Original Article

Experiences from First 100 Cases of COVID Associated Rhino-orbito-Cerebral Mucormycosis Epidemic Treated from a Tertiary Care Centre in Eastern India : An Otorhinolaryngologist Prospective

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Background : Early clinical presentations of Rhino-orbito-cerebral Mucormycosis (ROCM) are often underappreciated. Awareness and recognition of clinico-radiological features that may be more suggestive of mucormycosis can expedite management in this rapidly progressive disease.

Materials and Methods : All patients of Rhino-orbito-cerebral Mucormycosis (ROCM) admitted to our facility from 24th May, 2021 to 24th August, 2021 are studied. Clinical, radiological and surgical findings are recorded and analysed.

Observation and Results : Our experiences of dealing with first 100 cases presented in less than 3 months' time amidst COVID-19 pandemic with the hope of defining demography of population at risk, early diagnosis and recommendations for management of mucormycosis are summarised in details.

Conclusion : Strong clinical suspicion is mainstay for early diagnosis. Anti-fungal medications are the mainstay of management along with surgical debridement. MRI is essential tool for diagnosis, evaluating progression and surgical planning. Regular endoscopic follow-ups are vital in detecting remnant and thus reducing recurrences.

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***Key words* : Mucormycosis, COVID-19, Invasive Fungal Sinusitis, Eye Infection Fungal, Magnetic Resonance Imaging, Debridement.**

Viral pandemics are definite threat to civilization worldwide, but it's not unique. Many viral epidemics has made its mark in past few decades. SARS-CoV-2 was a novel one, completely unknown to humanity and its understanding is still evolving. But an epidemic caused by fungi is never seen before in medical history. Mucor is not completely unknown to medical science, rather a quite common fungi found almost everywhere but are rarely pathogenic to immuno-competent individuals. Mucormycosis is caused by fungus of *Mucorales* order, most common genera causing human infection are *Rhizopus, Mucor* and *Lichtheimia* accounting for about 80% of cases[1,2].

Mucormycosis has long been known to affect immunocompromised patients particularly those with uncontrolled diabetes[4]. But several factors are responsible for the spike in incidence of Rhino-orbito-cerebral Mucormycosis (ROCM) in era of COVID-19 pandemic, even in non-immuno-compromised patients. The prevalence of Mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population[5]. We here share our experiences of dealing with the first

Editor's Comment :

- High clinical suspicion is the mainstay of early diagnosis and treatment.
- Immunocompromised patients specially post COVID are most susceptible.
- Start Lyposomal Amphotericin in proper dose just after preliminary tests- MRI and smear for KOH.
- Early surgical debridement after stabilisation of patients.
- A multidisciplinary team comprising ENT specialist, Neurologist, Opthalmologist, Endocrinologist and Faction maxillary surgeon must take charge of mucor ward.

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100 cases presented to our institute in less than 3 months' time amidst COVID-19 pandemic with the hope of defining the demography of the population at risk, early diagnosis and recommendations for management of mucormycosis.

Materials and Methods

Study Setting & Design :

This prospective descriptive study was carried out in the Department of Otorhinolaryngology & Head Neck Surgery, IPGME&R & SSKM Hospital, which is the apex tertiary care hospital in West Bengal, India.

Aims and Objective

(1) Describe epidemiology and risk factors for COVID-19 associated mucormycosis.

(2) Elaborate clinical spectrum of Rhino-orbital-cerebral Mucormycosis (ROCM)

(3) Formulate surgical approach.

Patient Selection and Protocol :

All suspicious patients of Rhino-orbito-cerebral Mucormycosis (ROCM) admitted to our facility from 24thMay, 2021 to 24th August, 2021 were included in our study. Every patient is evaluated at presentation with detailed history, clinical signs, ENT, ophthalmic, and neurological examination to assess extent of disease along with imaging and electro physiological studies. Around 23 patients where operative interventions could not be done due to poor general health, underlying associated comorbid conditions, unfit for general anaesthesia or early death prior operative intervention were excluded.

Diagnostic nasal endoscopy and guided biopsies along with KOH smear was done for all the cases. The diagnosis was made by KOH smear on finding fungal filaments of the Mucorales order in presence of appropriate clinical and radiological signs. COVID Associated Mucormycosis (CAM) was defined as occurrence of Mucormycosis in a subject with current/ previous diagnosis of COVID-19 (RT-PCR/Rapid antigen test positive for SARS-CoV-2 or CT/signs suggestive of COVID pneumonia). Cases were considered as Early CAM when Mucormycosis was diagnosed within 2 weeks, intermediate CAM when they occurred after 2 weeks to 4 weeks & late CAM when diagnosed after 4 weeks of COVID-19 diagnosis.

