serum iron.[2]

Deferoxamine, commonly utilized in dialysis, is a bacterial siderophore and used by Mucorales as a xenosiderophore for acquiring iron from the host.[39,47,48]

Mucorales interact with epithelial cells, rhizopus adheres to and invades endothelial cells by specific recognition of the host receptor glucose regulator protein 78 (GRP78).[47,49] The fungal ligand that binds to GRP78 during invasion of the endothelium belongs to the spore coating (CotH) protein family Mucorales fungi harboring more copies of CotH cause more invasion.[47]

Its central nervous system spread can be attributed to invasion of local vessels and direct extension through the cribriform plate. Furthermore, retrograde extension of the fungi into the brain by means of nerves is another possibility.[50]

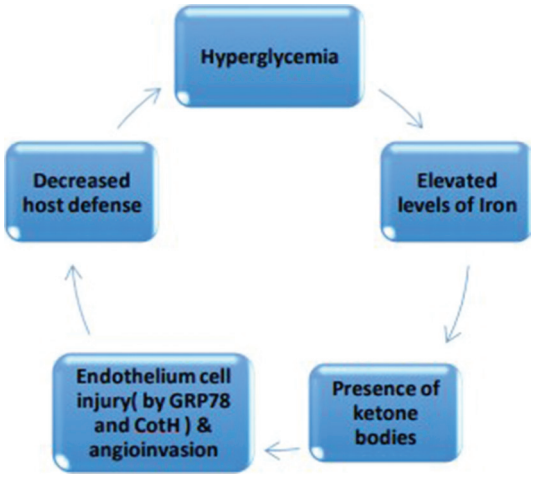

Figure 1: Pathogenesis cycle

Table 1: DATA of mucormycosis patients from year 2010-2020[3-38]

References	Year	Age/sex	Presenting symptom	Region	Medical history	Symptom duration	History of extraction	Treatment
Papadogeorgakis	2010	22/female	Facial edema, pain and double vision	Right paranasal sinus	DM	3 days	Yes	Subtotal maxillectomy IVAB posaconazole Obturator
Sujatha	2011	65/female	Nasal regurgitation with purulent discharge	Right eye and palate	DM HTN	15 days	No	IVAB Surgical debridement obturator
		57/male	Pain and swelling on face	Maxilla	DM	30 days	No	Debridement
Nirmala *et al*.	2011	12/male	Pain and swelling in the left maxillary posterior region	Maxilla	DM	4 days	No	IVAB
Marolda	2011	58/male	Edema and pain in right side of the face, peripheral facial paralysis, ophthalmoplegia	Maxilla	DM	-	No	Radical maxillectomy with orbital exenteration
Pandey *et al*.	2011	65/female	Exposed bone and halitosis	Maxilla	DM	1 month	Yes	Maxillary sequestrectomy Liposomal amphotericin B
		70/male	Intraoral unhealed wound exposed bone	Maxilla	DM Renal dialysis TN	1 week	No	Debridement Oral ketoconazole
		62/female	Pus discharge from upper left jaw	Maxilla	DM	1 week	Yes	Debridement of maxillary antrum IVAB
		42/female	Foul discharge from upper jaw	Maxilla	DM	2 months	Yes	Debridement of maxillary antrum IVAB
Kumar	2013	65/male	Pain and difficulty in taking food	Maxilla	DM	6 months	Yes	Surgical debridement
Madan	2013	58/male	Pain in right maxillary posterior with nasal congestion and headache	Maxilla	DM	4 months	Yes	IVAB
Pajpani	2014	82/female	Swelling and discomfort in the tongue	Tongue	Aplastic anemia	-	No	IVAB
Arakkal	2014	65/male	Painful ulcerations over the hard palate and nasal regurgitation	Maxilla	DM	6 months	Yes	IVAB
Nallapu *et al*.	2015	48/male	Pain in upper right back teeth and facial swelling	Maxilla	DM	30 days	No	Surgical debridement Liposomal amphotericin-B
		50/female	Pain, nasal regurgitation	Maxilla	DM	90 days	No	Itraconazole 100 mg BD
Nilesh	2015	72/male	Escape of fluid through nose (OAC)	Maxilla	-	-	-	Surgical debridement posaconazole
Motaleb *et al*.	2015	57/female	Diffuse painful swelling of right face, palatal necrosis	Right maxilla, nasal cavity, frontal and ethmoidal sinus	DM	14 days	Yes	Surgical debridement IVAB
Kumar N.	2015	63/female	Pain in upper jaw, nasal congestion, headache	Maxilla	DM	-	-	Surgical debridement IVAB
Arya A.	2015	54/male	Fluid discharge through nose, nonhealing extraction socket, epiphora	Maxilla and paranasal sinuses	DM Psoriasis	-	Yes	Surgical debridement Obturator IVAB voriconazole
Laihad	2015	46/female	Painful swelling of left face, difficulty in swallowing, facial paresthesia, trismus	Maxilla	-	-	-	HBO
Selvamani	2015	52/male	Painful swelling of right face, water discharge through nose	Maxilla	DM	-	-	Surgical debridement with anterior maxillectomy; IVAB

