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Management Of Covid-19 Associated Mucormycosis (CAM): An Endemic Experience During The Pandemic.

Dr Pushkar Gadre[1], Dr Imran Khan[2], Dr Murarji Ghadge[3], Dr Rajshekhar Halli[4], Dr Kiran Gadre[5]

Consultant Maxillofacial Surgeon (Ruby Hall Clinic, Pune)[1], Professor (Jamia Milia Islamia University, New Delhi)[2], Consultant ENT Surgeon (Ruby Hall Clinic, Pune)[3], Professor (Bharati Vidyapeeth Dental College, Pune)[4], Consultant Maxillofacial Surgeon (Ruby Hall Clinic, Pune)[5]

Introduction:

COVID-19 is associated with a significant risk of development of life-threatening complications depending on the host's immune status, presence of co-morbid conditions, drugs used to counter the massive inflammatory airways constriction and subsequent cytokine storm. [1-5] These complications can pave way to opportunistic infections with associated complications like mucormycosis—a fungal emergency and acute rare fulminant fatal infection. It has a highly aggressive tendency for contiguous spread, associated with a poor prognosis, if not accurately and promptly diagnosed and managed. [6] Classically, uncontrolled diabetes mellitus (DM) and other immunosuppressive conditions such as neutropenia and corticosteroid therapy are known risk factors for mucormycosis. [7] The establishment of mucormycosis requires spores inhalation onto the airways or any vulnerable epithelium; germinating into angio-invasive hyphae—utilising host conditions such as hyperglycemia, ketoacidosis, iron overload and neutropenia— causing endothelial damage, leading to local hemorrhage, thrombosis and necrosis; and eventual dissemination to involve multiple organs. [7,8] Amongst all types, Rhino-Orbito-Cerebral-Mucormycosis (ROCM) needs early recognition, and treatment for successful outcome.

The present series is an observational study of 47 cases of ROCM intended to discuss the incidence, presentation and management strategies.

Methodology:

Hospital records of patients, including other details, who had undergone treatment for Corona Associated Mucormycosis (CAM) during the period May 2021 to October 2021 at the centres/hospitals were reviewed retrospectively to analyse the incidence and the pattern of infection along with treatment instituted. The relevant demographic & other details of the patients are presented in **Table 1**.

Table 1: Master table depicting demographic and other relevant details

	Known comorbidities	Acquired comorbidities	Drugs used during Covid treatment	Time to mucormycosis from Covid -19 in weeks	HbA1C Levels at arrival	Previous surgical procedure	No. of times previous surgery performed	Surgical procedure performed	Total Dose of Amphotericin in grams	Follow-up in months	Complications	Outcome	Immediate oral Rehabilitation
ateral ndible	None	Post covid DM	Remdesivir Steroids	3	8	Extraction and biopsy	1	Pelvimandibulectomy from angle to angle	4.5	6	None	Good	None
xilla, moid, henoid, ntal uses	DM	Covid	Remdesivir Steroids	4	8	FESS	2	Rt. total maxillectomy, ethmoidectomy, sphenoidectomy, frontal exploration	5	7	None	Good	Obturator
ateral xilla, mod	DM	Covid	Remdesivir Steroids	3	7.5	FESS	1	Rt. Low maxillectomy, Lt. Maxillectomy, orbital floor removal, Lt. Ethmoidectomy.	4.5	6	None	Good	Primary closure
ndible	None	Post covid DM	Remdesivir Steroids	5	8	None	None	Rt. Pelvimandibulectomy with coronoidectomy	4.5	7	None	Good	Secondary healing
ateral xilla	DM	Covid	Remdesivir Steroids	3	8.5	Extraction and biopsy	1	Bilateral Low Maxillectomy	4.75	7	None	Good	Primary closure
ateral xilla	DM, HT	Covid	Remdesivir Steroids	3	8.2	None	None	Lt. maxillectomy orbital floor removal, Rt. Caldwell Luc	4.75	6	None	Good	Primary closure
xilla, moid, henoid, anterior eolus	Leukemia on Chemotherapy	Covid	Remdesivir Steroids	5	5.6	None	None	Lt maxillectomy, ethmoidectomy, sphenoidectomy, orbital floor removal, Rt maxillary alveolectomy till 13.	5	7	None	Good	Obturator
xillary, moid, henoid, bit	None	Post Covid DM	Remdesivir Steroids	3.5	10.1	FESS	2	Rt. Maxillectomyethmoidectomy, sphenoidectomy, orbital floor removal	4.5	6	None	Good	Primary closure
Maxilla	DM, HT	Covid	Remdesivir Steroids	3.5	9.8	None	None	Lt. Low maxillectomy.	4.75	8	None	Good	Primarycl sure
d Palate	DM	Covid	Remdesivir Steroids	4	8.3	Biopsy	1	Bilateral palatectomy saving alveolus and teeth	5	7	None	Good	Obturator
xilla, goma, alveolus 24	None	Post covid DM	Remdesivir Steroids	3	10.6	FESS	3	Rt. Low maxillectomy, zygomectomy Lt. alveolectomy till 25	5.25	6	Needed dialysis	Good	Obturator
Maxilla, goma, bital or	Operated for Rt. CA Mandible 16 years back with radiotherapy, DM, HT	Covid	Remdesivir Steroids	6	10.3	FESS	2	Lt maxillectomy, zygomectomy, orbital floor removal	5.25	6.5	Needed dialysis	Good	Primary closure
xilla, moid,	DM	Covid	Remdesivir Steroids	3.5	9.6	FESS	1	Rt. maxillectomy, ethmoidectomy, sphenoidectomy,	5.5	1	None	Good	Primary closure

