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Original Research Article

Post surgery mucor recurrence in COVID-19 associated mucormycosis patients of a tertiary care centre

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ABSTRACT

Background: Together with COVID-19 infection, we saw an outbreak of COVID associated mucormycosis (CAM). These patients were treated with antifungals, aggressive surgery, control of diabetes and other predisposing factors. But as demand increased, there was shortage of antifungals. So patients underwent relapses. The aim of study was to evaluate the causes and relevant factors predisposing to recurrence and tools used to evaluate recurrence and extent of disease in relation to primary disease.
Methods: Prospective study of 160 CAM patients who were discharged successfully after surgery and kept under regular follow up by endoscopy, CRP, blood sugar monitoring.
Results: Our study of 160 follow up cases of CAM in whom 21 patients had recurrence. There were 18 males and 3 females. The most common affected was between 50-60 years. 67% of recurrent cases had poor diabetic control, 81% suspicious of recurrence in endoscopy, 86% showed rising trend in CRP (>5 mg/dl). These patients were further evaluated with radiological investigations like MRI and CBCT (cone beam CT). MRI detected recurrence in 38% whereas CBCT detected 62%. Most common site of recurrence was maxilla. All recurrent cases underwent surgical debridement and were given 5 gm of liposomal amphotericin.
Conclusions: Mucormycosis is an invasive fungal disease. COVID patients in whom immunological status are altered, diabetic or immunocompromised should be kept under surveillance by endoscopy, CRP and blood sugar monitoring. Though CAM patients are treated with surgery and antifungals, they should be under regular follow up for more than 6 months. Diabetic control helps in curbing the rapid spread of CAM. Suspected cases should undergo radiological investigations like MRI and CBCT. Recurrent/residual disease of mucormycosis can be tackled and treated successfully.

Keywords: COVID associated mucormycosis, Amphotericin, CBCT, Maxilla

INTRODUCTION

The rapid global spread of the coronavirus disease led to the declaration of COVID-19 as a pandemic on 11 March 2020 (organization, 2020). Together with the COVID-19 infection, a rare fungal infection-mucormycosis colloquially known as black fungus has been increasingly found and due to the sheer magnitude of its outbreak Indian health ministry declared it as epidemic.[1] Mucormycosis (zycomycosis or phycomycosis) is an acute fulminant, fatal, opportunistic deep fungal infection caused by genera *Rhizopus*, *Rhizomucor* and *Absidia*. Mucormycosis occurs in patients with certain predisposing medical conditions such as immunosuppression and diabetes. Other risk factors such as the long-term use of steroids, oxygen therapy,

antibiotics, multivitamins and zinc, mucosal erosion secondary to the aggressive use of steam inhalation or the use of high-flow oxygen have also been considered as factors promoting fungus colonisation.[1]

Mucormycosis is categorized into rhinocerebral (most common form), pulmonary, cutaneous, gastrointestinal or disseminated. Rhinocerebral form can be further subdivided depending on the tissues being affected as rhino nasal or rhino maxillary, rhino orbital and rhino orbito cerebral.[2]

In our centre we operated 160 mucormycosis cases and 21 recurrent patients. All the patients were kept under follow up. The clinical features of mucormycosis include nasal stuffiness, foul smell, epistaxis, nasal discharge, unilateral facial oedema, diplopia, proptosis, pain and redness around eyes and/or nose, loss of vision, restriction of eye movements, palatal or palpebral fistula, blackish discolouration over bridge of nose/palate, prolonged fever, headache, toothache, loosening of teeth, jaw involvement, altered mental status.[2]

The follow up strategy we followed was endoscopy and CRP of all patients and suspected samples sent for KOH mount and fungal culture. In those patients who had endoscopic findings suspicious of recurrence, CRP elevated or any evidence of positive fungal stains in KOH, radiological investigations were done-MRI paranasal sinus+orbit+brain with T2 weighted gadalonium enhanced/CECT PNS depending on the symptoms. Due to financial constraints of some patients, MRI was not done and CBCT, a cheaper investigation compared to MRI was done. CBCT, which is a comparatively recent scanning technology in dentistry, provides images equivalent to CT at reduced costs and radiation doses. The radiation dose to the patient with CBCT is 40% lesser than that of multi-slice CT dose but is 3-7 times higher than conventional panoramic radiograph exposure dose.[3] If CBCT shows bony erosion and sinus involvement in an immunocompromised patient, invasive fungal sinusitis should be one of the differential diagnosis.