Contd...

Table 1: Contd...

References	Year	Age/sex	Presenting symptom	Region	Medical history	Symptom duration	History of extraction	Treatment
Ju	2015	66/male	Nasal obstruction and pain	Nose	TB	14 days	No	Wide excision of the necrotic portion of the nasal septum, craniectomy, and cranioplasty
		76/female	Facial and peri-orbital swelling	-	HTN DM TB	10 days	-	Wide excision
Reddy	2015	65/female	Nasal regurgitation of food with purulent discharge from the nasal cavity and right	Maxilla	DM HTN	15 days	No	Surgical debridement
		57/male	Pain and swelling on left side of the face	Maxilla	DM	3 weeks	No	Sinus debridement IVAB
		35/male	Palatal ulcer and nasal regurgitation	Maxilla	DM TB	-	No	Sinus debridement IVAB
Krishnagiri	2015	65/male	Stroke with right-sided ophthalmoplegia and left-sided hemiplegia due to MCA territory infarct	Palate	DM	-	No	Radical debridement of nasopharynx IVAB
Padmaja *et al*.	2016	14/female	Unconscious state, with skin lesions on nose and extending to both cheeks	Nose	-	-	No	IVAB
Gutierrez-Delgado *et al*.	2016	47/male	Paresthesia, pain, and swelling in the left zygomatic bone	Zygoma	DM	3 months	No	Debridement
Gunasekera	2016	39/male	Swelling, numbness of left side of the face and difficulty in moving the left eye	Maxilla	DM alcoholic	1 month	No	Surgical debridement IVAB
McSpadden	2016	63/male	Acute right submandibular neck edema	Mandible	CMML post BMT	73 days	Yes	Surgical debridement
Sivakumar *et al*.	2017	42/male	Black discoloration of the palate	Palate	Fracture of maxilla	2 weeks	No	Debridement IVAB
Afroze *et al*.	2017	50/female	Pain and swelling on face	Maxilla	DM Asthma	4 months	Yes	Maxillectomy
Ermias *et al*.	2017	18/female	High-grade fever, dry cough, fast breathing and difficulty of swallowing.	Hard palate	DM	8 days	No	Surgical debridement
Arora *et al*.	2017	55/female	Halitosis and chronic nonhealing wound of the left maxillary region	Maxilla	Hypothyroidism DM	1 month	Yes	IVAB Surgical debridement of maxillary sinuses
Richa S	2017	75/male	Denture instability and facial swelling	Maxilla	DM	4 months	No	Surgical debridement Liposomal amphotericin-B
Nilesh	2018	52/male	Escape of fluid through nose (OAC)	Maxilla	-	-	-	Surgical debridement
		37/male	Pain at extraction site	Maxilla	-	-	-	Surgical debridement
Yeo *et al*.	2018	59/F	Nasal obstruction	left middle turbinate	DM Asthma	-	No	Endoscopic debridement and middle turbinectomy
Pushkar G	2018	49/male	Teeth mobility with pus discharge	Maxilla	-	4 months	Yes	IVAB Sinus debridement, obturator
Diljith R	2018	60/male	Discharge from left nostril	Maxilla	DM TB	2 years	Yes	Amphotericin B Debridement obturator
Rajesh A	2019	48/male	Pain and swelling in right posterior teeth	Maxilla	DM	1 week	Yes	Local debridement Posaconazole 300 mg
Jangam *et al*.	2019	42/female	Pain and mobile teeth in the upper left back region	Maxilla	DM	6 months	Yes	Surgical debridement