henoid								orbital floor removal					
xilla, it, skull e	DM HT	Covid	Remdesivir Steroids, Tocilizumab	2.5	10.2	FESS	5	None	None	NA	Succumbed prior to surgery	Poor	NA
xilla, moid, henoid, goma,	None	Covid, drug induced DM	Remdesivir Steroids	4	9.8	None	None	Rt. maxillectomy, ethmoidectomy, sphenoidectomy, zygomectomy, orbital floor removal	4.5	1	None	Good	Primary closure
no ebral, moid, henoid, goma, bit	None	Covid, drug induced DM	Remdesivir Steroids, Tocilizumab	1	11.1	None	None	Lt maxillectomy, ethmoidectomy, sphenoidectomy, zygomectomy, orbital exenteration	6	12	None	Good	Primary closure, Obturator
xilla, moid, henoid	DM	Covid	Remdesivir Steroids	4	8.7	None	None	Lt maxillectomy, ethmoidectomy, sphenoidectomy	4.5	1	None	Good	Primary closure
ateral xilla	None	Covid, drug induced DM	Remdesivir Steroids	3.5	9.2	FESS	1	Bilateral Low Maxillectomy, Caldwell Luc	5	12	None	Good	Primary closure obturator
ateral ndible	DM, HT, IHD, CABG 5 years back	Covid	Remdesivir Steroids, Tocilizumab	2.5	13	Extraction	2	None	NA	NA	Succumbed prior to surgery	Poor	NA
Maxilla	DM	Covid	Remdesivir Steroids	4	7.2	FESS	1	Lt subtotal maxillectomy	4.5	6	None	Good	Primary closure
moid, henoid, bit	DM	Covid	Remdesivir Steroids Tocilizumab	4.5	11.1	FESS	3	None	NA	NA	Succumbed prior to surgery	Poor	NA
ndible, ateral xilla, ensive nocerbr olveme	DM, HT, Dengue	Covid	Remdesivir Steroids, Tocilizumab	2	13.2	None		None	NA	NA	Succumbed prior to surgery	Poor	NA
xilla, moid, bit	DM, HT, IHD, MI	Covid	Remdesivir Steroids Tocilizumab	3	10.7	FESS	3	Lt maxillectomy, ethmoidectomy, orbital exenteration,	NA	NA	Succumbed post surgery	Poor	NA
xilla, moid, henoid,	None	Covid	Remdesivir Steroids	5	8.6	None	None	Lt maxillectomy, ethmoidectomy, sphenoidectomy, debridement of skin	6.5	8	Very delayed skin healing	Good	Primary closure

