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Mucormycosis a Conundrum in COVID-19 Second Squall; Otolaryngologist Gauntlet a Juggernaut in Triage and Tutelage

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Abstract

Background and Aim: There is a rapid increase in the incidence of mucormycosis cases during the second wave of COVID-19. The aim of our study is to evaluate the risk factors, pathogenesis, management and challenges faced during the management in otolaryngologist's perspectives.

Methods: We conducted a cross sectional study on 50 post-COVID histopathologically proven mucormycosis patients from May 2021 to July 2021 in a tertiary care hospital Otolaryngological Department of Thanjavur Medical College. We collected details about COVID-19, symptoms, treatment taken, co morbidities, CT and DNE findings and management and analyzed with SPSS software.

Results: Overall 50 patients 66% are males belongs to middle aged to elderly population. Pre-existing diabetes was present in 72% patients and new onset in 28% with a statistically significant relation to the development of diabetic ketoacidosis [p value <0.05]. In our study we had a good recovery in 72% of the patients.

Conclusion: Mucormycosis is a fatal disease with significant morbidity and mortality. Management of this condition in post COVID patients is challenging due to various factors. Early diagnosis, prompt surgical and medical management with proper management of co morbidities will help to overcome these challenges and provides a satisfactory outcome.

Keywords: Mucormycosis; COVID-19; Diabetes mellitus; Surgical debridement

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Introduction

There was an unprecedented rise in mucormycosis cases, colloquially called the 'black fungus', amidst a massive second-wave of COVID-19 pandemic in India [1]. COVID-19 mainly causes respiratory symptoms which may be a rhinitis, or severe pneumonia [1]. Rhino-orbital mucormycosis is an invasive fungal infection which affects the paranasal sinuses and cause erosion of the orbital contents and can extend into skull base mucormycosis is a fatal [2], rapidly destructive, opportunistic infection, often seen in immunocompromised individuals. It is caused by fungi, of the order Mucorales, family Mucoraceae, which include the genera *Absidia*, *Mucor*, *Rhizopus*, *Rhizomucor*, and *Cunninghamella*. The germination of *Mucor* spores is favored due to hypoxia, in COVID-19, hyperglycemic states, metabolic acidosis, diabetic ketoacidosis , increased free iron levels and decreased oxidative and non-oxidative fungicidal mechanism of leukocytes due to immunosuppression because of various factors such as COVID-19 mediated, steroid induced or underlying comorbidities along with different other risk factors including prolonged hospital stay.

Mucormycosis is a debilitating condition with a mortality of 50%. Early suspicion of diagnosis, assessing the extension of disease by nasal endoscopy and radiological investigations, timely intervention of otolaryngologist by endoscopic surgical debridement along with concurrent intravenous antifungal agents and control of the original precipitating cause can reduce morbidity and mortality. Challenges faced by otolaryngologist in the management of this condition includes sudden surge in number of *Mucor* cases, non-availability of the antifungal drugs in initial period, lack of protocol for the proper prioritization of the patient selection, along with this the challenges of COVID-19. Infection both in terms of lung involvement which creates more anesthetic challenges. General anesthesia with endotracheal intubation is again risky for health care team due to viral transmission in aerosols [3].

Materials and Methods

A cross-sectional descriptive study on 50 biopsy proven mucormycosis patients with laboratory confirmed COVID-19 infection in the Department of Otolaryngology, Thanjavur Medical College, Thanjavur during the period from May 2021 to July 2021. Details of each patient was collected on excel sheet and analyzed using SPSS on the basis of various associations and correlations.

Data collected and evaluated on the basis of age, sex, date of admission, date of onset of mucormycosis symptoms and COVID-19 symptoms, signs and symptoms of mucormycosis and regarding features of COVID-19 infection, history of comorbidities, exposure to various risk factors including excessive use of steroids, treatment taken.

Detailed otolaryngological, ophthalmological and neurological evaluation to assess the extent of the disease. Blood investigation includes routine blood count, blood sugar, urea, creatinine, serum electrolytes, and plasma acetone. Diagnosis is confirmed based on histopathological examination (Figure 1) and microbiological examination of nasal swab and debrided tissue for fungal culture and KOH mount preparation (Figure 3) from the nasal cavity, paranasal sinuses and orbital fat. CT scan of paranasal sinuses and orbit (Figure 4), MRI paranasal sinuses with orbit with brain, and nasal endoscopy were done in all 50 patients selected for our study (Figure 1).