Treatment is aggressive surgical debridement, strict glycemic control and injection amphotericin B. Surgical debridement in our set up included endoscopic sinus surgery debridement, maxillectomy (partial/total) with/without zygoma debridement, exploration of pterygoid plates and pterygopalatine fossa, debridement of orbital floor/walls, orbital exenteration if necessary.

Aims

The aims of the study were to evaluate the causes and relevant factors predisposing to recurrence in post surgery; the tools used to evaluate the recurrence and extent of the disease in relation to primary disease.

METHODS

Study place and period

160 CAM patients of Department of Otorhinolaryngology and Head and Neck Surgery, NSCB medical college, Jabalpur who were discharged successfully after surgery and kept under regular follow up between April 2021 to September 2021.

Study type

This was a prospective observational study.

Inclusion criteria

Patients who gave consent; patients who received both surgical and medical treatment and discharged asymptomatically with recurrence at new site; patients with radiological evidence of recurrence of mucormycosis were included in the study.

Exclusion criteria

Patients with negative consent; patients lost to follow up or succumbed to death were excluded.

Procedure

After taking written informed consent, patients underwent a thorough history taking and comprehensive ear, nose, throat and neck examination. Endoscopy, KOH, CRP, RBS/HBA1C was done in all patients. All suspected recurrent cases underwent radiological investigations (MRI/CBCT).

Ethical approval

Institutional Ethics Committee was approved for this study.

Statistical analysis

The data of the present study was fed into the computer and after its proper validation, checked for error, coding and decoding compiled and analysed with the help of SPSS 20 software for Windows.

RESULTS

Our study group comprises of 160 follow up cases of CAM in whom 21 patients had recurrence. There were 18 males and 3 females. The patients aged between 50-60 years (55%) were most affected and least affected were between 30-40 years (10%).

Out of 21 patients, 90% of cases were known diabetes. 12 patients were affected with other systemic conditions, one

patient each with anaemia, pneumonia, pituitary adenoma and 7 with hypertension.

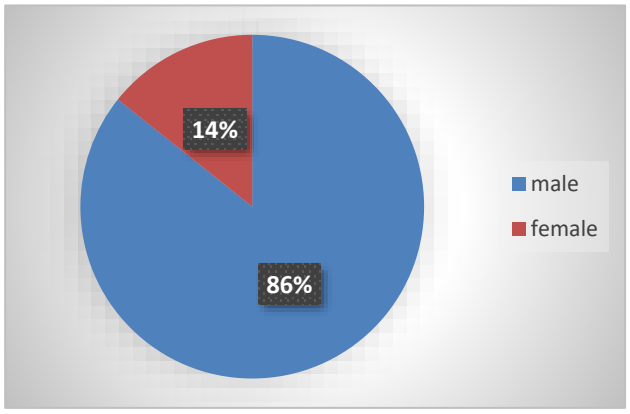

Figure 1: Sex distribution of patients.

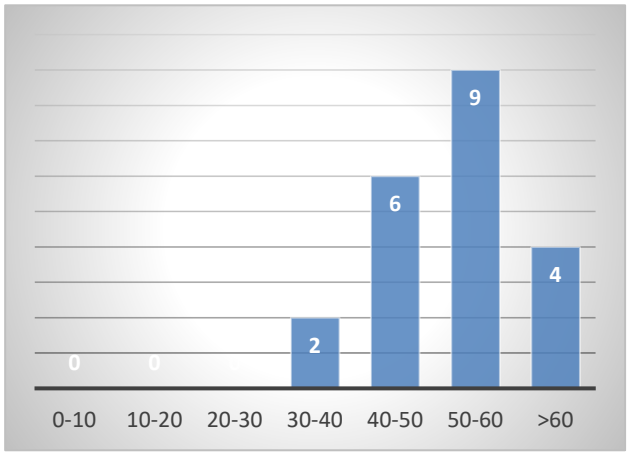

Figure 2: Age distribution of patients.