All subjects on admission underwent Magnetic Resonance Imaging (MRI) of Paranasal Sinuses (PNS), orbits & brain, both plain [T1, T2/T2 Fluid Attenuation Inversion Recovery Sequence (FLAIR), T2 Fat Suppression (FS), Gradient Echo Sequence (GRE), Diffusion Weighted Imaging (DWI)] along with contrast studies and Magnetic Resonance Angiography (MRA) of brain vessels as per need except in cases with contraindications. Radiological findings were studied in details to identify areas of involvement and pattern of spread for surgical planning.

Debridement of necrotic tissue and involved areas through endoscopic or open approach along with orbital clearance or exenteration were done as indicated. and sent for KOH smear, culture and HPE.

Analysis and Results

A total of first 100 Rhino-orbito-cerebral Mucormycosis patients attending our tertiary care institute were analysed in this study. All were admitted in our dedicated Mucormycosis ward, all of their data were documented. Except for 4 patients of simultaneous pulmonary mucormycosis no other forms were encountered in this study. About 27 cases were referred from other centres untouched to our centre, out of which 19 were operated elsewhere before admission.

Our study group had an age distribution of patients ranging from 18 years to 71 years. Commonest age group was 41-50 years with 41 patients followed by 51 - 60 years with 36 patients. 63 of them were male and 37were female (male: female:1.72:1).There is a slight muslim predominance with 57 cases. 76 patients were from rural background. 59 patients belonged to lower middle class.

All the patients had a history of COVID-19 either prior or during presentation except in 9 cases where symptoms suggested of SARS-CoV-2 defined illness, however, did not have any previous RT-PCR reports. None were vaccinated for COVID-19. Early CAM was observed in 14cases, intermediate CAM in 55 cases late CAM in 47cases. Twenty-six cases had evidence of SARS-CoV-2 associated pneumonia. 43 patients had history of prior hospital admission for COVID. 26 patients had been treated with oxygen therapy (via nasal cannula/face mask/non rebreathing mask) eighter in hospital setup or untrained home setup. 16 patients required prior invasive ventilation for COVID management.

At time of presentation all 100 patients were diabetic, 57 of them were known diabetic patients and 43 has developed T2DM while undergoing COVID management. 78 patients had history of steroid intake during SARS-CoV-2 infection and 22 subjects did not have definite history or documentation of steroid use. Among these 41 cases, 17 had documented uncontrolled hyperglycemia even with low dose short duration corticosteroid therapy. 2 patients were receiving dialysis prior COVID and 7 patients received intermittent dialysis during COVID management. Hypertension was present in 44 patients out of whom 23 patients acquired it during COVID management.

We had1 patient each for bronchogenic carcinoma, low grade non-Hodgkin lymphoma and renal transplant. No chemotherapy or HIV patients were encountered in the study group. About 44 patients suffered from COVID-19 pneumonia prior mucormycosis (Figs 1&2).

Unilateral nasal blockade and discharge, often blackish and serosanguinous was present in 54 patients. Significant observations included occurrence of upper jaw tooth pain and loosening of teeth in 31 cases and blackish discoloration over palate and palatal necrosis in nearly 21 cases.Unilateral cheek swelling, pain, eye lid swelling, lid ulcerations, blackish discolorations in around 26 cases.

Among orbital findings, extraocular movement abnormalities were seen in 53 patients, of which isolated lateral rectus involvement was seen in 3 subjects. Diminution of vision was observed in 49 cases. Bilateral extra-ocular movement restriction was observed only in 8 cases. Unilateral complete ophthalmoplegia was seen in 47 cases. Optic nerve involvement was observed in 33 cases which was unilateral in 25 cases and bilateral in 8 cases.

Among diverse spectrum of neurological symptoms, headache was observed in53 and proptosis/ptosis was seen in 49 and facialnumbness in 44 were most common. Clinical objective signs of unilateral trigeminal nerve involvement (sensory more than motor) were noticed in 37 cases. Two subjects had signs of bilateral trigeminal nerve involvement. Facial nerve involvement in mucormycosis was seen in 11 subjects.

Dysarthria and double vision were reported in 7 and 5 subjects respectively. Nasal regurgitation of food (liquids more than solids) and nasalintonation of speech were found in 9 cases. 16 developed disorientation during course of the illness. Focal deficit in form of limb weakness and seizures were noticed in 6 and 2 cases respectively.