Treatment includes both medical and surgical line of management is planned according to the nasal endoscopic and diagnostic evaluation of CT which reveals the involvement of paranasal sinus. Medical management includes injection Liposomal Amphoterecin B given in all patients at a dose of 3 mg/kg to 5 mg/kg diluted in 100 ml of 5% dextrose given slowly over 3 h with serial monitoring of renal function and serum electrolyte. Injection regular insulin was also started in all the 50 patients with regular monitoring of blood sugar levels. Amphotericin is started empirically as soon as possible once there is a clinical, radiological and endoscopic feature of mucormycosis.

Surgical line of management is planned according to the extent of disease. Based on the diagnostic evaluation by endoscopy and CT, patients can be divided into 2 groups. 1) endoscopic surgical debridement (Figure 5) 2) Endoscopic sinus surgery with medial orbital decompression (Figure 6) 3) partial or total maxillectomy according to the maxillofacial involvement.

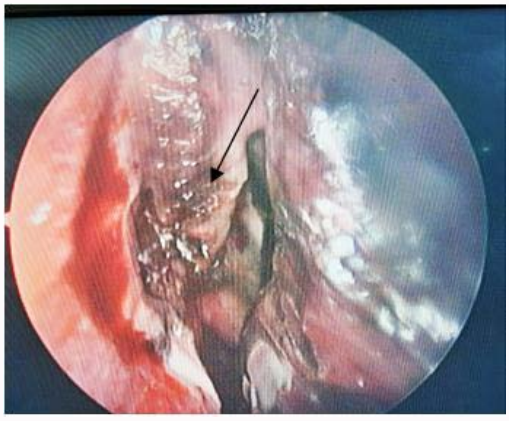

Figure 1: Showing endoscopic picture of blackish eschar in middle turbinate (black arrow).

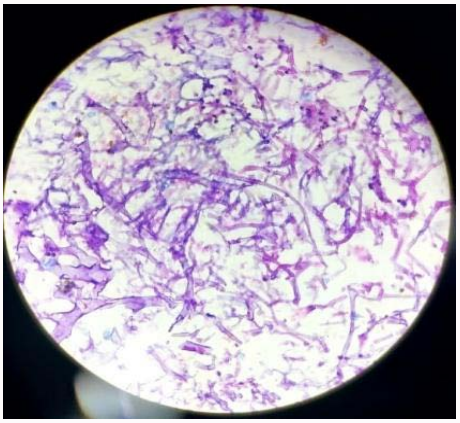

Figure 2: Showing histopathological image with H&E stain of branching aseptate hyphae.

In cases of sinonasal debridement, Modified Denker's approach is used in selected cases for a better visualization of the lateral extent of the disease, pterygopalatine fossa and infratemporal fossa can be approached.

In cases of proptosis with partial or complete loss of vision, medial orbital decompression is also performed which results in improvement of ocular symptoms and restoring vision. If there is erosion of maxilla, based on extension either posterior, lateral, anterior wall partial maxillectomy or total maxillectomy by Weber Ferguson incision is performed.

Data analysis

This cross sectional study estimated the prevalence of mucormycosis in COVID-19 patients and its perspectives in clinical presentation, diagnosis and treatment.

Results are divided into two sections:

1. Descriptive statistics using frequency distribution.
2. Inferential statistics using chi square test and fisher exact test.

Results

Age and demographic profile

A total of 50 patients selected for the study out of which 33 were male (66%) and 17 were female (34%). Age limit from 30 to ≥ 75 years with a mean age 52.56 years. Fifty percent of the cases were in 4^{th} to 6^{th} decades of life according to our study. As they belong to the working age group in our society, deterioration due to this illness makes them the dependent population. As the case load increases, which also reflects badly on the economy of our country.

Signs and symptoms of mucormycosis

Among the study populations (50), more than 70% of the mucormycosis patients had facial pain and swelling; next to it were headache (68%) Nearly 60% patients had eye pain, swollen eyes and significant lid edema on examination. Other ophthalmic symptoms were diminution of vision, proptosis, ptosis, and double vision.

