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Mucormycosis - An Adamant Parasitic Fungal Infection Requiring Multiple Surgeries

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ABSTRACT

Introduction - Mucormycosis is a life threatening invasive fungal infection that mostly occurs in immunocompromised patients. Aim of our study is to analyze the management of mucormycosis in rhinoorbital mucormycosis cases and dire requirement for more than one surgical intervention for their management. The limitations of first surgery, progressive nature of disease, and difficult anatomical regions were the areas to address in most of our patients in this series.

Methodology - Our case series consists of 34 confirmed cases of mucormycosis using standard staining and histopathological confirmation on biopsy. The study group being subjected to complete modern diagnostic, CT, MRI scrutinization. Detailed follow up with serial endoscopies, post-surgery. Re confirmation of residual on progressive mucormycosis disease condition being subjected to repeat of these investigative tools and confirmation with PET scan.

Results – Total of 34 patients were included in our study majority of them were diabetic. Only 3 patients underwent single stage debridement however 29 patients underwent debridement in two successive stage and two patients required third surgery for disease clearance.

Conclusion – Repeated surgical debridement is must for complete disease eradication in case of rhinoorbitocerebral mucormycosis. Also, medical management can prolong the survival of patients with disease in areas which are inaccessible by surgical clearance. Serial radiography with CT, MRI and PET scan are not only contributary but mandatory.

KEYWORDS: Mucormycosis Liposomal amphotericin Debridement Posaconazole

ARTICLE DETAILS

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BACKGROUND

Mucormycosis was first described by Paltauf in 1885 since then many authors described this condition but in the covid pandemic there was an upsurge of this disease post COVID 19 in India, leading to overburdening of healthcare system.[1]

Suspected cases of mucormycosis requires early diagnosis, following histopathological confirmation of disease immediate interventional treatment is required consisting of parentral liposomal amphotericin (Lip. Amph.) and surgical debridement of all necrotic and diseased tissue. Delayed treatment is associated with rapid deterioration of patient's health and finally patient succumb to death due to fulminant course of disease. Initially patient have vague symptoms of facial pain, nasal discharge or on & off nasal obstruction which most of the patient's ignore and may lead to more advanced manifestations like orbital involvement, intracranial manifestations like Internal Carotid artery (ICA) thrombosis, cavernous sinus thrombosis, meningitis, encephalitis, features of raised Intracranial tension (ICT) as well as skin involvement and cranial nerve palsies.

Our case series is from a mucormycosis dedicated center in which we had studied 34 confirmed cases of Rhino-orbital mucormycosis (ROM) in various stages of the disease and underwent serial debridements. Patient's of ROM were followed for period ranging from 9 months to 1.5 years. These patients underwent repeated debridements based on the post operative CT findings and histopathological confirmation. Repeated surgical debridement with combination of antifungal therapy can result in good outcomes in majority of cases and a few with advanced intracranial affliction.[2]

Aim of our study is to analyze the management of mucormycosis in rhinoorbitocerebral mucormycosis (ROCM) cases and dire requirement for more than one surgery in most of our patients in this series along with post operative rehabilitation.