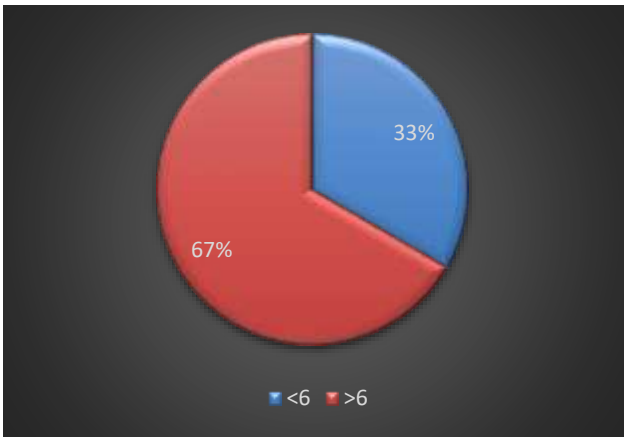

Figure 3: Diabetic status/HbA1C of CAM recurrent patients.

67% of cases were having poorly controlled diabetes in post surgery follow up period (HbA1C >6).

Endoscopic follow up was done in all patients. Findings such as yellow/extensive crusting, foul smelling discharge and any fungal debris were considered suspicious of recurrence. 81% of patients in our study showed these findings in endoscopy.

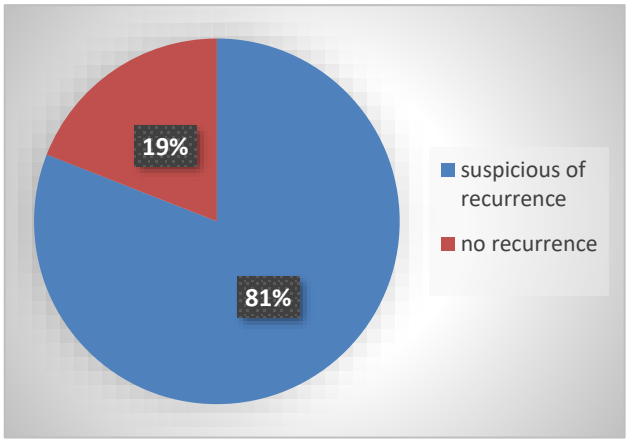

Figure 4: Post surgery endoscopy.

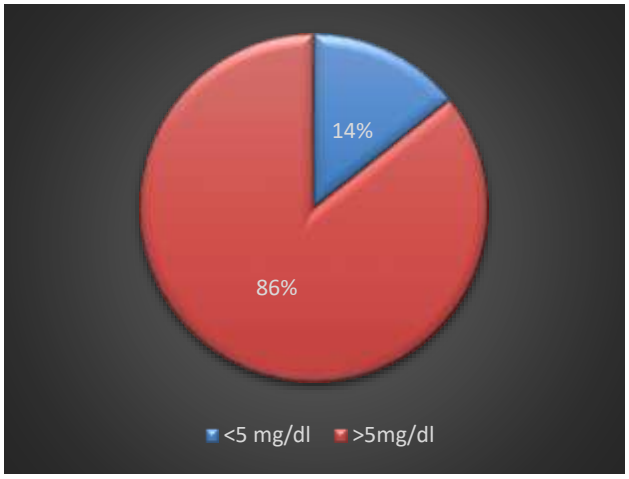

Figure 5: Post surgery CRP.