Orbital involvement and vision loss

Among the study populations (50), orbital involvement seen in 60% of mucormycosis patients, 18% of the patient had complete vision loss.

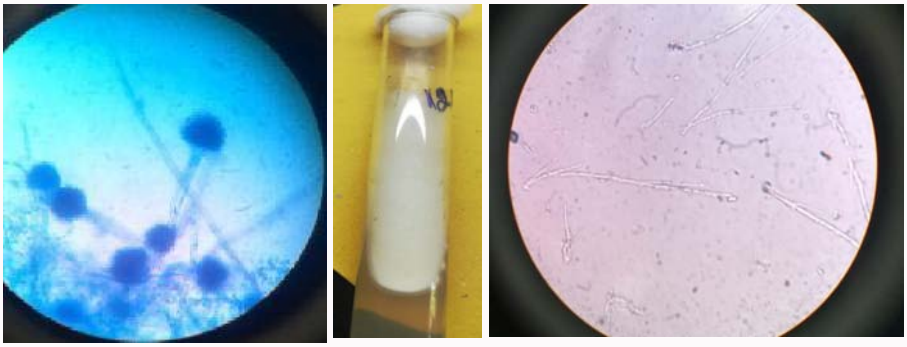

Figure 3: Showing microbiological picture of mucor species in lactophenol cotton blue stain (ribbon shaped hyphae), fungal culture in SDA Agar medium and KOH mount.

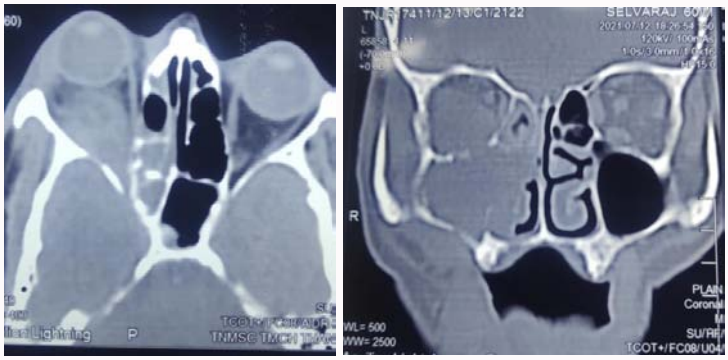

Figure 4: Showing CT PNS image of orbital extension and erosion of wall of maxillary sinus.

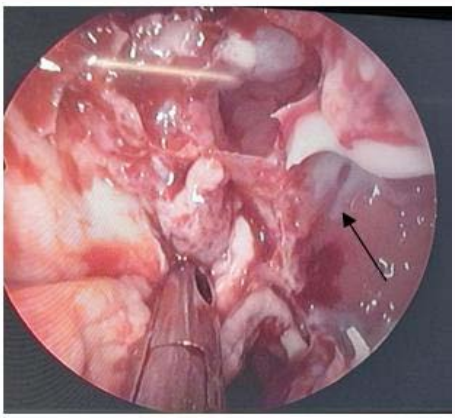

Figure 5: Showing endoscopic picture of exposed posterolateral wall of maxilla (black arrow) and other opened sinuses.

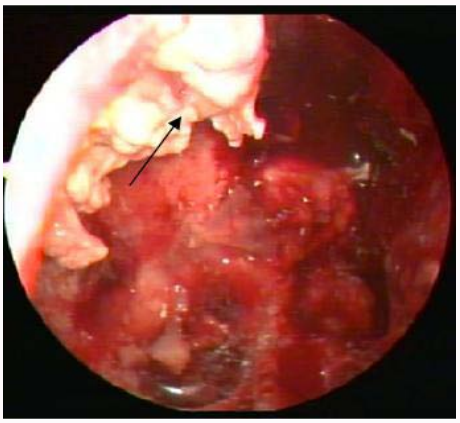

Figure 6: Showing prolapsed orbital fat into nasal cavity after orbital decompression (black arrow).

Risk factors for mucormycosis in COVID-19 patients

Among the study populations (50), more than 50% of the study population had steroid treatment for COVID infections, more than 70% were known case of type 2 diabetes and fifty percent of the study populations developed DKA. In the study 14 patients were having new onset diabetes detected during their COVID-19 illness. Excessive and unmonitored use of steroids is a risk factor for mucormycosis in COVID-19.