Diagnostic nasal endoscopy was done in all suspected cases on presentation for visual examination, sample collection and later for surgical follow-ups. About 46 had traces of characteristic blackish eschar seen on DNE. A significant number of cases had only pale mucosa without any characteristic feature suggestive of mucor, about 37 of them. Rest were obscured with crusting and serosanguinous or purulent discharge. Endoscopic deep tissue specimen was collected in all the cases. Immediate KOH mount was prepared which on microscopical examination showed broad aseptate branched fungal hyphae in favour of Mucorales species except in 3 cases where aspergillus species detected. Fungal culture was positive in 36 cases only (Fig 4).

	11-20 years	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years	Above 70 years
Female	0	1	3	19	15	2	0
Male	1	3	7	22	21	5	1

Fig 1 — Age wise and sex wise distribution

MRI mostly showed a continuous mass involving various areas of nose & paranasal sinus progressing to orbit or cranium, of variable low to intermediate intensity with areas of non-enhancement. Maxillary sinus was involved in 63 cases. Findings ranged from mucosal thickening to complete opacity in the entire maxillary sinus with or without air pockets. Ethmoid sinus was the next most common sinus involved followed by Sphenoid sinus and frontal being the least commonly involved sinus. Maxillary sinus with sphenoid sinus together was the most common multi-sinus involvement. Bony erosion was amongst the common presentation found almost all the cases except for the few initial cases. Of that, thinning/erosion of lamina papyracea was the most common finding. About 21 cases had hard palate erosion ranging from minor erosion to perforation. Anterior wall of maxilla & frontal bone was not involved in any of our cases. Septal perforation was suggested in 23 cases.

In Fig 5, MRI cut from patient with significant involvement of left intra & extra conal orbital space, left nasolacrymal duct, left infra trmporal fossa extending to check, with thrombosis of left superior ophthalmic vein and widening of left cavernous sinus without any significant involvement of any of the sinuses.

Involvement of the posterior wall of the maxilla was specially considered in all cases as guided by review of literature. It was found that there was necrotic debris behind posterior wall of maxilla in pterygopalatine fossa in most of the cases, even when posterior wall of maxilla looked intact which was seen in around 8 cases.

The orbit was involved 47 of our patients, of which 10 patients had only thickening of the extraocular muscles, 34 had preseptal cellulitis or intraorbital abscess, in 37 patients there was involvement of the intraconal compartment, 16 cases had radiological involvement of the optic nerve. Periorbital oedema, chemosis, exophthalmos and variables degrees of ulceration, crusting

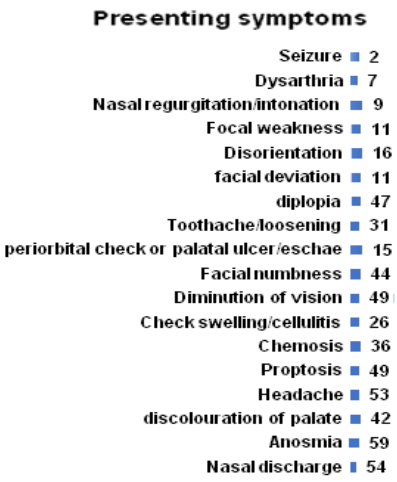

Fig 2 — Symptoms of ROCM cases

& necrosis were seen in all cases of orbital involvement. Among extraocular muscles, involvement of medial rectus was most commonly observed in 27 subjects followed by inferior rectus involvement in 26 cases. Orbital soft tissue involvement was observed in 30 subjects. Orbital apex was invaded by mucormycosis in 23 cases. About 14 cases had bilateral involvement.

For all 47 patients in whom the orbit was involved, there was definitive evidence of involvement of the pterygopalatine region except in 14 cases where no necrotic tissues were found after exploration of the pterygopalatine fossa. Involvement of the pterygopalatine region along with infiltration of the posterior periantral fat planes with soft tissue attenuation was present in 79 patients on MRI. There was also a contiguous extension from this to infratemporal fossa in 16 patients.

The pre-maxillary tissue was oedematous & cellulitic in 13 patients. Ulceration, necrosis & frank Eschar of the overlying cheek skin was seen in 6 cases. Breech in anterior wall of maxilla was not evident in any of our cases. Zygomatic bone was involved in 2 case.

Skull base osteomyelitis is a rare complication, usually seen relatively late in the course of the disease because angio-invasive nature of fungus which facilitates extensive spread of infection into the deep soft tissues through the perivascular channels even before bone destruction. Skull base involvement in form of clivus and greater wing of sphenoid was found in 14 and 19 cases.