aneous olveme								lesion					
d Palate	HT	Covid	Remdesivir Steroids	6	7	None	Non e	Palatectomy	4.5	9	None	Good	Obturator
ateral xilla, moid, henoid, bit	DM, HT, Dialysis for 5 years	Covid	Remdesivir SteroidsToc ilizumab	4.5	13 .4	None	Non e	None	NA	N A	Succu mbed prior to surgery	Poor	NA
xilla, moid, henoid, it aneous olveme	DM, HT	Covid	Remdesivir Steroids Tocilizumab	2	11 .3	FESS	1	Rt. maxillectomy, ethmoidectomy, sphenoidectomy, orbital exenteration, debridement of skin lesions.	5.25	2	None	Good	None
ateral xilla, bits	DM	Covid	Remdesivir Steroids	3	12 .3	FESS	2	Bilateral maxillectomy, orbital floor removal	NA	N A	succum bed post-surgery	Poor	NA
ateral ndible	None	Covid	Remdesivir Steroids	3	7. 8	Extract ion	2	Pelvimandibulectomy from angle to angle	4.5	6	None	Good	None
ateral xilla, moid, henoid, bits	DM	Covid	Remdesivir Steroids Tocilizumab	4	9. 8	Extract ion and biopsy	1	Bilateral maxillectomy, ethmoidectomy, sphenoidectomy, Lt orbital exenteration	NA	N A	succum bed post-surgery	Poor	NA
xilla, moid, henoid, bit	DM	Covid	Remdesivir Steroids Tocilizumab	3.5	7. 9	Extract ion and biopsy	1	Lt maxillectomy, ethmoidectomy, sphenoidectomy, orbital exenteration	5.5	9	None	Good	Obturator
nocerbr xilla, anial olveme	DM	Covid	Remdesivir Steroids Tocilizumab	2.5	13 .2	FESS	3	None	NA	N A	Succu mbed prior to surgery	Poor	NA
xilla, Orbit, moid, henoid	DM, Dialysis	Covid	Remdesivir Steroids Tocilizumab	2.5	12 .9	FESS	1	None	NA	N A	Succu mbed prior to surgery	Poor	NA
xilla, moid, henoid, ntal	HIV, HCV, HBSAG , DM, Cirrhosi s	Covid	Remdesivir Steroids Tocilizumab	2	11 .9	None	Non e	None	NA	N A	Succu mbed prior to surgery	Poor	NA
Maxilla	None	Covid	Remdesivir Steroids	5	7. 5	None	Non e	Lt. low maxillectomy, Caldwell Luc	4.5	8	None	Good	Obturator
xilla, goma, moid, henoid	DM	Covid	Remdesivir Steroids	6	13 .8	Extract ion and biopsy	1	Rt maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy,	4.5	6	None	Good	Primary closure
xilla, moid, henoid	None	Covid	Remdesivir Steroids	6	8. 2	None	Non e	Lt maxillectomy, ethmoidectomy, sphenoidectomy	4.75	1. 5	None	Good	Primary closure
xilla	DM	Covid	Remdesivir Steroids	6	8. 2	FESS	1	Rt maxillectomy,	4.5	1. 5	None	Good	Primary closure

xilla	DM	Covid	Remdesivir Steroids	4	8.6	None	None	Rt maxillectomy,	4.5	6	None	Good	Primary closure
ateral xilla	DM	Covid	Remdesivir Steroids	5	8	None	None	Bilateral maxillectomy	4.5	7	None	Good	None
ateral xilla, goma, moid, henoid, ntal, bit	DM	Covid	Remdesivir Steroids	1	10.2	Biopsy	1	Bilateral maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontal exploration, orbital floor removal	5.2	1.5	Needed dialysis	Good	Primary closure
ateral xilla, goma, moid, henoid, ntal, bit	Pancytopenia	Covid	Remdesivir Steroids Tocilizumab	1	5.6	Biopsy	1	Bilateral maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontal exploration, Rt. orbital floor removal, Lt. orbital exenteration	1.2	NA	succumbed post-surgery	Poor	None
ateral xilla, goma, moid, henoid, ntal, bit	DM	Covid	Remdesivir Steroids	1	8.3	Biopsy	1	Bilateral maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontal exploration, orbital floor removal	4.5	1.5	Needed dialysis, PEG	Good	Obturator
xilla, goma, moid, henoid, ntal, bit	DM	Covid	Remdesivir Steroids	1	7.6	FESS	1	Rt. maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontalexploration, orbital floor removal	6.8	2	Potassium correction	Good	Primary closure
ateral xilla, goma, moid, henoid, ntal, bit	DM	Covid	Remdesivir Steroids	1	10.4	FESS	1	Bilateral maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontal exploration, orbital floor removal	4.5	1.5	None	Good	Primary closure
Maxilla, goma, moid, henoid, ntal, bit	DM	Covid	Remdesivir Steroids	1	10.2	FESS	1	Lt. maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontal exploration, orbital exenteration,	4.5	1.5	None	Good	Primary closure
Maxilla, goma, moid, henoid, ntal, bit	DM	Covid	Remdesivir Steroids	1	8.2	FESS	1	Lt. maxillectomy, zygomectomy, ethmoidectomy, sphenoidectomy, frontal exploration, orbital exenteration.	4.5	1.5	None	Good	Primary closure