METHODOLOGY

In our study, we retrospectively reviewed 34 patients from september 2021 till november 2022 with age ranging from 24 to 70 yrs. After obtaining clearance from institutional ethical committee, patients who were diagnosed histopathologically and radiologically as cases of mucormycosis were included in the study. The patients with a mean age of 49.93 years were evaluated for the presenting symptoms of nasal obstruction (unilateral or bilateral), nasal discharge, headache, anosmia, facial anesthesia and orodental complaints. Diagnostic endoscopy was done for all the patient's and materials such as nasal crust, or the mucosa of middle turbinate was biopsied. Fungal stains and histopathology in all these cases were consistent with the features of mucormycosis, showing broad, aseptate, branching fungal hyphae. Out of 34 patient's, 26 were diabetic. A meteoric correction was done for the underlying IC status in coordination with different specialities experts. Out of 34 cases, 10 patients had rhinorbital, 3 patients had rhinocerebral, 14 patients had ROCM and 7 patients had limited disease of sinonasal mucormycosis type. All the patients underwent CECT PNS with orbital cuts. Contrast enhanced MRI (CEMRI) were limited to the cases with orbital and intracranial (IC) extension.The final assessment & planning of surgery was done after the consultation of different specialities (EYE, neurosurgeons & Radiologist) In consult with ophthalmologists, neurosurgeons and radiologists assessment and planning was undertaken for them. The risk versus benefit analysis was done for all cases requiring extensive debridement's like those leading to disfigurement example – Maxillectomy and Orbital exenteration. (Figure 1) Patients were counselled well before undergoing surgery. All the treatment options, risks of undergoing anesthesia and surgery, post operative expectations, deformities and recurrent nature of disease were well explained to all the patients. The surgical route preferred was endoscopic assisted intraoral or intranasal debridement in all patients. Skin incision was avoided in view of lack of underneath support post maxillectomy leading to high chances of post operative wound dehiscence and facial disfigurement as well as dermatological mucormycosis involvement. Surgical planning was done according to the extent of disease seen clinically and radiologically. All patients underwent first debridement by an experienced surgeons as per the extent and burden of disease. Aggressive debridement procedures i.e, total or extended maxillectomy with or without orbital exenteration was performed in cases showing involvement of whole maxilla and /or orbit in the imaging. All patients received liposomal amphotericin B (Limited sinonasal disease with or without orbital involvement Total cumulative dose -7000mg, Intracranial disease Total cumulative dose – 10000mg). Patients were also prescribed nasal douching post operatively and were instructed to maintain local hygiene and repeat endoscopic suction clearance. Those undergoing maxillectomy were managed with Ryle's tube feeding with frequent betadine and dilute hydrogen peroxide mouth washes until healing of post operative exposed wound. After completion of their amphotericin dose patients were discharged and kept on regular follow up with regular endoscopic cleaning of nasal cavity on their subsequent visits. Those undergoing maxillectomy were rehabilitated with primary dental obturator. (Figure - 2) Six weeks post operatively surgical completeness was assessed using PET-CT. Patients showing FDG uptake underwent biopsy for confirmation of disease followed by re-debridement once disease confirmed. All the cases were followed up for 9 months to 1.5 years following their surgery to look for any residual and recurrence. Patients with residual or recurrence underwent serial debridements as per the disease identified radiologically. (Table 1)

Table 1: Showing patients undergoing multiple surgeries.[3]

S.NO	FIRST SURGERY (BROWN CLASSIFICATION MAXILLARY DEFECT)	SECOND SURGERY (BROWN CLASSIFICATION MAXILLARY DEFECT)	THIRD SURGERY (BROWN CLASSIFICATION MAXILLARY DEFECT)
1	Left Subtotal Maxillectomy with Right Inferior Maxillectomy (2c)	Left sided endoscopic redebridement (2c)	
2	Endoscopic right sided modified Denker's approach (1)	Right sided Revision debridement via modified denker's approach with right sided orbital decompression for residual orbital disease (1)	

3	Functional endoscopic sinus surgery [elsewhere] (1)	Left sided Debridement via Caldwell Luc (1)	
4	Left Functional endoscopic sinus surgery (1)	Debridement of anterolateral maxillary wall with left inferior maxillectomy via sublabial approach (2a)	
5	Right Functional endoscopic sinus surgery [elsewhere] (1)	Right sided Endoscopic debridement (1)	Right sided debridement of posterolateral maxillary wall with pterygopalatine fossa disease via Sublabial approach (1)
6	Left Subtotal Maxillectomy with debridement (2a)	Left sided revision endoscopic debridement of pterygopalatine fossa disease (2a)	
7	Bilateral inferior maxillectomy (2c)	Endoscopic ethmoidectomy and sphenoidectomy (2c)	
8	Bilateral inferior maxillectomy with endoscopic debridement of medial wall of maxilla (2c)	Redebridement [Zygomectomy] (2c)	
9	Marginal mandibulectomy [elsewhere]	Redebridement right pterygopalatine fossa disease via modified Denkers's approach	
10	Right total maxillectomy with right orbital exenteration (4a)	Endoscopic sphenoid redebridement (4a)	
11	Bilateral Functional endoscopic sinus surgery and debridement with right side Lynch Howarth incision (1)	Endoscopic sphenoidectomy and debridement of right superomedial orbital disease via lynch Howarth incision (1)	
12	Bilateral inferior maxillectomy (2c)	Endoscopic ethmoidectomy (2c)	
13	Left sided subtotal maxillectomy with endoscopic ethmoidectomy and spehnoidectomy (2a)	Left sided Redebridement [Zygomectomy] (2a)	
14	Debridement of pterygopalatine fossa disease via right modified denker's approach (1)	Endoscopic right sphenoidectomy (1)	
15	Debridement via right sided modified Denker's of infratemporal disease and bilateral Lynch Howarth approach of superomedial periorbital disease (1)	Redebridement via bilateral Lynch Howarth in remnant periorbital superomedial disease (1)	
16	Right sided debridement of infratemporal and pterygopalatine disease via modified denkers Denker's approach (1)	Endoscopic ethmoidectomy (1)	Endoscopic sphenoidectomy (1)
17	Bilateral subtotal maxillectomy with endoscopic ethmoidectomy (3b)	Endoscopic sphenoidectomy (3b)	
18	Right subtotal maxillectomy (3b)	Endoscopic bilateral sphenoidectomy (3b)	