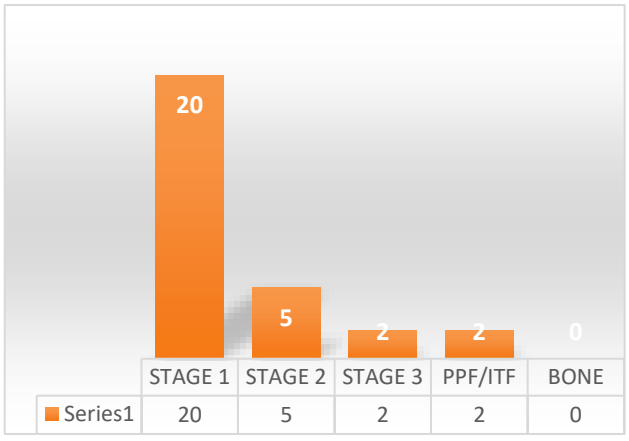

Figure 6: Extend of disease in initial MRI.

In post surgery follow up of patients using CRP, it was seen that 86% showed increasing trend of CRP (>5 mg/dl).

Patients in whom endoscopy showed suspicion of recurrence and rising trend in CRP were further evaluated using radiological investigations.

Initial pre op MRI (before first surgery) showed disease in nasal cavity (turbinate) and paranasal sinuses in majority of cases with black turbinate sign. Only 2 patients had pterygopalatine fat stranding and 2 patients with intracranial extension. Orbital involvement (lamina papyracea and extraconal compartment) was seen in 5 patients but vision was present (counting fingers 6 feet).

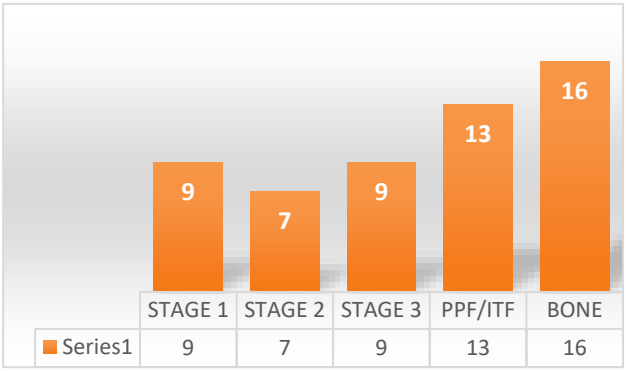

Figure 7: Extend of disease in second MRI.

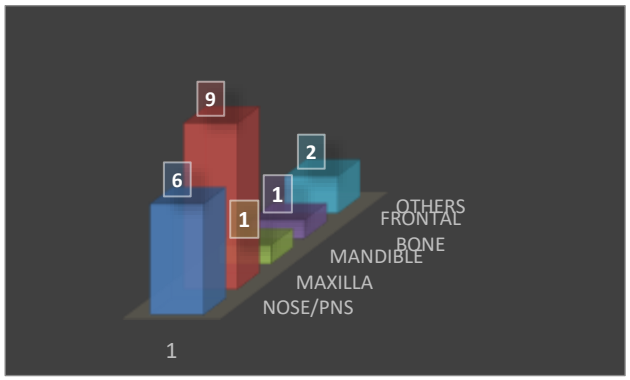

Figure 8: Extend of disease in CBCT.

Repeat MRI in suspicious cases of CAM (second MRI) showed involvement of pterygopalatine and infratemporal fossa in 13 patients. Orbital involvement with involvement of medial wall and inferior wall seen in 7 patients. Intracranial extension was seen in 9 patients. MRI showed some suspicion of erosions of bone such as maxilla in 16 patients.

On basis of MRI report, 38% of cases showed actual recurrence.

CBCT was used as special diagnostic tool in our study which showed recurrent disease in 62% of these 21 recurrent cases and of that most common site was maxilla (alveolus) 47% followed by paranasal sinuses 32%.

It was seen that comparing MRI and CBCT in our study, 38% showed recurrence in MRI and 61.9% detected to have recurrence in CBCT.