Intracranial involvement was found in 27 patients, of which 22 had only cavernous sinus thrombosis. Around 9 frontal lobe abscesses and 2 temporal lobe abscesses were seen. No occipital lobe involvement was seen. 6 patient had multiple abscesses suggestive of mycotic emboli. Though meningeal involvement was seen in 29 cases, no sign of meningitis was clinically found in these cases possibly due to focal involvement. Direct fungal invasion to brain parenchyma was seen in 5 cases with evidences of stroke in 19 cases.

Stroke correlated well with the side where internal carotid was involved/more involved (in case of bilateral ICA involvement) and most common observation was presence of watershed infarction (superficial and deep territory) with 4 patients having ACA/MCA and MCA/PCA territory watershed infarction. Among the stroke patients, Internal Carotid Artery (ICA) at the level of cavernous sinus was encased by mucormycosis in 10 cases, while MR angiography showed normal calibre of ICA on the affected side in 1 subject. Internal carotid artery thrombosis was seen in 4 cases. Bilateral ICA involvement was observed in 2 subjects. Additionally, 4 subjects demonstrated ICA involvement without any evidence of infarction.

Average hospital stay for patients were 26 to 37 days. Operative timings were not considered as multiple and multilevel procedures were performed in these cases in ongoing COVID-19 pandemic requiring multiple biosafety protocols. Every patient was packed post-surgery with Amphotericin B impregnated packs which was removed after 2nd days. Suction and irrigation are done under endoscopic guidance on 2nd day. Repeat MRI is performed after 10 days unless any deterioration of symptoms or endoscopic evidence of residual disease is seen. Patients are followed up weekly till adequately healed mucosalised cavities are achieved mostly by weekly endoscopies and if needed by MRI. Five patients were re-operated (3 debridement and 2 exenteration) for residual or progressive disease within 10 days of first procedure. Despite all our efforts, 32 patients expired eighter due to the disease or underlying comorbid complications. Rest of the patients are under stages of mucosalhealing process with no residual or recurrences with minimum 3 months of endoscopic follow-up.

Discussion

The term Rhino-orbital-cerebral Mucormyco-sis refers to the entire spectrum of disease caused by mucorales when it involves nose, sinuses, orbit and brain which is often discussed in continuum[1,3-5]. In COVID times, reuse of disposable masks, contaminated rebreathers, contaminated water

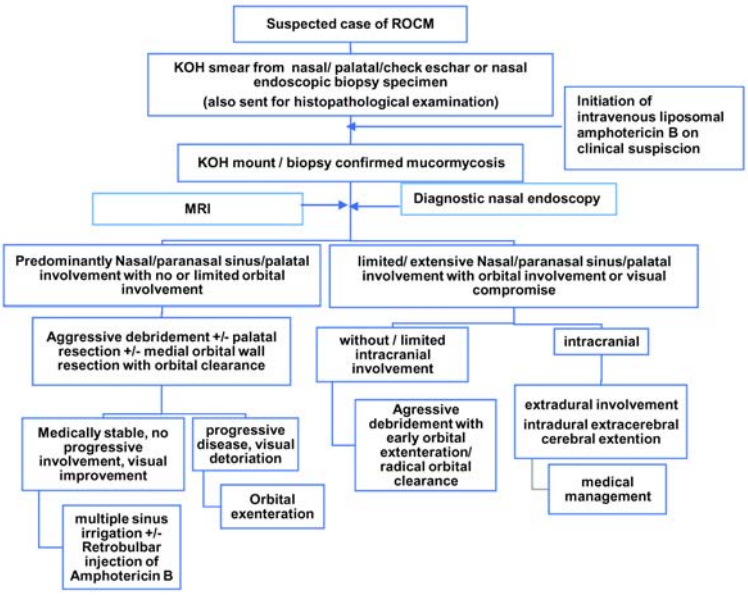

Fig 3 — Management protocol in a suspected case of ROCM

Fig 4 — Diagnostic nasal endoscopic picture in a case of mucormycosis

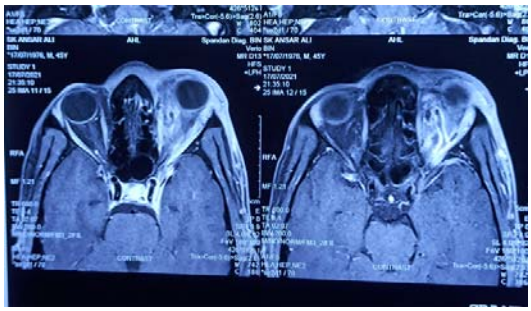

Fig 5 — MRI cut from patient with significant involvement of left intra & extra conal orbital space

chambers of oxygen supplies and contaminated suction equipments are also implicated due to reduced availability in hospital & excessive use by non-medical personals without proper sterilisation control.