HT= hypertension, DM= Diabetes, PEG= Percutaneous endoscopic gastrostomy, HIV =Human immunodeficiency virus, HbsAg = Hepatitis B, HCV Hepatitis C virus, CABG= Coronary artery bypass grafting, MI Myocardial infarction, IHD=Ischemic heart disease

Summarized protocol followed in all the cases: Management of these cases of invasive fungal infection (IFI) required multidisciplinary collaboration and aggressive surgical therapy. Whereas, surgical management of ROCM was done by the team of maxillofacial and Ear Nose Throat (ENT) surgeons, the associated co-morbidities and medical requirements were managed by respective medical and surgical specialists.

Appropriate antibacterial and anti-fungal agents and surgical treatment was instituted post Gram stain, AFB stain, KOH mount, culture (aerobic / anaerobic) and sensitivity test, and histopathological reports.

Anti-fungal agent, lyophilized amphotericin-B (L-AMB), was initiated in dosage of 3-5mg/kg/day, in confirmed mucormycosis cases and was guided by renal parameters. Minimum total dose administered was 4.5 gms and maximum was 8 gms. Renal parameters and blood sugar levels (to maintain a level of 150-200 mg/dL) were monitored daily or alternate day depending on necessity.

Interventional treatment: All surgical procedures mentioned in **Table 1** were carried out via intraoral approach, and functional endoscopic sinus surgery (FESS) was done by ENT surgeon to clear the ethmoidal, sphenoidal, and frontal sinuses, in all cases except, where orbital exenteration was done. In cases of orbital exenteration, this clearance was achieved through orbit.

In cases where primary closure was achieved, antrostomy was done and the defect was packed with povidone iodine-soaked roller gauze, which was removed 48 hours post-surgery. In cases where no primary closure was achieved, roller gauze dressings soaked with povidone iodine was done for 10 days and was followed by temporary obturator fabrication wherever deemed necessary. Ostectomy was done till fresh active bleeding bone was encountered during the surgery. Minimum period of follow up was for 6 months except where cases were lost to follow up or deceased.

Statistical analysis: All the data was entered into a computer by giving coding system, proofed for entry errors. Data obtained was compiled on a MS Office Excel sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States). Data was subjected to statistical analysis using statistical package for social sciences (SPSS v 26.0, IBM). Variables were summarized as absolute & relative frequencies. Absolute & relative frequencies of different variables were compared using the Chi-square test with level of statistical significance 0.05. Descriptive statistics like frequencies and percentage for categorical data, Mean & SD for numerical data were depicted.

Results:

Retrospective analysis was carried out in 47 cases of CAM (Table 1) which were in the age range of 25-82 years. Maximum affected cases were above 60 years range (24), followed by 51-60 years range (9). Male predilection (M: F 35:12) was observed.

Diabetes mellitus (DM) was present in 40 cases with 33 known DM, 4 post Covid DM & 3 drug induced DM to post COVID -19 therapy. DM was the most commonly known co-morbidity seen with a frequency of 46.8% and there was a statistically highly significant frequency (p-0.002) with higher frequency in age group >60 years. The correlation between DM and involvement of mandible was statistically significant (P-0.01) being the rarest entity to be considered. Average time to CAM from COVID-19 was 3.3 weeks.

The most common site of involvement was Maxilla (37) followed by ethmoid & sphenoid sinuses, orbit, mandible, palate, and zygoma, There was cranial involvement in 4 cases. The involvement of mandible by ROCM in 5 cases was deemed to be rare and seldom reported.