58% of patients who had received steroids for COVID-19 disease presented with post-COVID mucormycosis symptoms. This excessive use of systemic steroids itself contributes to the increased blood sugar level.

Duration between COVID positive and onset of mucormycosis

Management of mucormycosis: Among the study populations (50), More than 50% managed with orbital decompression.

Surgical Outcome: Among the study populations (50), more than 70% of the study populations had good outcome. 1 out of 50 patients died in our study, was operated had extensive spread of mucormycosis.

Discussion

We conducted a cross sectional study on 50 patients with COVID associated mucormycosis who were managed by the

Table 1: Age and demographic profile.

S. no	Variables	Frequency (50)	Percent (%)
1	**Gender**		
	Male	33	66
	Female	17	34
2	**Age group (years of age)**		
	30 to 45	12	24
	46 to 60	28	56
	61 to 75	9	18
	>75	1	2

Table 2: Showing frequency of vision loss.

Orbital Involvement	Frequency	Percentage
Present	30	60
Absent	20	40

Table 3: Showing incidence of diabetes, DKA.

S. no	Variables	Frequency	Percent (%)
1	**Steroid (50)**		
	Present	29	58
	Absent	21	42
2	**Type 2 diabetes (50)**		
	Known case	36	72
	New onset	14	28
3	**DKA(50)**		
	Present	25	50
	Absent	25	50

Table 4: Showing duration between COVID positivity and onset of mucormycosis. Based on our study most of the patients developed mucormycosis symptoms within 2-3 weeks of COVID infection.

Duration between covid positive and onset of mucormycosis (50)		
<10 days	8	16
11 to 20 days	16	32
21 to 30 days	20	40
31 to 40 days	3	6
>40 days	3	6

Table 5: Showing frequency of management of mucormycosis. Among the study populations (50), more than 50% managed with orbital decompression.

Endoscopic Management(50)	Frequency	Percentage
Fess with orbital decompression	26	52
Fess with debridement	24	48

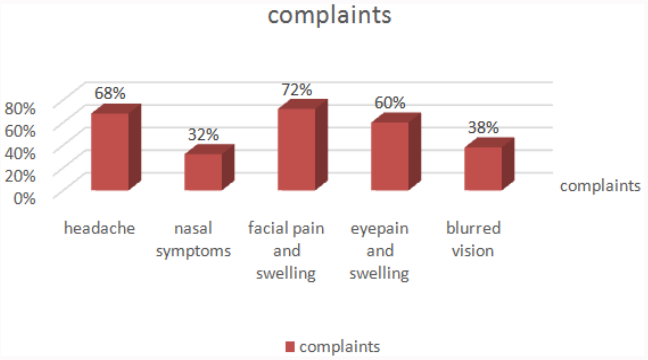

Chart 1: Showing distribution of various symptoms.

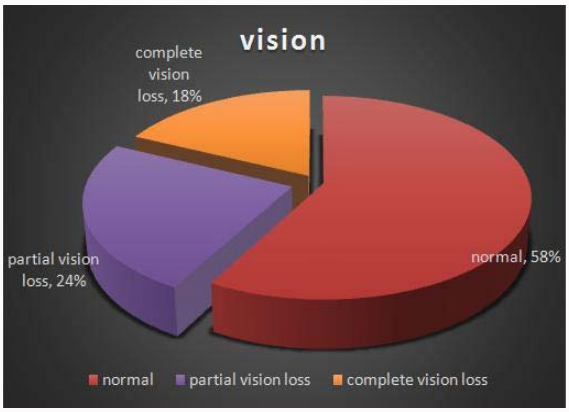

Chart 2: Showing frequency of vision loss.