19	Functional endoscopic sinus surgery (elsewhere) (1)	Right sided debridement via modified Denker's approach of pterygopalatine fossa disease (1)	
20	Bilateral Inferior Maxillectomy with Endoscopic ethmoidectomy (2c)	Endoscopic sphenoidectomy (1)	
21	Bilateral Endoscopic Sinus surgery (1) (Elsewhere)	Bilateral Endoscopic ethmoidectomy with right side orbital exenteration for orbital disease	
22	Left sided endoscopic sinus surgery (1)	Left sided endoscopic ethmoidectomy with left orbital exenteration for orbital disease	
23	Bilateral endoscopic Sinus surgery (1)	Bilateral ethmoidectomy and sphenoidectomy (1)	
24	Right partial inferior maxillectomy with bilateral ethmoidectomy (2b)	Right endoscopic Sphenoidectomy (2b)	
25	Left sided inferior maxillectomy with bilateral endoscopic ethmoidectomy (2b)	Endoscopic redebridement (2b) (Zygomectomy)	
26	Bilateral endoscopic sinus surgery [elsewhere] (1)	Right orbital exenteration for orbital disease	
27	Right partial inferior maxillectomy (2b)	Right side ethmoidectomy and sphenoidectomy (2b)	
28	Bilateral functional sinus surgery (1)	Bilateral sphenoidectomy (1)	
29	Left side subtotal maxillectomy (3b)		
30	Left side inferior maxillectomy with bilateral ethmoidectomy and sphenoidectomy (2b)	Endoscopic redebridement (Zygomectomy)	
31	Right sided debridement of infratemporal and pterygopalatine fossa disease via modified denkers approach and right orbital exenteration for orbital disease	Anterior septectomy	
32	Left endoscopic sinus surgery with medial and inferior orbital wall decompression (1)	Left side orbital exenteration	
33	Right partial inferior maxillectomy (2a)		
34	Debridement of necrotic palatal foci (1)		

RESULTS

Total number of cases (n) = 34

Comorbidity	28 (82.35%)
Palatal involvement	23 (67.64%)
Mandibular involvement	1 (2.94%)
Orbital involvement (Intraconal and extraconal)	24 (70.58%)
Intracranial	17 (50%)
PET uptake	18 (52.94%)
Multiple surgery	31 (91.17%)

Thirty four diagnosed ROCM patients (26 males and 8 female; mean age 46.50 years were analysed. The main risk factors were diabetes mellitus (n = 26, 76.47 %) or other comorbidities (n = 4, 11.76 %) and rest 4 had no comorbidity

(9.67%). The main presenting complaints were facial swelling, nasal discharge, ulceration in palate, headache, generalised malaise, fever. Common signs visible were black nasal crusting, palatal ulceration. (Figure 3) Three patients underwent single stage debridement (8.82%), 29 patients underwent second debridement (85.29%) and 2 patients underwent third debridement (5.88%) Most common areas involved were Infratemporal Space, Pterygopalatine fossa, Pre antral space, Extraconal compartment of Orbit, Cavernous sinus. Total 9 (26.47%) patient's had residual disease on CT scan and on PET scan after second surgery. They had either skull base involvement or intracranial extension and hence were kept on medical management. Post removal of hard palate patients had difficulty in swallowing, articulation and speech but this was resolved by using dental obturator. Patients also had to undergo regular suction and cleaning on every follow-up visit.