DISCUSSION

The COVID-19 pandemic which originated in Wuhan, China in late 2019 and paralyzed the world in 2020 posed unique problems to certain high-risk groups, especially the diabetics.[5] We were in the middle of the COVID-19 pandemic and the second wave had brought in a sudden surge of mucormycosis, a disease, which was very rare once, had now started to become endemic. Mucormycosis the so called black fungus was an angioinvasive infection due to filamentous fungi of the class *Zygomycetes* and the order *Mucorales*.[1] Typically, the disease was seen during the COVID-19 recovery period, suggesting that multiple factors facilitate fungal colonisation.

As per the existing literatures most commonly affected age group was between 41 years and 60 years.[1,4] In our study we have seen maximum number of patients found in 50-60 years of age (43%) and minimum between 30-40 years. There was not much sex predilection for mucormycosis in general but in our study it showed a male predominance of 86%.[4]

The most significant aspect in dealing with CAM patients was the recurrent disease. We used a protocol for follow up with endoscopy, CRP, RBS/HbA1C.

In our study 90% patients in their first visit to us were proven diabetic and 67% of cases were having poorly controlled diabetes in post surgery follow up period (HbA1C >6). Uncontrolled diabetes was the single most common predisposing factor specially when associated with ketoacidosis.[4] Its seen in our study that hypertension had no direct causation on CAM and its recurrence. In 95% hypertension was found to be controlled. In post surgery follow up of patients using CRP, it was seen that 86% showed increasing trend of CRP (>5 mg/dl). Endoscopy was done in all patients of follow up. Patients showed yellow/extensive crusting, foul smelling discharge and any fungal debris. 81% of patients showed suspicious of recurrence after endoscopy. Patients in whom endoscopy showed suspicion of recurrence, rising trend in CRP, uncontrolled diabetes were further evaluated using radiological investigations.

Out of all patients who received both surgical and medical treatment and discharged asymptomatically, 21 patients developed symptoms. After admission, these patients were reevaluated with our follow up protocol and further with radiological investigation. Depending on duration of time period from surgery to recurrence, it was found that 43% developed recurrence at a new site by 2-3 months, 14% in 3-4 months, 33% in 1-2 months and 5% each in less than 1 month and after 4 months.[7,9]

We did MRI paranasal sinus+orbit+brain with T2 weighted gadalonium enhanced/CECT PNS depending on the symptoms and CBCT in 19 patients.[6,7] MRI showed T2 hyperintense soft tissue thickening and heterogeneous post contrast enhancement as the main finding.[6] Initial MR imaging of patients showed predominant involvement of the maxillary and ethmoid sinuses. Maxillary and ethmoids were the most commonly involved (69%), there were mucosal thickening and opacification of these paranasal sinuses (Figure 8C). The sphenoid sinus was also found to be involved in 20 cases. Frontal sinus was not significantly involved in our study. Hypertrophy of nasal turbinates with nasal secretions was seen with nasal involvement. Post contrast enhancement was seen in the thickened mucosa and involved tissues. However, areas of non-enhancing soft tissue were seen within the affected turbinates and paranasal sinuses, known as the black turbinate sign (69%). In 5 patients (17%) there was extrasinus extension into orbital compartment involving lamina papyracea and extraconal involvement and only in 7% of our study there was extension into the pterygoid plates and pterygopalatine fossa.[9]

There was fat stranding in pterygopalatine fossa. Only 2 patients showed skull base and intracranial extension.