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Table 1: Contd...

References	Year	Age/sex	Presenting symptom	Region	Medical history	Symptom duration	History of extraction	Treatment
Harsha	2019	40/female	Pain over the rightside of upper jaw and paresthesia over lateral part of nose and lip on right side	Maxilla	Fracture of the right maxilla DM	6 months	No	Right maxillary sinus curettage HBO therapy
Mtibaa *et al.*	2020	39	Purulent rhinorrhea and right nasal obstruction	Maxillary sinus	DM	20 days	No	IVAB Trepanation of the maxillary sinus HBO

DM: Diabetes mellitus, HTN: Hypertension, TB: Tuberculosis, TN: Trigeminal nerve, IVAB: Intravenous amphotericin B, HBO: Hyperbaric oxygen, OAC: Oroantral communication, MCA: Middle cerebral artery, CMML: Chronic myelomonocytic leukemia, BMT: Bone marrow transplant, BD: Bis in die

Mucor mainly spreads by angioinvasion causing mechanical and toxic damage to the intima of the blood vessel, resulting in thrombosis. It later invades the lymphatics and veins also. The thrombus causes emboli and vascular obstruction accountable for tissue necrosis.[43]

COVID-19-ASSOCIATED MUCORMYCOSIS PATHOGENESIS

COVID-19 patients are more vulnerable to fungal infection due to the immunocompromised system with reduced CD4+ and CD8+ lymphocytes and decompensated pulmonary functions which are seen in DM. Regardless of the involvement of the endothelial cells, the hyperinflammatory response in individuals with diabetes may exacerbate the "cytokine storm" and increase COVID-19 severity.[51,52]

These types of fungal infections are also more likely to occur in those patients who require intensive care unit or mechanical ventilation. The rate of secondary infection during a hospital stay in patients with COVID-19 (bacterial and fungal) has been reported to be 8%. In majority of COVID-19 patients which are attended by pulmonary and intensive care teams, it is important to sensitize the early signs and symptoms of mucormycosis to prevent delayed diagnosis and ensure timely referrals.[51]

DIAGNOSIS OF MYCOTIC INFECTIONS

Laboratory strategies employed for the diagnosis of fungal infections are:

1. Microscopic examination of fresh clinical specimens or histopathological preparations
2. Culture of the etiologic agent from clinical material
3. Serology and skin testing
4. Radiographic techniques
5. Polymerase chain reaction (PCR) methods to detect specific fungal DNA in clinical specimens.[53]

Invasiveness of fungal disease histopathologically can be determined by:

1. Hyphal forms within the submucosa with angiocentric invasion
2. Tissue necrosis with inflammatory cell infiltration in host.[54]

RADIOLOGIC IMAGING

Radiologic imaging can document the extent of the anatomic involvement, but it is not sufficiently specific to ascertain the diagnosis. Nowadays, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) with gadolinium scans are employed as early diagnostic tools.[3] Bone scintigraphy is more accurate compared to CT scans because bone erosion and remodeling in CT may be confused with osteomyelitis.[5]