Diabetes is the single most common underlying condition in ROCM[3-5] along with other immuno compromising conditions like burns, AIDS, severe trauma and organ transplant patients on immuno-suppressants or multiorgan failure are at risk for lowering immunity and initiation of mucormycosis[3-5]. Another factor that may predispose to mucormycosis is the use of antifungal prophylaxis or treatment, which is effective against *Aspergillus* but not Mucorales (voriconazole and echinocandins)[5]. The COVID-19 pandemic, with unchecked steroid usage, in association with diabetes and irrational use of multiple antibiotics & antifungals make the land fertile for unusual fungal growth, as evidenced by recent surge of mucormycosis[6,7]. COVID-19 patients are more vulnerable because of compromised immune system with decreased CD4+ and CD8+ lymphocytes[6,7].

Susceptible patients get infected by inhaling spores into nasal and sinus mucosa or oral cavity. This fungus is known to be angio-invasive; it digests elastic tissue and penetrates vessel wall, causing arteritis and intramural spread. The fungus invades vessels wall, causing mechanical and toxic damage to the intima leading to thrombosis. These thromboses cause emboli and vascular obstruction responsible for tissue necrosis. This produces the characteristic blackish necrotic eschar on which fungus thrives and invades further.The fungus also causes osteitis and osteomyelitis of sinus wall along with pressure necrosis and subsequent erosion leading to extension into orbit & anterior skull base.Various elements lead to orbital extension, primarily due to anatomical relationship to paranasal sinuses; a paper-thin bone of the lamina papyracea separates the orbit from ethmoid sinuses and the direct spread of infectious organisms which permits due to lack of valves in the inferior and superior ophthalmic veins in the midface. Colonization of pterygopalatine fossa and resulting involvement of infraorbital nerve may explain the initial retro-orbital pain and paraesthesia in this region. In association with the marked orbital inflammatory process in a patient with mucormycosis optic nerve infarction may develop following the presentation. Due to central location of the sphenoid sinus, the infection can easily spread to the surrounding skull base structures like cavernous sinus, sella, internal carotid artery, meninges, clivus, prepontine cistern, rarely basilar artery, etc. Hematogenous spread occurs by formation of mycotic emboli and thrombus due to extension of fungal hyphae. The fungus usually involves more proximal portions of the vessels causing vascular damage in large areas. The thrombus or the embolileads to cerebral infarction. This spread could lead to vasculitis and eventually meningitis or cavernous sinus thrombosis. Perineural spreadoccurs along the nerves and their for a minae resulting in cranial nerve palsies and anterior skull base spread. The infection can also spread by olfactory nerves through the cribriformplate, into the anterior skull base.

A clinician must consider mucor with high index of suspicion and sound clinical judgement to pursue invasive testing early to reach a diagnostic consensus. Vague symptoms like fever, nasal blockage or discharge, headache, facial pain with swelling, upper jaw tooth pain and loosening of teeth, hemiplegia or stroke, cognitive dis-order etc can be primarily seen & often misled or delay diagnosis. Signs of deep-seated retro-orbital orbital pain, facial hypoesthesia, abrupt vision loss, ophthalmoplegia, chemo-sis, proptosis, ptosis and periorbital cellulitis usually draws the patient to serious medical attention (Fig 3).

PAS staining showing branched hyphae suggestive of mucormycosis from sample collected by diagnostic nasal endoscopy at x400 magnification (Fig 6). Post-operative histopathological examination showing mucor infiltration in bone from intra-operative sample collected from region of lamella papyracea (Fig 7).

A CT scan is the most widely used imaging modality for evaluating usual sinus disease or bony erosion but MRI is superior in delineating extent of disease, bone erosion & identifying tissue necrosis[4,8]. Multiple sequences of MRI provide complete overview of the disease process specially asset of T1, T1 with contrast, T2, T2 fat suppressed and on need basis MRA or DW studies are crucial for proper surgical planning. Nevertheless, MRI and CT scan may be normal in limited cases, especially at beginning of infection, which reinforces the necessity for a careful endoscopic nasal evaluation and biopsy in ‘at risk’ patients.