Amongst the previously performed surgical procedures, FESS was the commonest (42.6%) followed by other procedures like biopsy and extractions. All the cases underwent radical surgical procedures amongst which maxillectomy was performed in highest number of cases followed by ethmoidectomy and sphenoidectomy.

The highest mortality rate was seen in individuals with DM and cranial involvement suggesting it to be as high-risk factor associated with cases of Mucormycosis as a complication in Post COVID recovery phase of a treatment regimen. Our overall mortality was 23.4% which is relatively less. (Table 2)

Table 2: Mortality

	Frequency	Percent
N	36	76.6
Y	11	23.4
Total	47	100.0

Tocilizumab was administered in 30% of cases along with Remdesivir and Steroids as a regimen during their COVID-19 treatment, of which 11 patients succumbed. (Table 3)

Table 3: Drugs used during Covid-19 treatment

	Frequency	Percent
Remdesivir, Steroids	33	70.2
Remdesivir, Steroids, Tocilizumab	14	29.8
Total	47	100.0

Post-surgical complications were minimal, and outcome was good in majority of the cases. Minimum follow-up period was 6 months in majority of the cases except who were lost for follow-up or deceased.

Discussion:

The long-term effects of COVID-19 are poorly understood, in their article reporting 50 long-term effects of COVID-19, Sandra Lopez-Leon et al [9] conclude that from the clinical perspective, multi-disciplinary teams are crucial to developing preventive measures, rehabilitation techniques, and clinical management strategies with patient perspectives designed to address long COVID-19 care. Mucormycosis would be one such addition to the still unknown long list of afflictions.

In their editorial, Verma DK, Bali RK [10] mention that current evidence does not suggest a direct causal effect relationship between COVID-19 and mucormycosis. They emphasize further need to investigate and establish evidence of nature of

relationship between the two, whether causal, contributory or coincidental or combination of influence of the virus on cell-mediated immunity, association of immunocompromised conditions and treatment protocols affecting immune mechanisms creating ideal conditions for IFI.

Mucormycosis is always considered a life-threatening infection with an earlier reported incidence ranging from 0.005 to 1.7 per million population and with a high (46%) fatality rate [11]. ROCM is the most common among all 6 known types of mucormycosis, and is sequelae of inhalation of spores by a vulnerable host [12]. It is evident through earlier reported studies, that specific pathophysiologic features of COVID-19 permit secondary/opportunistic fungal infections, to occur as an associated complication, due to deregulated immune system, during and post-treatment phase of the disease course. [13,14] The reduced numbers of T lymphocytes, CD4+T, and CD8+T cells alter the innate immune system in COVID-19 cases that persist in the recovery phase as well. [15]

The common initial presenting clinical features of CAM-individuals depend on which area/organ is most affected or affected first. [16-18] Our patients had similar presentation, but the rapidity of progress was alarming, particularly the loss of vision, sometimes in matter of hours.

The common initial presenting clinical features of CAM are: general systemic symptoms like fever, malaise, headache, swelling and pain of facial region. Ophthalmic presentations were periocular tenderness, proptosis, ptosis, chemosis, ophthalmalgia, ophthalmoplegia, decreased/loss of vision. (Fig 1)