Mucosal thickening, air–fluid levels, and bony erosion [Figure 2] are seen in CT scan. Bony sequestration involving maxilla and zygoma is diagnostic of aggressive osteomyelitic activity. In highly immunosuppressed patients, is highly suggestive of an aggressive fungal infection. Often in CT or MRI, the first sign of orbital involvement is extraorbital muscle thickening. Characteristic involvement of the basal ganglia on CT and MRI scans suggests the diagnosis of mucormycosis in patients with isolated cerebral infection.[55]

ENDOSCOPY

For confirming tissue ischemia and the extent of disease, nasal endoscopy is done. The appearance of pink tissue at endoscopy may often be misleading in the initial phase of fungal invasion. If the suspicion for disease is high, blind biopsies of sinus mucosa are undertaken to confirm the diagnosis.[55,56] Stress should be given on the role of endoscopy prior and after surgical debridement to verify residual disease which may warrant further surgery.

MICROSCOPIC EXAMINATION

Hyphae are microscopically identified with stains like H and E, periodic Schiff, and Grocott's methenamine silver (GMS),

and particularly, the type of hyphae whether septate (or) nonseptate is seen by GMS staining.[5]

Fresh material is preferred over paraffin-embedded tissue because formalin damages DNA. Grinding of the tissue should never be done as it may result in breakage of hyphae, leading to misdiagnosis.[45] Application of fluorescent stains (e.g. calcofluor-white, blankofluor) enhances detection of hyphal elements. Potassium hydroxide (KOH) method dissolves human material and makes fungal cells easily identifiable. Early diagnosis is often done with help of a KOH medium. Since the sensitivity of this method is comparatively low, phase-contrast microscopes can be used for the same.[1,57] The ideal stain, however, for the direct examination of fungus is a mixture of KOH and calcofluor-white.[53]

Due to the fragility of Mucorales hyphae which are frequently damaged during sample collection results in poor culture sensitivity. As a result, only approximately one-third of all microscopically positive specimens lead to a positive culture. Culture on Sabouraud's agar can be used.[4] Specificity is also an issue because isolation from nonsterile sites is usually indicative of contamination instead of disease.[58]

In tissue, Mucorales hyphae can often be distinguished by their broad (3–11 μm diameter), empty, thin-walled, mostly aseptate, ribbon-like hyphae that branch at right angles.[55] Nucleic acid amplification techniques that target the ribosomal DNA gene targets 18S, 28S, and internal transcribed spacer region are all used.[58] Detection of nucleic acid by PCR can potentially assist in speeding up the diagnosis of mucormycosis.[55]

CLINICAL MANIFESTATIONS

Rhino cerebral mucormycosis

Depending on the extent of disease clinically, it is classified into three stages:

1. Rhino-maxillary mucormycosis
2. Rhino-orbital mucormycosis
3. Rhino-orbital-cerebral mucormycosis.

Initial symptoms of rhinocerebral mucormycosis commonly includes headache, sinus pain, mouth or facial pain, congestion, blood tinged nasal discharge, ear symptoms, hyposmia, and anosmia. When extending from the sinuses into the mouth, the infection can produce sudden mobility of tooth, pus discharge from crevices, halitosis, painful necrotic ulcerations, perforation of the hard palate, rolled out gingival margins [Figure 3], and erosions of alveolar bone. The suggestive lesions are initially red, then violaceous and eventually black with thrombosis and tissue necrosis. Necrotic eschars are signs of rapidly progressing infections.[1,45,59]

Periorbital edema, proptosis, chemosis, and preseptal and orbital cellulitis indicate early signs of orbital invasion. Pain and blurring or loss of vision often indicates extension into the globe or optic nerve. Involvement of contralateral eye is suggestive of cavernous sinus invasion and thrombosis.[55]

The angioinvasive nature of the fungus may result in internal carotid artery thrombosis with extensive cerebral infarctions. Cerebral vascular invasion may lead to hematogenous dissemination of the infection.[55]