DISCUSSION

ROCM being the commonest presentation of the class of Zygomycetes fungus of the order of mucorales. The order includes genres like Rhizopus, Mucor, Rhizomucor and Absidia, These genres are almost always found in soil on decomposing matter and gain entry primarily by inhalation, and almost everyday a person may get exposure, but due to low virulence the ROCM manifestation is not seen in general population. Factors such as DM, neutropenia, hematological malignancy, bone marrow transplant, corticosterioids and use of deferoxamine, It is interesting to note that in HIV patients who generally have impaired neutrophil counts the manifestations of mucormycosis is seldom occurrence.[4] Mucormycosis is fatal in these immunocompromised persons and considered third most common fungi. Neutrophilic chemotaxis and phagocytosis is poor in patients with Diabetes mellitus as local inflammatory self-defence is poor. Mucor fungi thrive on low oxygen concentration tissue and on ketone reductase system. Iron is further beneficial for fungal growth, deferoxamine, an iron chelating agent makes available this substrate for fungal growth. In rhinoorbital type of mucormycosis the orbital involvement in most of our cases resulted from anoxic necrosis of lamina papyracea due to disease of ethmoid sinus, sphenopalatine, maxillary sinus and Cavernous sinus thrombosis (CST). First there was conjunctival chemosis followed by pre-septal orbital inflammation leading to extraconal / intraconal invasion by disease from adjacent sinuses i.e ethmoid or maxillary sinus leading to ophthalmoplegia further extending to superior / inferior orbital fissures cavernous sinus, Internal carotid artery (ICA) and ophthalmic artery thrombosis and further spreading disease intracranially. However, we also saw cavernous sinus thrombosis in early stage of disease due to thromboembolic nature of disease. It is also seen that these fungal hyphae penetrate the endothelium of the vessels, resulting in damage, clot formation leading to vascular occlusion and tissue anoxia which further leads to necrosis. ROCM-induced vascular thrombosis leads to tissue necrosis and poor diffusion of antifungals at infection site leading to poor response and further deterioration of patient's condition, hence debridement of necrotic tissue is must for eradication of disease leading to better survival of patients undergoing surgery. [5-7]

Our study is poised to analyze why majority of patient in our series require more than one surgery. Following were the diagnostic tools used in our study –

First Diagnostic tool used was Endoscopic evaluation with biopsy and histopathological analysis for mucor. Radiological impetus was provided by Contrast enhanced computed tomography (CECT) of nose and paranasal sinuses complimented with CEMRI for intracranial and infraorbital extension of disease was the second diagnostic tool. (Figure 4,5,6) Periodic post op endoscopic debridement and nasal douching and subsequent IV amphotericin were administered. Eight weeks post-surgery reassessment of surgical completeness was assessed using a repeat CT/MRI and all patients underwent PET CT to identify residual or recurrence. Further patients underwent histopathological assessment with confirmation of residual mucormycosis on HPE after endoscopy done. In our study all patients underwent PET-CT scan 8 weeks post debridement. Those scans were compared with previous pre operative CT scans. Those patients in whom FDG uptake was seen they underwent redebridement. Debrided tissues were sent for biopsy. In all cases who underwent redebridement post PET-CT their biopsy report suggested broad aseptate fungal hyphae. Post debridement they all received liposomal amphotericin B intravenously with dose of 1mg/kg 24 hourly on first day followed by the maintenance dose of 3mg/kg 24 hourly, till the total dose of 7 grams for extracranial disease and 10 grams for intracranial disease. Patients showed symptomatic improvement. While those who did not showed any of the uptake in scan were declared disease free and kept on follow up. Our study revealed that the sites more prone to recurrence according to frequency were as follows – Infratemporal Space, Pterygopalatine fossa, disease with extension into infra orbital fissure, Pre antral space, Extraconal compartment of Orbit, Cavernous sinus, Pterygoid bone, Greater wing of sphenoid, Clivus, Zygomatic bone, Intraconal part of Orbit, palate and upper alveolus. At these anatomical sites, debridement was either technically difficult or just not a possibility.

PET-CT is a technique that is useful for evaluation of mould infection extent, as it can detect small infectious foci before the onset of the anatomical abnormalities assessed by conventional radiological tool.[7] In our study post-surgery PET-CT helped us in localization of infective foci due to uptake of FDG glucose by mucor. (Figure 7) The role of FDG pet in mucormycosis was also demonstrated in study conducted by Liu et al.[9]

Blitzer et al. reported increase in survival rate from 57.5% to 79% in patients underwent radical surgery.[10] In previous

study it was also found that orbital extension is associated with poor survival.[11] Talmi et al. had reported 100% mortality when intracranial extension became symptomatic.[12] However in our study we encountered 17 patients (50%) patients with intracranial disease extension and all the patients survived post-surgery while intracranial part of disease were left for medical management and patients still are in follow up for long term survival results.