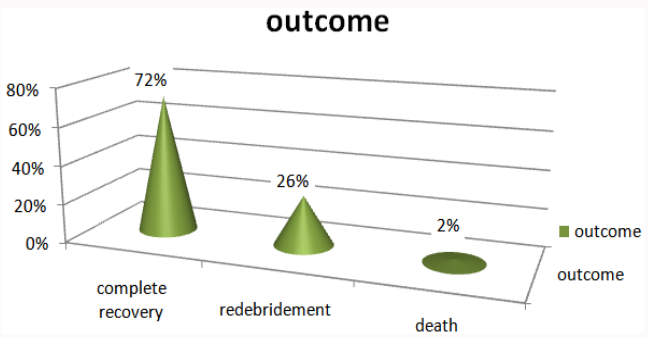

Chart 3: Frequency distribution of outcome.

department of Otorhinolaryngology. This study was focused on the clinic epidemiological profile of the disease, risk factors, diagnosis, management and outcomes and difficulties faced in the management.

The age and demographic profile of the patients we encountered are mainly middle aged to elderly persons with 66% are males. Decreased incidence of mucormycosis in females is pointing to the protective role of estrogen in preventing fungal infection [4].

Recent studies show that there is a positive association between COVID-19 and hyperglycemic state. Misra et al. [5] have studied about the behavior of new onset diabetes in those who diagnosed with COVID-19. The interesting observation is that these patients had more severe hyperglycemia which is proportional to the severity of COVID-19 infection various factors leading to this condition includes increased release of inflammatory mediators leading to cytokine storm, excessive steroid use, and virus mediated pancreatic beta-cell damage.

Direct virus mediated beta cell damage is caused by direct attachment of virus to the ACE receptors of pancreatic beta cell which lead to beta cell destruction and lead to the development of insulin dependent diabetes mellitus. Many incidence of SAR-CoV-2 associated acute pancreatitis is also reported. Insulin dependent diabetes usually presents with hyperglycemic states with diabetic ketoacidosis.

Another mechanism is triggering of beta-cell autoimmunity by

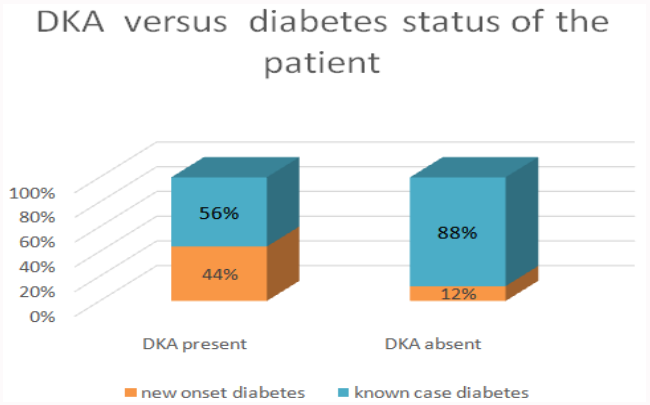

Chart 4: Showing correlation of DM and DKA in POST COVID patients (p value <0.05 significant), P value by fisher exact test. Among the study populations, more than 50% of the known case of the diabetes patients had developed DKA following COVID-19 infection and treatment.

virus which produces antibody against pancreatic beta-cell antigens. The etiopathogenesis of type 1 diabetes associated with other viral infections like mumps, cytomegalovirus rubella virus is due to the release of antigens from the damaged pancreatic beta cells into the systemic circulation leads to the activation of T lymphocytes which is the causative factor for the development of autoimmunity and further pancreatic damage [6].

Severe systemic inflammatory response triggered by COVID-19 infection produce an increased stress to our immune system which further worsens the glycemic status. SARS-CoV-2 infection triggers the release of hyperglycemic hormones like glucocorticoids leading to uncontrolled blood glucose levels in diabetic patients, severe COVID-19 lead to disseminated activation of the immune system which causes release of pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor (TNF) alpha, both of which are known to induce insulin resistance and hyperglycemia [7].

In our study we found a statistically significant relationship between the diabetes and development of diabetic ketoacidosis with a p value of 0.01 in patients with COVID-19 infection both in known cases and new onset cases of diabetes. In the case of new onset diabetes among 14 patients, 11 developed diabetic ketoacidosis. This shows a trend towards insulin dependent Diabetes Mellitus. (Type 1 DM). In the case of known case of TYPE 2 DM more than 50% developed DKA.