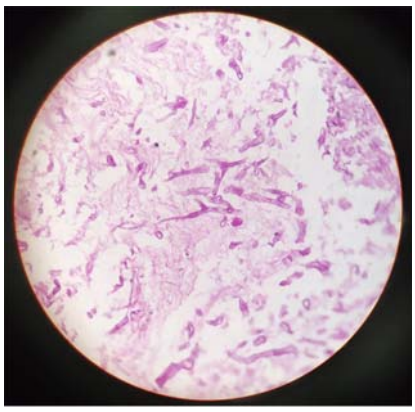

Fig 6 — PAS staining showing branched hyphae suggestive of mucormycosis from sample collected

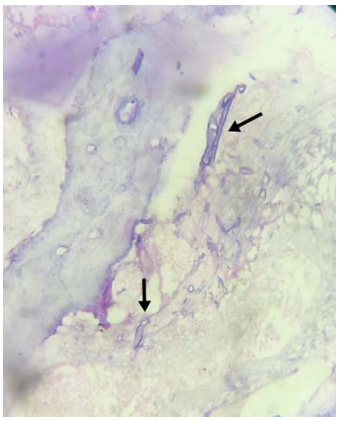

Fig 7 — Postoperative histopathological examination showing mucor infiltration in bone

MRI of sinuses and orbits usually do not show predictable patterns as seen in our cases with most of the cases showing iso to hypo-intense appearance on T2W images. T2W signal or enhancement patterns are variable and thus not reliable markers for invasive fungal infection. Extra-sinus extension in forms of fat stranding in the premaxillary, retro-maxillary fat, orbital fat stranding and altered fat in pterygopalatine fossa is more important to suggest invasive fungal infection on imaging, in the appropriate clinical setting.

Meticulous nasal endoscopy is the crux of diagnosis; idea is to identify discolouration (often a black necrotic turbinate), granulation, ulceration or crusts in nose, most frequently near the middle turbinate,septum and more rarely inferior turbinate along with necrotic tissues. Dried blood resembling black necrotic tissue or a purulo-sanguineous exudate with thin, pink and watery presentation and with an uncomfortable smell may be detected on the nasal septum, turbinates and palate. Endoscopic guided biopsy specimen usually yields better sample. If possible, MRI is to be done prior biopsy, as minimal debridement done for biopsy can be misinterpreted as inflammation by MRI.

Definitive diagnosis is based on histopathological and microbiological examination. In tissue specimen, mucorales presents as broad aseptate hyphae, 10-50 μm large, with right-angled branching. Cultures may be negative even if histopathology shows the characteristic organism. The rates of successful tissue cultures are only 33-50% probably because of hyphae damaging during manipulation, suboptimal standard culture conditions and prolonged antifungal pre-treatment. Agents causing mucormycosis can contaminate specimen or colonise airway, so isolation of fungi in culture do not necessarily prove infection. Interpreting the culture results in context of patient's actual clinical condition is necessary to determine initiation of antifungal therapy. Serum tests like 1,3-beta -D-glucan aspergillus galactomannan assay which are increasingly being used for suspected invasive fungal infections are characteristically negative for mucormycosis as the do not share same cell wall components. However, a simple direct microscopic smear with KOH offers a quick reliable diagnosis to initiate management.

Anti-fungal medications are the mainstay of management along with surgical debridement[3,4,9]. Prompt and aggressive surgical debridement of all necrotic tissue is of paramount importance for a successful outcome. The survival rates are different depending on therapeutic approach: AMB alone (61%); surgery alone (57%); and AMB plus surgery (70%)[9].

High-dose lAMB (5-10 mg/kg/d iv), for a minimum of 6 to 8 weeks, is considered to be the gold standard[3,4]. Drug is to be started with highest tolerable dosage and not escalated gradually. cAMB was more commonly used (1 mg/kg per day iv) due to lower costs and availability, especially in view of epidemic situation and out of proportion demand. lAMB is better tolerated, and higher doses can be achieved with reduced risk of nephrotoxicity. Renal function and electrolytes are monitored in all forms of AMB therapy. Poscanazole (POSA) and isavuconazole (ISAV) are approved by the FDA and the European Medicine Agency (EMA) for treatment of mucormycosis. POSA and ISAV can be given orally or intravenously (2x300mg/day 1, followed by 1×300 mg/day for POSA, respectively, 3×200 mg/days 1-2, followed by 1×200 mg/day for ISAV).