PRINCIPLES OF TREATMENT OF MUCORMYCOSIS

The basic principles of mucormycosis treatment include:

1. Risk stratification for severity of the disease
2. Intense attempts for early, clinical, and laboratory diagnosis
3. Timely initiation of an efficient antifungal therapy (monotherapy or combination therapy) along with aggressive surgical debridement of necrotic lesions

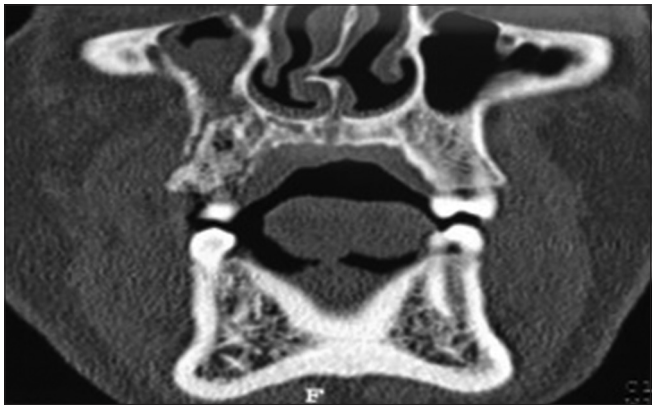

Figure 2: CT scan showing bone erosion.

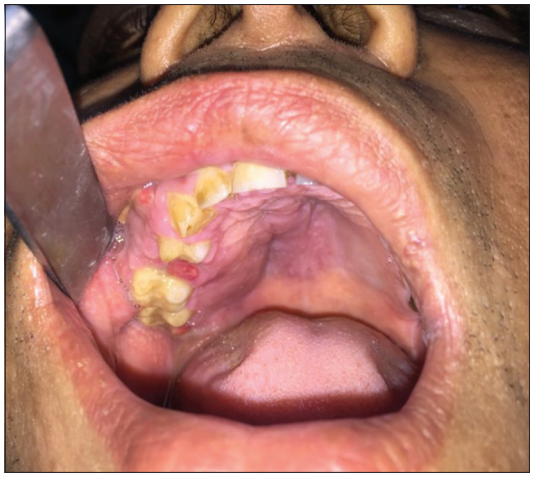

Figure 3: Buccal and palatal thickened gingiva.

4. Reversal of immunosuppression (discontinuation of chemotherapy and increase of neutrophils) and feasible control of the ketoacidosis.[40]

SURGERY

Surgical removal of infected tissues is of paramount importance in the treatment of rhino-orbital-cerebral disease. The effect of surgery on outcome is difficult to be defined. Surgical management should be initiated at the earliest to limit the fulminant spread of infection to contiguous structures.[55] For extensive disease, final treatment includes maxillectomy, orbital exenteration, and/or craniofacial resection.[40] The global guidelines for diagnosis and management of mucormycosis in 2019 by ECMM and Mycoses Study Group Education and Research Consortium strongly recommend an early complete surgical treatment whenever possible in addition to systemic antifungal treatment.[51]

Surgical debridement

1. Reduces the progression of the disease
2. Reduces fungal load
3. Provides a specimen for culture.

Early aggressive debridement should be performed on patients with a biopsy-proven disease or any patient suspected of having an invasive fungal disease and extension should be done till clear bleeding margins are exposed [Figures 4 and 5]. Endoscopy clearance is required if residual disease within the sinonasal cavity is suspected. Long-term clinical follow-up and regular postoperative imaging are required till radiological clearance of disease is established, thereby deciding the duration of antifungal therapy.