In our cases 2 patients (5.88%) had carotid artery and 8 patients (23.5%) had cavernous sinus involvement. The carotid artery involvement due to fulminant RCM is reported by Delbrouck et al.[13] ROCM can also spread by perineural invasion.[14] Hyperbaric oxygen therapy (HBOT) has demonstrated direct *in vitro* fungistatic action, reduction of tissue hypoxia leading with enhancement of cellular defences, synergistic effects with antifungals and augmentation of tissue repair mechanism. [15-16]

In our cases we also saw multiple cranial nerve involvement with most common involvement of cranial nerve I followed by CN V (V2, V1, V3), II, III,IV and lastly VII. We also saw that majority of patients underwent more than one surgery for disease clearance. Majority of individuals had residual disease after initial treatment either medical or surgical debridement, most apt for mucormycosis. We identified following causes for disease recurrence after primary surgery -

- Inability to identify complete extension of disease preoperatively on radiology
- Inadvertently left disease during surgery due to lack of identification of complete extension of disease intraoperatively
- No previous exposure of most of the surgeons to such extensive mucormycosis involvement of brain and facial structures
- Hesitation on part of surgeon to perform extensive debridement in severe cases of mucormycosis due to destructive nature of surgery and fear of post op reconstruction such as in case of inferior partial maxillectomy /total maxillectomy/orbital exenteration.
- Deliberately leaving disease foci at anatomically inaccessible sites like optic nerve, Inferior orbital fissure, cavernous sinus, Clivus, Greater wing of sphenoid etc
- Initial reliance of dealing with mucormycosis on medical management and thus leaving fate of the patient over Liposomal amphotericin B. Recurrence of disease in such cases also raise questions over the effectiveness of liposomal amphotericin B against mucormycosis and possible resistance to drug.
- Unprecedented number of patients presenting with mucormycosis and shortage of more efficacious liposomal amphotericin and subjecting such to lipid emulsion formulation with side effects.
- Despite of complete disease clearance in a majority on the first surgery, thromboembolic events are progressive in nature thereby causing further tissue necrosis and extension of disease thereby requiring a repeat surgery.
- Surgical procedures that were done intraorally and intranasally avoiding skin incision as majority of patients have dermatological involvement, thereby providing a lesser approach to disease in some areas.

  In our patients we gave liposomal amphotericin till cumulative dose of 7000 mg in extracranial disease however in cases of intracranial involvement we extended cumulative dose till 10000 mg and this dose was given from period of 1 month till 3 months. Delay in completion of medication was due to –

- Deranged Blood urea nitrogen level
- Allergic reactions towards liposomal amphotericin
- Unavailability of liposomal amphotericin due to crisis caused by imposed lockdown
- Non liposomal amphotericin was next alternative with more complications
- Dyselectrolytemia

In our study recovery of the patient's was considered based on A) – No necrotic tissue or local progression of disease at the surgical site detected endoscopically in the follow up visits B) No new lesion identified in the Imaging or histopathology.

CONCLUSION

From our study, we conclude that in cases of mucormycosis careful monitoring and repeated surgical debridement is must for complete disease eradication. Apart from Diagnostic nasal endoscopy, CECT and MRI, there is an important role of FDG PET in diagnosis of residual disease, for further planning in case there is a need of revision surgery. Also, medical management can prolong the survival of patients with disease in areas which are inaccessible by surgical clearance as those patients having surgically inaccessible disease survived in our study and are still on follow up for long term results.

ABBREVIATIONS

Lip Amph – Liposomal Amphotericin
ICA – Internal carotid artery
ICT – Intracranial tension
ROM – Rhino orbital mucormycosis
ROCM – Rhino-orbito-cerebral mucormycosis
CT – Computed tomography
CECT – Contrast enhanced computed tomography
MRI – Magnetic resonance imaging
CEMRI – Contrast enhanced magnetic resonance imaging
PET-CT – Positron emission tomography-computed tomography
IC - Intracranial

DECLARATION

Ethics approval and consent to participate : Before commencing the study ethical approval was taken from our Maulana azad medical college department of ENT ethics committee. Written informed consent was taken from the participants before including in our study in accordance with the declaration of Helsinki.