Management of persistent resistant hyperglycemia & diabetic ketoacidosis were major challenge to our medical team. Impaired renal function which includes increased potassium wasting and hypokalaemia, metabolic acidosis due to distal renal tubular acidosis & polyuria due to diabetes insipidus were common with use of amphotericin B. Acute renal failure, renal transplant & single kidney patient needed special attention regarding dose adjustment. Early initiation of antifungal, its maintenance fighting metabolic complications and renal replacement therapies have major role in deciding prognosis.

Early and adequate debridement enormously reduce fungal & inflammatory load. Fungus continue to grow in necrotic soft tissue elements, thrombotic vessels and also in dead osteomylitic bone where amphotericin does not reach. Debridement helps better penetration of antifungals. Adequate debridement also prevents direct extension into orbital or cerebral. In

case of lack of response to medical modalities, it is the way to stop progression of infection and buy time for medicinal therapies to work.

Wherever possible all procedures were performed in single sitting possibly through endoscopic endonasal route for disease clearance in nose, sinuses, peri sinus areas, orbital, skull base & approachable cranial cavity through endonasal route. One must ensure that all cavities are properly marsupalized for drainage of left out sinuses and cavities after the surgery. Surgical planning also involves preparation of a corridor for easy endoscopic follow-up for recurrence, minor suction-clearance process for crust removal and amphotericin irrigation.

When the disease is confined to sinuses, radical endoscopic approach is considered and unlike usual FESS, mucosa is taken off with disease except in uninvolved areas, wide meatotomies and turbinectomies were performed even on suspicion of fungus involvement. Normal posterior part of bony septum was only removed in cases with bilateral ethmoidal and sphenoidal involvement for surgical access except for devitalised necrotic brittle bone from septum in 19 cases. Palatal involvement was involved in 21 cases and were removed endoscopically in 5 cases and as a part of open maxillectomy in 16 cases.

Some structures are invariably involved like turbinate & medial wall of maxilla, and are removed eighter for disease or more extensive surgical approaches. Endoscopic modified denker's approach was used in every endonasally done case. Endoscopic trans-maxillary approach involving removal of posterior wall of maxilla was done whenever MRI showed disease in pterygomaxillary or temporal fossa region, or else recurrent, residual or advanced cases. Endoscopic transprerygoid approach is performed to explore pterygopalatine fossa in all our cases and contrary to usual consensuses no mucor or necrosis was identified in 14 cases. Most of the times maxillary artery and sphenopalatine artery was found thrombosed & it was traced laterally till blood flow is established. Root of pterygoid wedge was drilled in all the cases with exposure of the vidian nerve as medial limit and maxillary nerve representing the lateral limit, which can be drilled deep to reach intra-petrosal ICA. The maxillary nerve is followed from the roof of maxillary sinus to the infraorbital fissure.

Intra-operative picture showing pus being drained from orbit after incising the periorbita following endoscopic danker approach for maxillectomy, ethmoidectomy and medial orbital wall resection with traces of blackish eschar along orbital floor (Fig 8). Intraoperative picture following endoscopic extended medial maxillectomy with exposure of necrotic pterygoid wedge and pterygomaxillary fossa following removal of posterior wall of maxilla (Fig 9). Intraoperative picture during endoscopic orbital clearance showing exposure of optic nerve and surrounding necrotic tissues (Fig 10).

Orbital exenteration is done were done in 22 cases in association with department of ophthalmology for extensive orbital disease with no visual potential & ophthalmoplegia, where the disease is limited to orbit without or minimal extension to cavernous sinus. The decision to exenterate lies with treating multi-disciplinary team because there is no firm consensus regarding the indications and timing of exenteration. Orbital medial wall resection was done whenever T2W fat suppressed images directed intraorbital disease and globe sparing orbital clearance was done in25 cases under endoscopic guidance. Every effort was made while debridement to preserve vision and spare nerves and muscle wherever possible. Orbit was opened for inspection by endoscopic medial orbital wall removal in 7 redo cases with visual disturbance and found to have only inflammatory oedema.With angled telescopes & debriders, globe sparing orbital clearance is quite rewarding in expert hands. It'smuch less radical, allows for an early aesthetic appearance even if visual potential fails, and does not subject the patient for any further complex costly reconstructive procedure. It also helps in direct trans-nasal cauterization of ophthalmic artery as it emerges from optic foramen under better magnified visualization of the orbital involvement.

Irrigation of orbit and sinuses with amphotericin B (1 mg/ ml) increases local concentration of the drug and has been shown to improve outcomes. Retrobulbar injection of amphotericin B can be given in patients who are unable to undergo aggressive surgical debridement (1 ml of 3.5 mg/ml with the antecedent retrobulbar injection of anaesthetics)[4].