Early surgical excision of the infected sinuses and appropriate debridement of the retro-orbital space can often prevent the infection from extending into the eye, resulting in high cure rates (>85%). Intraoperative frozen sections can be used to demarcate the margins of infected tissues, sparing uninvolved tissues from debridement when possible (the "aggressive-conservative" approach).[55]

ANTIFUNGAL AGENTS FOR MUCORMYCOSIS

The European Conference on Infections in Leukemia (ECIL) 2017 and the European Confederation of Medical Mycology (ECMM) 2019 have given the following recommendations for mucormycosis, i.e. liposomal amphotericin B (L-AMB) as first-line treatment in adults. ECIL suggested that AMB lipid complex (ABLC) could be used in patients but without central nervous system (CNS) involvement. For neonates and pediatric population, L-AMB and ABLC are strongly recommended as first-line treatments. For neutropenic patients, posaconazole tablets or intravenous (IV) form are moderately supported and oral suspension form is marginally recommended, while isavuconazole is used as marginally supported therapy. For solid organ transplant patients, posaconazole and isavuconazole are marginally recommended in prophylaxis. Combinations therapy is not included in first-line treatment because of their lack of evidence in efficacy.[60]

Amphotericin B

AMB is considered the drug of choice for the primary treatment of mucormycosis. AMB binds with ergosterol, a component of fungal cell membranes, and leads to fungal death. This is the primary effect of AMB as an antifungal agent.[44]

It is infused with 5% dextrose solution because it remains stable. The recommended dosage of AMB deoxycholate is 1–1.5 mg/kg/day which results in a high toxicity rate. Complications include nephrotoxicity, thrombocytopenia, hypokalemia, rigors, and anemia.[45,61]

L-AMB having minimal nephrotoxicity with better therapeutic index than the traditional AMB deoxycholate is considered as the first line therapy of mucormycosis. The standard

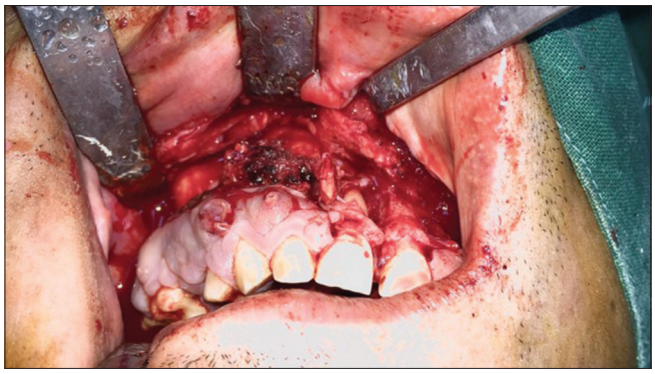

Figure 4: Surgical debridement of necrotic maxilla.

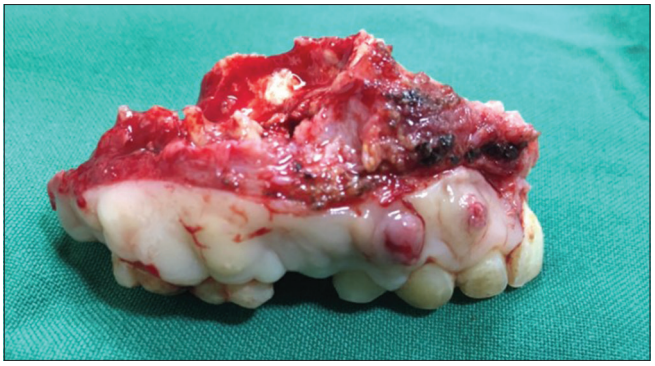

Figure 5: Excised Specimen of maxilla in toto.

daily dose of L-AMB suggested by current guidelines is 5–10 mg/kg/day. Since the cost is very high, poor patient compliance is often seen to complete the therapy.[5,40,45,55,54] Regular monitoring of renal function is mandatory during AMB therapy.