Significance of this correlation is that mucormycosis is an opportunistic fulminant infection which occurs in patients with uncontrolled diabetes mellitus and diabetic ketoacidosis. Hyperglycemic states increase the expression of GRP78 which acts as an endothelial receptor for *Mucor* fungus. Acidotic state which occurs with hyperglycemic states, leads to deterioration of cellular immunity. In normal individuals iron is found in the bound state with transferring and ferritin. In acidic pH the ability of iron binding decreases which lead to increased availability of serum free iron to the fungi. Fungal hypha produce a substance called rhizoferrin, which has higher affinity for iron. This iron-rhizoferrin complex is then taken up by the fungus through siderophores or iron permease for its important metabolic functions which increase the invasiveness of the fungi. Phycomycetes can grow fast and can destroy the sinuses within a day. There is impairment of chemotactic and phagocytic activity in DKA [8,9]. The *Rhizopus* species produce an enzyme called ketoreductase which has the ability to utilize patient's ketone bodies and can thrive well in low pH. Increased use of multivitamin tablets containing zinc and iron also increase the availability of free iron. Our study also suggests a statistically significant relation between DKA and development of mucormycosis.

Injury to the airway epithelium in COVID-19, can create an opportunity for fungus to invade tissues [5,10]. The blatant misuse use of steroids in the symptomatic management of COVID-19 paved the way for its role as a risk factor of mucormycosis [11]. The indiscriminate use of steroids even in mild COVID-19 infection provides a 'fertile soil 'for the development of mucormycosis in an already diabetic patient. Along with the adverse effect of steroid induced hyperglycemia corticosteroids inhibits the migration, ingestion and phagolysosome fusion of macrophages. A total dose of methyl prednisolone of 2 g to 7 g can be a predisposing factor for the development of mucormycosis [12]. In diabetics even a short duration of steroid therapy can lead to mucormycosis [13]. In ECCM study it has been found that 46% of patient who developed mucormycosis had history of steroid usage one month before and 44% had received immunosuppressant's [14]. The use of steroids in the treatment of COVID-19 infection must be under judicious monitoring and to be started only after proper triage of the patients.

Evolution of mucormycosis in patients is depends on the severity of underlying risk factors and immune status of the patient. Each patient has to be evaluated with high index of suspicion for the earlier diagnosis and better outcome. The clinical presentations may vary from sinusitis to signs of intracranial extension. As the pattern of spread differs in each patient, the symptomatic profile also varies from patient to patient. Facial pain and unilateral facial swelling are the, major symptoms of the patient we found in our study. The common sinus involved is maxillary sinus (94%) followed by ethmoid sinus (92%). The red flag signs to look for are cranial nerve palsy, diplopia, periorbital swelling, proptosis, orbital apex syndrome. Intracranial extension suspected if there is associated disorientation and altered sensorium. Cavernous sinus involvement is also common which presents commonly with cranial nerve palsy and eye signs.

Early diagnosis and initiation of management is important for a good outcome in mucormycosis. Histopathological examination of biopsy specimen using hematoxylin and eosin staining reveals branching aseptate hypha, typical of *Mucor* species, along with evidence of angioinvasion and tissue necrosis [10]. Fungal culture, KOH mount and staining by lactophenol cotton blue by microbiologist reveals ribbon shaped aseptate hypha with absent rhizoids provides further confirmation. CT and MRI is helpful in assessing the extent of the disease. Post-contrast enhancement is seen in the edematous diseased mucosa. Non-enhancing areas seen with in the diseased turbinate help in early detection of mucormycosis known as the "black turbinate sign" [15-18].

Medical management of all the patients is with Liposomal Amphotericin B injection in the dose of 3 mg/kg to 5 mg/kg body weight diluted in 100 ml 5% dextrose over 2 h to 3 h for a minimum period of 10 days. Challenges in the medical management is mainly about the management of adverse effects of Amphotericin B. This to a certain extent is tackled by the use of Liposomal Amphotericin in the place of conventional Amphotericin B. Lipid complex Amphotericin B is less nephrotoxic than conventional Amphotericin B. This lipid based formulation increases the circulation time and alters the biodistribution of the associated Amphotericin B. Because drugs