When second MRI was proceeded, there were mucosal thickening and opacification of the paranasal sinuses in 17%. Intraorbital extension involving both intraconal and extraconal compartments with destruction of lamina papyracea in 13%. When our initial MRI showed extension into the pterygoid plates and pterygopalatine fossa in 7% in the second MRI it spiked to almost double (13%) together with extension into infratemporal fossa and 9 patients showed intracranial extension. Though bone involvement cannot be fully evaluated by MRI in our study 30% showed suspicious of bone erosion. In such cases and when patients refused MRI due to financial/personal reasons, CBCT was used as a cheaper alternative.[2] Also for 19 patients who came with fresh complaints of loosening of tooth, CBCT was advised. The patients underwent CBCT which revealed a moth-eaten appearance, sparse trabecular pattern with decreased bone density and loss of cortical plates of alveolar bone of maxilla.[2,3] However the loosening of teeth can also be due to the avascular necrosis as a sequelae to mucormycosis/treatment of mucormycosis like aggressive surgery which was initially done. It was seen that CBCT showed expansion, sclerosis, erosions and irregular lytic destruction of maxilla (alveolus). Maxilla was one of the primary bones of the face and forms the upper jaw. The alveolar process of maxilla held the upper teeth and plays an important role in mastication and speech. Though maxillary necrosis occurred rarely compared to the mandible due to its high vascular supply.[8,9] In our study we found that the most common site of CAM recurrence was maxilla (alveolus) 47% followed by paranasal sinuses 32% and mandible 5%. This may be due to the necrosis of the greater palatine artery in CAM patients. One of the case showed recurrence in R side coronoid process which was detected in CBCT whereas failed to be detected in MRI. Thickening of nasal mucosa and mucosal thickening of sinuses was seen in 32% of cases.

CT and MRI techniques were used as early diagnostic tools.[8] Osteomyelitis of facial bones needed to be investigated thoroughly as there was no difference in clinical presentation between bacterial and fungal osteomyelitis.[10] CBCT, which was a comparatively recent scanning technology in dentistry, provided images equivalent to medical CT at reduced costs and radiation doses.[3] CBCT aided us to recognize the maxillary and nasal extension allowing the early intervention leading to better prognosis of the patient. Since CBCT gave us detailed description of maxilla, nasal cavity and alveolar involvement, we had done CBCT in our cases. CBCT showed recurrent disease in 62% in place where MRI detected recurrence in 38% in our study.

CBCT was more useful for bony recurrences whereas MRI detected disease in soft tissues. Since in the present study alveolus was detected as the most common site of recurrence, CBCT was more effective.

Figure 8 shows CBCT images of a patient of CAM recurrence after initial surgery. Figure 8 shows patient with right sided palatal involvement together with maxilla involvement. Figure 8 shows involvement of right sided maxilla especially anterior and inferior walls. Both these patients underwent surgical treatment.

Figure 9: MRI and CBCT showing recurrent disease.

The recurrent cases after pre anaesthetic check-up were surgically treated. Intraoperatively 12 patients showed erosion of maxilla including alveolus and underwent total maxillectomy (Figure 10A). One patient showed fungal debris in premaxilla. In one case isolated alveolus was involved from 3rd molar right side to the left 3rd molar

without involvement of any pterygoid plates. So bilateral alveolectomy was done (Figure 10 B and C).[10] Out of the maxillectomy patients, 2 patients showed involvement of zygomatic process of maxilla. 19 patients underwent endoscopic debridement. In 17% cases, the remnant of turbinate which was spared during first surgery since it was found to be healthy on table was removed. All the sinuses were reexplored and any remnant of disease or mucosal thickening was removed. Though exploration of pterygopalatine fossa was done during initial surgery, 7% showed changes in second MRI in pterygoid area, so this area had to be reexplored. Infraorbital part of maxilla lateral to infraorbital nerve was identified and explored. Infraorbital nerve was diseased in 9 patients and it was resected. The infraorbital nerve was traced till foramen rotundum. Foramen rotundum was affected in 7 patients. Greater wing of sphenoid was seen diseased in these patients and drilling was done. In such cases drilling was done until the medullary component of bone appeared to be healthy. Medial and lateral pterygoid plates were removed if diseased. In our study in 2 cases medial pterygoid plate was removed and 3 cases lateral pterygoid plates removed. In 4 cases, it was seen that vidian nerve was diseased. The diseased nerve was removed. Part of diseased floor of sphenoid bone removed. In 3 cases internal carotid artery lateral to sphenoid sinus was encroached with disease. These patients were kept for wait and watch policy. 2 cases (blind eye) reported to have cavernous sinus thrombosis. For all patients with blind eye (6 patients), medial and inferior orbital bone was removed and lamina papyracea exposed to inspect extraconal muscles and to rule out fungal debris in eye. 1 patient underwent right sided condylectomy since CBCT showed isolated involvement of coronoid process. Intraoperatively it was seen that in 19 patients, posterior bony part of septum was pale and diseased and so it was removed. Intracranial extension via ethmoid fovea was seen in 3 patients. Disease was removed and the resulting small defect in skull base was covered with temporalis fascia graft (2 patients) and nasal mucosa (1 patient). No evidence of CSF leak noted. These 3 patients were kept under neurosurgery follow up.