Consent for publication : Written consent was taken from the involved participants for publishing their data, images and details.

Availability of data and material : All data generated or analysed during this study are included in this published article

Competing interests : No competing interest

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Conflict of Interest - None

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Figure 1 : Showing facial disfigurement surgeries A - Bilateral inferior maxillectomy, B – Right orbital exenteration

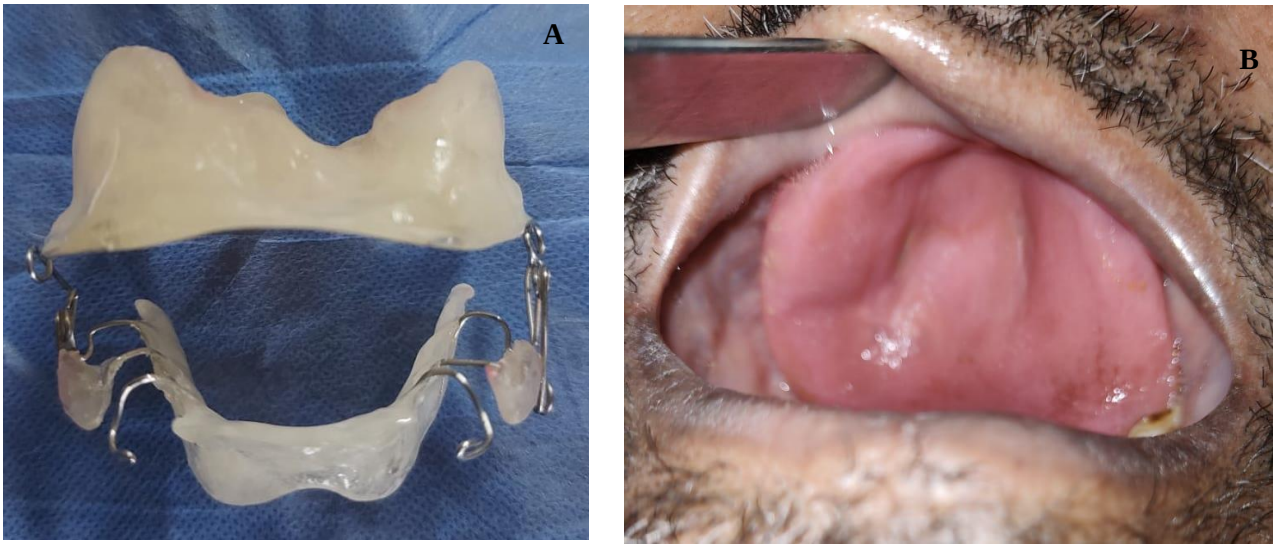
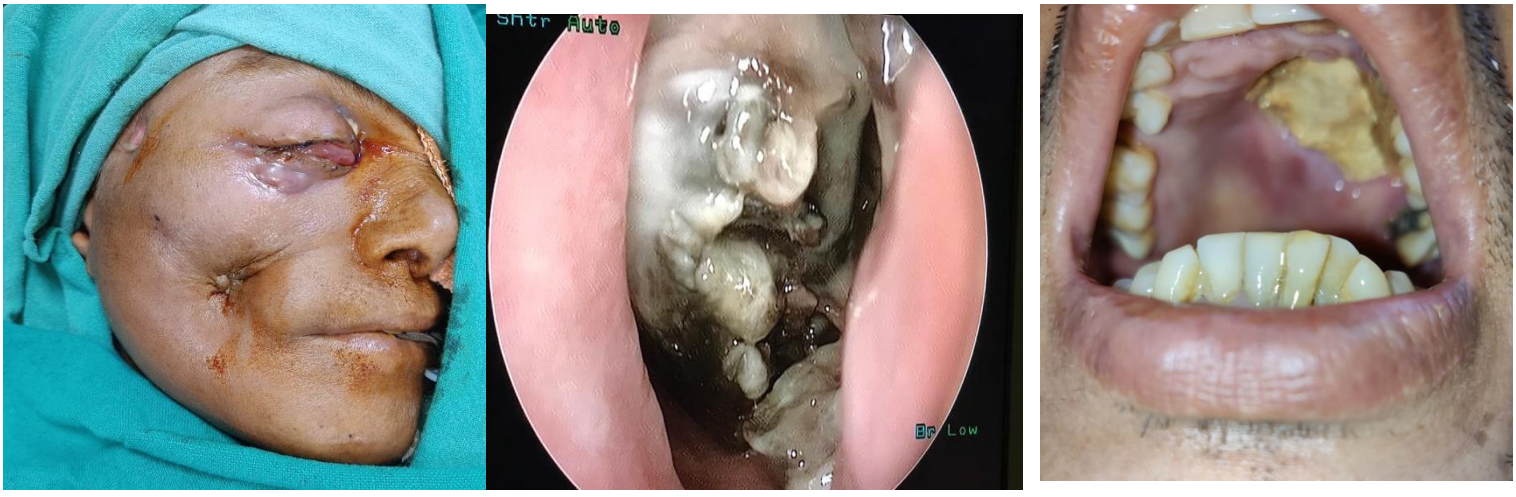