Posaconazole

IV and delayed-release (DR) tablets of posaconazole were recently developed and lead to better bioavailability and drug exposure than oral form. Due to higher serum levels, suspension DR tablets and IV forms are moderately recommended, while the oral suspension is only marginally recommended by ECMM as first-line treatment. Routine therapeutic drug monitoring (TDM) is strongly recommended.[60]

Current dosage for posaconazole in oral suspension form is 400 mg twice a day when taken with meals, or 200 mg four times a day when not taken with meals. Delayed Release(DR) tablets dose is 300 mg every 12 hours on first day and later 300 mg daily dose is given which is considered as a salvage treatment of mucormycosis.[40,55]

Isavuconazole

Isavuconazole is the biologically active agent of the prodrug isavuconazonium sulfate which is approved in the United States and in Europe for the treatment of mucormycosis when AMB is not feasible. IV and oral formulations are available. 200 mg of loading dose three times a day is given for 2 days and 200 mg daily thereafter. It is safe compared to other azoles, thus alleviating the need for TDM.[40] It is less hepatotoxic than other azoles and presents a better tolerance profile than L-AMB.[60]

ADJUNCTIVE THERAPY

The ECMM and ECIL strongly recommend that reversal of immunosuppression is a crucial pillar of therapy for mucormycosis, along with surgery and appropriate administration of antifungal agents.[60] Reversal of acid state by administration of sodium bicarbonate is able to partially block the ability of *R. oryzae* to invade endothelial cells, thereby restoring host iron chelation and neutrophil function. Iron chelators, a potential adjunctive therapy, act by means of reducing the available iron, thus inhibiting the fungal growth. G-CSF is moderately recommended in case of neutropenia and hyperbaric oxygen in diabetic patients.[40,45,60]

TREATMENT DURATION

There is no standard duration of treatment for mucormycosis. Decisions are made on an individual basis, and principally, antifungal therapy of mucormycosis is continued until resolution of all radiological, laboratory, and clinical signs and symptoms. In most of the cases, the antifungal therapy is given at least 3–5 weeks.[40]

COVID-19-ASSOCIATED MUCORMYCOSIS MANAGEMENT

COVID-19 has created a unique scenario where all aspects of the management are compromised, i.e. hyperglycemia is aggravated by the most effective therapy for severe COVID-19, due to glucocorticoids, coexisting ARDS and multiorgan dysfunction preclude timely diagnostic imaging and testing and the hospitals are overwhelmed by COVID-19 patients; hence, other essential services, including diagnostics and surgeries, are affected. Tocilizumab used in COVID-19 can be discouraged as it is targeting immune pathways. Hence, the mortality is higher than in non-COVID patients.[62]

The World Health Organization strongly recommends not using systemic corticosteroids in the treatment of nonsevere cases. Those patients who are in need of oxygen, with severity score on imaging, and excessive activation of body's inflammatory response, can be treated with glucocorticoids for a short period of time (3–5 days). The dose should not exceed the equivalent of methylprednisolone 1–2 mg/kg/day or dexamethasone 0.2–0.4 mg/kg/day. The National Institute of Health recommends the use of injection dexamethasone 6 mg/day for a maximum of 10 days for patients who are ventilated or require supplemental oxygen.[51] Therefore, stress should be given on judicious use of steroids to avoid flaring up of the fungal infections and encourage an early diagnosis of mucormycosis. For proven mucormycosis, early aggressive resection and IV antifungal drugs should be started for 2–3 weeks depending on the severity and are shifted to oral antifungal only after the biopsy is negative.[52]

CONCLUSION

It is important to reemphasize the extreme importance of preexisting diseases with iatrogenic factors that play in the progress of mucormycosis. Mucormycosis in the presence of predisposing conditions, especially uncontrolled diabetes, can cause lethal outcomes. Early diagnosis of the disease before it spreads from the portal of entry to the brain or lungs can increase survival rates. However, most important is aggressive surgical debridement with judicious use of antifungal agents. Modern lifestyle, poor host resistance, financial implications, and long-term therapy are key factors determining the outcome of the disease.

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Conflicts of interest

There are no conflicts of interest.

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