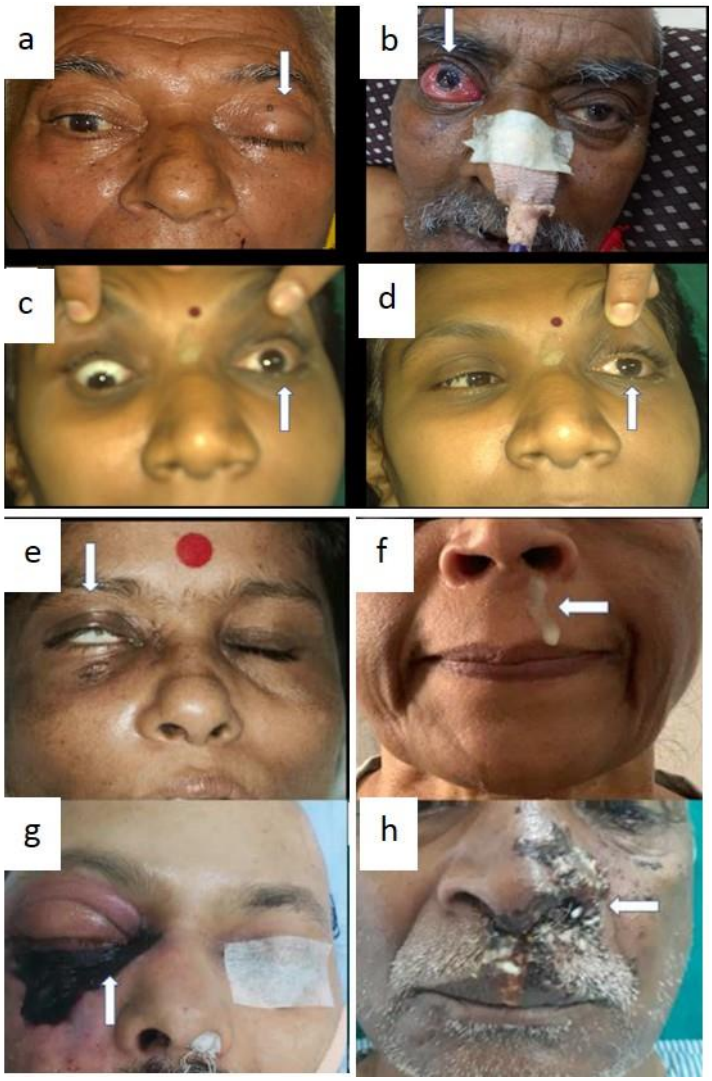

Fig 1 Showing clinical features of orbital, neural & cutaneous involvement in CAM, (a). Patient showing ptosis and proptosis of left eye (white arrow), (b). Severe chemosis right eye (white arrow), (c) and (d). Ophthalmoplegia lack of movements of left eye (white arrow), (e). Patient showing Bell's palsy right eye (white arrow), (f). Pus discharged nasally (white arrow), (g). Eschar formation with necrosis and gangrene of right lower eyelid (white arrow), (h). Multiple vesicle and abscess formation in nasal and upper lip region (white arrow).

Rhinosinus symptoms are nasal blockage/stuffiness, discharge, epiphora, tenderness/fullness over sinus region, epistaxis, postnasal discharge, anosmia.

Dentoalveolar symptoms were notably pus discharge from gums, mobile teeth, trismus, ulceration, necrosis and eschar formation on gingiva and palate, foul smelling discharge, halitosis, nonhealing socket along with rare presentations as mandibular osteomyelitis as reported in literature database. [16-18] (Fig 2)