Figure 2 : Showing prosthesis used for rehabilitation post total maxillectomy (A) and partial maxillectomy (B)



A **B** **C**

Figure 3 : Showing A – Disease involving the right eye and the skin, B- Endoscopic view of right nasal cavity with black crusting, C – Palatal ulceration with slough

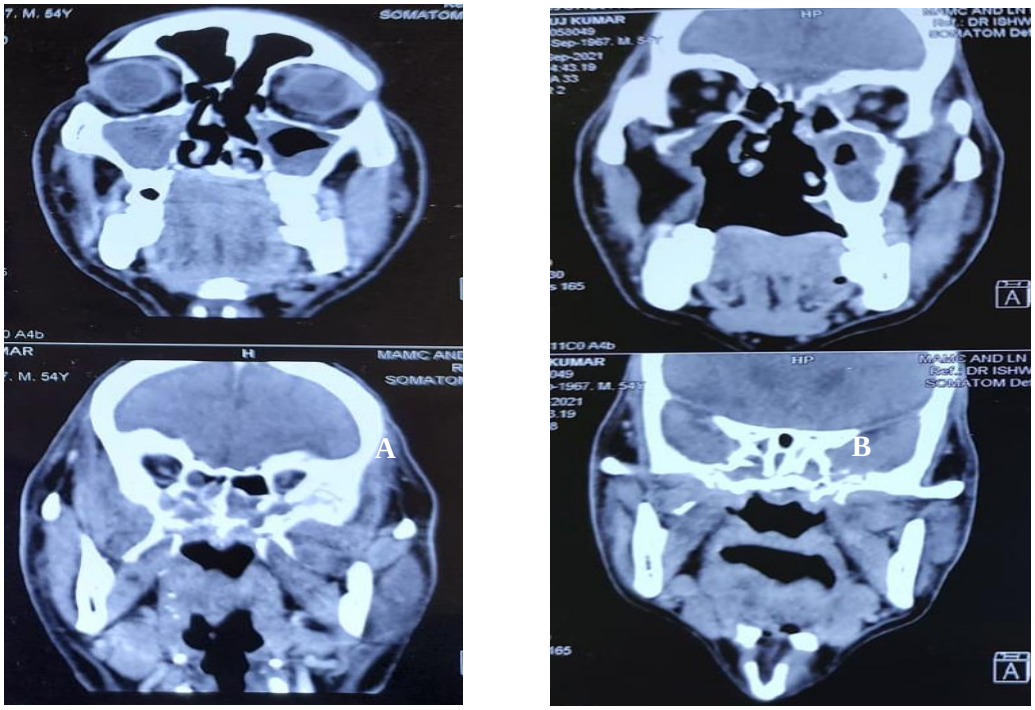


Figure 4: Showing A - Pre operative disease extension in bilateral maxillary sinus, right hard palate, bilateral pterygopalatine region. B - Post right subtotal maxillectomy with removal of bilateral pterygoid process