Apart from the radiological reporting of disease, surgery was extended on basis of intraoperative findings. In 15 cases where recurrence was suspected in single side as per investigations and surgery planned accordingly on table under endoscope, other side showed disease. Hence surgery was extended to the opposite side for complete clearance of disease.

All postoperative patients were subjected to regular saline irrigations, antifungals and regular nasal endoscopic examination with suction clearance.

Gamba et al had previously showed that early disease manifested as mucosal thickening on CT scans, usually without air fluid levels.[7] Recognition as mucormycosis was facilitated by knowledge of the clinical setting or by identification of invasive disease. Likewise in our study, initial imaging showed limited disease.[7] Careful attention to often subtle extra-sinus extension in the form of fat stranding in the premaxillary, retromaxillary fat, orbital fat stranding and altered fat in pterygopalatine fossa was more important to suggest the diagnosis of invasive fungal infection on imaging.

Figure 10: (A) Specimen of diseased maxilla after revision surgery; (B and C) specimen after alveolectomy.

In 2018 Therakathu et al reported that only few case reports of chronic mucormycosis involving bone were available. He also reported that some of the patients in their study who presented with acute mucormycosis went on to develop chronic infection with bone involvement following the initial treatment.[8] The involved bones showed expansion, sclerosis, erosions and irregular lytic destruction.[3] In our study CBCT showed destructive bony changes in 47% after initial treatment.

The probable cause of recurrence may be because the disease was in close proximity to inaccessible vital structures which was not dealt earlier, immunosuppression, uncontrolled diabetes, inadequate antifungal therapy. Patients may have overlooked the symptoms of mucormycosis (especially pain), confusing it with dental pain and therefore presented late to us. Dental symptoms were not addressed at initial hospital visits and priority was given to nasal or sinus symptoms and so bone involvement was initially not evaluated. Imaging techniques like MRI may show nonspecific features during the early stage of the disease like mucosal thickening which may delay diagnosis. Hence a high clinical suspicion was mandatory for early pick up of this condition. Moreover CBCT was not used in initial line of investigation which showed bone involvement. There may be under-reporting of radiological investigations.

Amphotericin B was the drug therapy of mucormycosis. It should be given in correct dose as per weight of the patient. Injection amphotericin B (1.0-1.5 mg/kg/day) or injection liposomal amphotericin B 5-10 mg/kg/day (intra cranial involvement-10 mg/kg /day) or injection amphotericin B lipid complex 5 mg /kg/day was considered the ideal dose.[4,5]

All the CAM patients were started on liposomal amphotericin and recurrence in patients were noted maximum for those who received only 2 gram and 2.5 gram and least recurrence seen in patients who received 4 gram and 5 grams. All the recurrent cases who were diagnosed recurrent disease clinically, endoscopically or with radiological investigation underwent surgical debridement and were given total dose of 5 gm of liposomal amphotericin.

Limitation

The lost to follow up cases were excluded from the study population and maximum dose of 5 grams amphotericin was given to patients based on our supply.

CONCLUSION

Mucormycosis is an invasive fungal disease. COVID patients in whom immunological status are altered, diabetic or immunocompromised patients should be kept under surveillence by endoscopy, CRP and blood sugar monitoring. Though CAM patients are treated with aggressive surgery and antifungal therapy they should be under regular follow up for more than 6 months. Diabetic control plays a significant role in curbing the rapid spread of CAM. Suspected cases should undergo radiological investigations like MRI and CBCT. Recurrent/residual disease of mucormycosis can be tackled and treated successfully.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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