Open trans-facial faciomaxillary approaches in various forms of maxillectomy were devised in extensive case with pan sinus and extra sinus involvement with periorbital, orbital & facial involvement difficult to approach through endonasal route in association department of maxillofacial & plastic surgery whenever needed. If there is dural involvement, then additional transcranial surgery is done in a team approach with the neurosurgeons. These surgeries included craniofacial exposure and resection to include the sinonasal and intracranial areas. 4 cases of frontal lobe abscess were drained in association with department of neurosurgery in same sitting by open craniotomy approach.14,5 & 2 external maxillectomy, external fronto-ethmoidectomy and external fron to-ethmoido-sphenoidecomy were performed

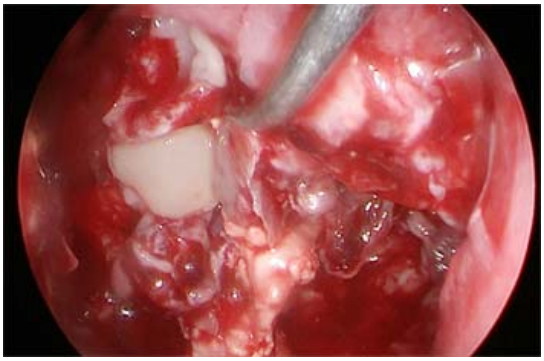

Fig 8 — Endoscopic Intra-operative picture showing pus being drained from orbit after incising the periorbita

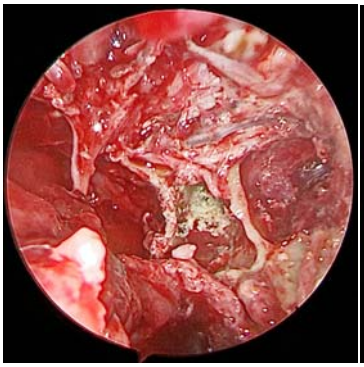

Fig 9 — Intra-operative picture following endoscopic extended medial maxillectomy with exposure of bilateral maxillary sinuses and anterior face of sphenoid with sphenoid sinus in view

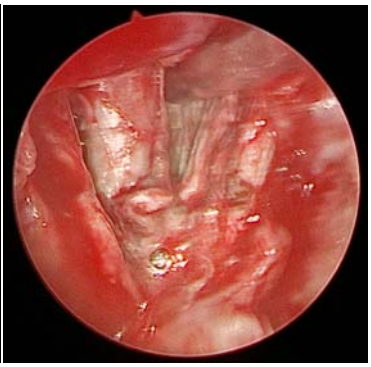

Fig 10 — Intra-operative picture during endoscopic orbital clearance showing exposure of optic nerve and orbital apex

respectively. There were fewer instances when the fungus in brain was not easily approachable without significant morbidity and risk of mortality or there were multiple intracerebral abscesses and, in these situations. We decided to rely on medical treatment alone. We do not recommend any reconstructions in same sitting in view of high possibility of recurrence, for adequate follow-up and for not unduly prolonging the already extensive surgery.

Also, there is a special need for adequate sterilisation protocols of endoscopic micro instruments housing several joints and screws which might fungal particles in view of an implantable fungal disease in question in an epidemic situation. Endoscopic approach provides enlarged closeup & wherever needed angled views for far reached spaces around the corners for precise disease clearance. Though we have devised open approaches for extensive diseases with skin involvement or orbital exenteration but still advocate the role of combined endoscopic clearances of deeper confines.

Though our limited knowledge of this dreaded rare disease has boasted several times in this pandemic, we got here with loss of many life & left many with severe morbidity. But this disease once considered almost fatal has seen a steady rise in survival rate by our combined effort in treating, learning from seniors and colleagues & importantly educating our junior colleagues. We sincerely hope that we don't have to see this nightmare again. We hope knowledge gathered in this venture will aid early diagnosis & precise management of Rhino-orbito-cerebral Mucormycosis.

Conclusion

Strong clinical suspicion is the mainstay for early diagnosis. Maximal tolerable medical therapy is to be initiated on clinical grounds even if microbiological proof couldn't be obtained. MRI is essential tool for diagnosis, evaluating progression and surgical planning. Adequate debridement aims a radical approach till normal bone and normally bleeding tissues are identified. Regular endoscopic follow-ups are vital in detecting accidental remnant or early recurrent disease. Healthy epithelisation of surgical site along with normalisation of biochemical & radiological parameters dictates end point of antifungal therapy.

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