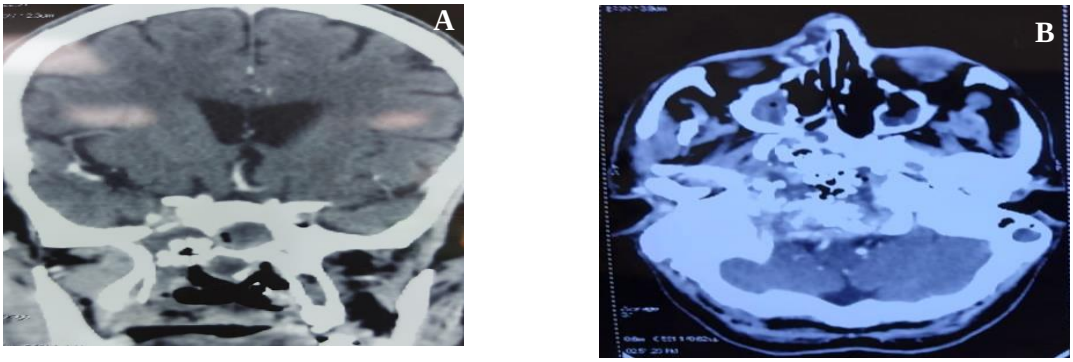


Figure 5 : Showing A, B – Coronal and Axial extension of disease in sphenoid eroding right wall and extending intracranially

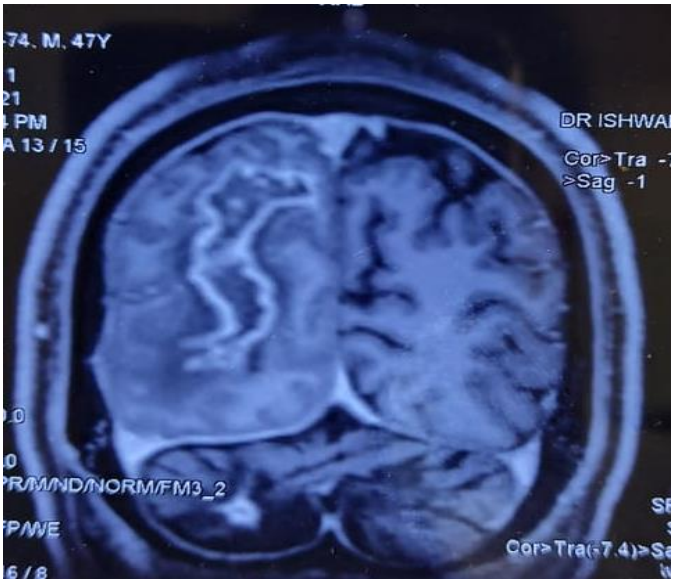


Figure 6 : Showing right sided intracranial changes due to disease

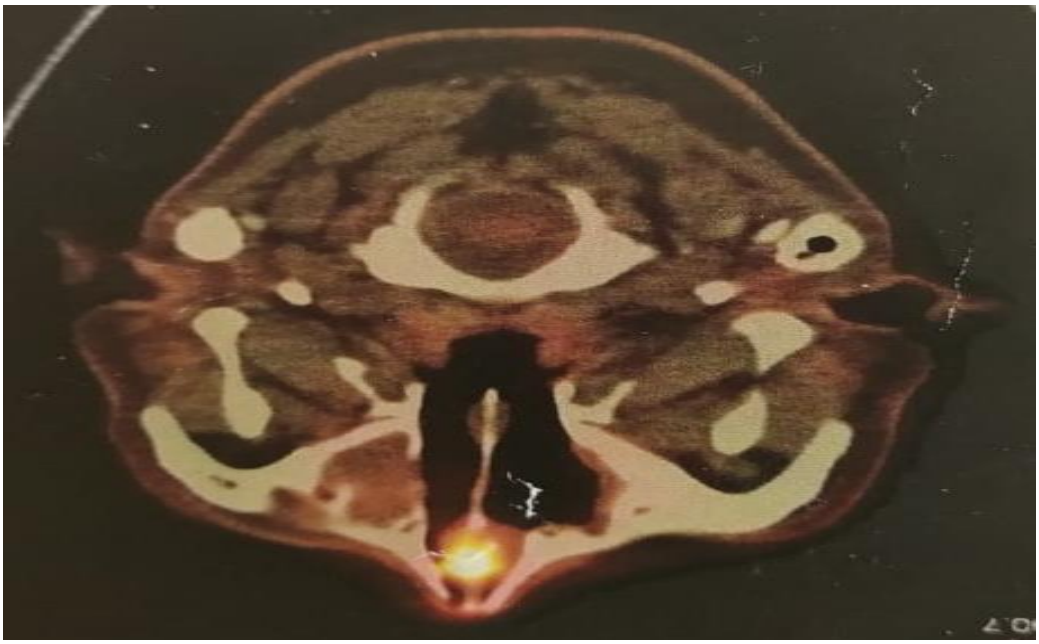


Figure 7: Showing FDG uptake in anterior part of nasal septum