complexed with lipids will remain in the blood vessels for longer time periods which helps them to achieve greater concentration in tissues with increased capillary permeability along with the circulation. The inflamed tissues have high capillary permeability when compared to normal tissues due to endothelial damage. This method of increasing the localization of drugs to diseased sites is referred to as passive targeting. It enhances delivery of the agent to the fungi, infected organs, and phagocytes with lower toxicity, while maintaining antifungal efficacy through significantly higher sustained tissue levels of the drug. In the target site the drug lipid complex is broken down with the help of lipases from surrounding inflammatory cells. The lipid formulation has increased ability to cross the blood brain barrier to reach the CSF compared to conventional Amphotericin B [19]. Amphotericin is started empirically in suspected patients continued in the post-op period. Proper maintenance of charts for hemoglobin levels, urea, creatine levels, serum electrolytes, blood sugar, and input and output of the patient. On discharge the patient is given tablet Posaconazole for a period of 21 days. Management of underlying comorbid conditions is necessary for a good outcome.

Coexisting COVID-19 severity, multiple comorbidities, poor general condition of the patients makes it a difficult scenario in terms of anesthesia complications. Surgical protocol for endoscopic debridement based on involvement of paranasal sinus, erosion of orbital content and invasion of skull base. In surgical treatment, due to the different patterns of spread and extension of the disease, a general surgical protocol cannot be adapted in the case of mucormycosis. Each of the cases has to be planned individually and at some instance has to be modified intraoperatively makes it a challenging situation for the operating surgeon. This is one of the major challenges faced by otolaryngologists in the surgical debridement. Surgical modalities vary from mere sinus debridement to extensive debridement up to infratemporal and temporal fossa. In complicated cases destructive procedures like orbital exenteration and maxillectomy has to be considered. In our study population we have got a good recovery in 72% patients with post operative DNE showing based on the post-operative follow-up is by weekly diagnostic nasal endoscopic examination and planned accordingly. Only 26% required redebridement based on our study.

In a developing country like India the explosive rise in the number of COVID-19 cases lead to major infrastructure related problems like decreased availability of hospital beds, scarcity of hygienic oxygen supplies, usage of tap water in flow meters, improper sanitation of nasal cannula and oxygen masks, prolonged usage of nasal cannula causing mucosal abrasions can also be contributing factors for development of mucormycosis.

It has been well-documented that Otorhinolaryngologists are at high risk of getting exposed to COVID-19 as the patient are taken up for emergency surgical procedure within a short period of COVID-19 RT-PCR negative results these as they come in close contact with the patient during examination as high viral loads of COVID-19 being present in the upper aero digestive tract in the infected patients. Diagnostic nasal endoscopy and debridement was done with proper precautions during COVID-19 pandemic for facing this challenge.

- All patients were subjected for COVID-19 by RTPCR swab test and CT thorax was also done in positive patients. Earlier positive patients were taken up for emergency surgical debridement after resolution of COVID symptoms and one negative COVID RT-PCR report.
- Operating surgeons used Personal Protective Equipment (PPE) and N95 mask with face shield while execution of emergency surgical debridement.
- Minimal team members was present during surgical procedure, for minimal exposure to the operating team.

Conclusion

Rising incidence of mucormycosis in COVID-19 second squall is "mystery and misery" situation because of its sudden increased morbidity and mortality. Since the major prey for the fulminant mucormycosis are debilitated and immunocompromised individuals, the management of these patients is really challenging in various aspects. Early suspicion of the diagnosis and timely intervention is very much important in reducing the morbidity and mortality. Examination of post COVID diabetic patients by an otolaryngologist is mandatory in follow up. Proper preoperative and postoperative diabetic control is one factor important in determining a successful surgical outcome. COVID-19 makes the situation tough for otolaryngologists in terms of exposure to the infection during emergency endoscopic surgical debridement. Despite of all these challenges we achieved a successful outcome of about 72%. We conclude that in spite of all the challenges we can overcome this fatal disease by a multidisciplinary approach. Physician must be alert about mucormycosis symptoms during and post-COVID infection especially in diabetic and immunocompromised patients. Otolaryngologists by early diagnosis, proper clinical and diagnostic evaluation and prioritization of the cases (triage) based on diagnostic evaluation, case based surgical approach, prompt preoperative empirical and postoperative antifungal therapy along with concurrent control of comorbid conditions by the physician lead to a good outcome which not only increase the chance of survival but also improves the quality of life by preventing permanent cosmetic disabilities and helps in restoration of impaired vision.

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