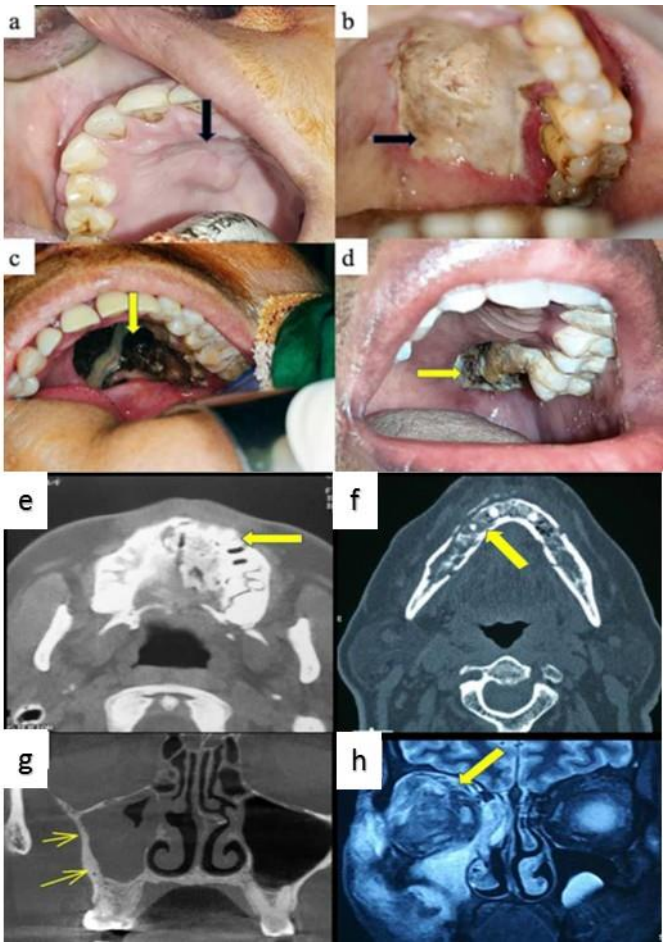

Fig 2. Showing clinical features of dento-alveolar involvement & imaging in CAM, (a). Early palatal abscess (black arrow), (b). Necrosis of palatal mucosa and yellow, denuded bone (black arrow), (c). Eschar formation with necrosis and gangrene palatal mucosa (yellow arrow), (d). Necrosis of palate causing sequestration of bone and mobile teeth (yellow arrow), (e). Osteomyelitis of maxilla with sequestration (yellow arrow), (f). Osteomyelitis of mandible CT scan showing osteolysis of buccal and lingual cortices, loss of trabecular bone pattern, evidence of sequestra, and mandibular involvement crossing midline (yellow arrow), (g). Right maxillary sinusitis (double yellow arrow), (h). Disruption of ocular architecture (yellow arrow).

Imaging findings of CAM were chronic sinusitis to pan sinusitis, proptosis, retrobulbar collection, erosion of sinus walls, and bony changes suggestive of chronic osteomyelitis. (Fig 2) The host tissue infarction and necrosis due to angioinvasion by the fungal hyphae is a characteristic feature of mucormycosis, and hence referred to as IFI. [19]

DM, sustained neutropenia, lymphopenia, prolonged use of systemic corticosteroids, malignant pathologies of the blood, organ transplantation, and other immunocompromised states are the major risk factors as reported in earlier studies & also noted in our series. [20] Prolonged use of steroids is known to predispose to fungal infection, but COVID-19 situation gives a new insight that short term high dose of steroids can also lead to fungal infection reiterated in our series. [21]

DM along with COVID-19 is the most common comorbidity in the present case series, while other conditions like hypertension, MI, or intake of immunosuppressants like steroids having their own share. In an earlier reported interventional study, an overall survival rate of 60-77% for ROCM has been reported in diabetic cases by Yohai RA et al. [22] Cranial lesions (15.6%) and orbital lesions (35.5%) in diabetes were comparable with our series. A significant correlation between site & mortality revealed 33.3% of cases with orbital extension succumbed in our series (p-0.003). This alarms poor prognosis among ROCM with acquired diabetes as a risk factor. Our series revealed a correlation between DM and affliction of mandible as a separate entity of CAM being significant (p-0.01).

Probable effect of short-term high doses of steroids with Remdesivir, and severe immunosuppressive Tocilizumab could be microthromboembolism and endarteritis leading to avascular necrosis of jawbone. Avascular necrosis with immunocompromised status predisposing to pyogenic infection and empirical overuse of broad-spectrum antibiotics to treat COVID-19 induced pneumonia give way to opportunistic fungal infection.

Our series emphasizes that FESS is effective procedure only when the sinus mucosa is involved, once there is permeation of fungi into bone, multiple FESS procedures do not contribute to further treatment benefits. This is evidently seen from our series,

wherein FESS was performed as primary surgery in 20 cases, where probably imaging did not reveal bone involvement in early stage, but later needed radical surgery.

Treatment with HBO has been proposed as adjunct for mucormycosis, in diabetics with sinusitis, or cutaneous mucormycosis. [23] Yet, the lack of prospective studies and controls make the efficacy of the treatment method debatable. Immune-augmentation strategies, such as administration of interferons, statins, granulocytes transfusion have been suggested as adjunct therapies with limited evidence, the relative benefit of adjunctive strategies must be balanced against the cost and potential for harm on an individual patient basis. [24]

For want of adequate evidence and / or socio-economic reasons, Posaconazole and Isavuconazole, HBO, and other adjunct treatment modalities were not used in our cases, yet our cases remained disease free in the follow-up phase. Successful management of mucormycosis requires early diagnosis, reversal of underlying predisposing risk factors, radical surgical debridement and prompt administration of active antifungal agents. [25-26] It is prudent to have a psychiatric counseling and discuss the importance of nutrition, plan of future rehabilitation, more importantly taking into consideration the financial angle.

Rationale of orbital exenteration:

Planning for eyeball exenteration is very tricky issue. There is lack of literature support, due to rarity of disease, on exact timing and stage of ROCM when orbital exenteration is indicated. It needs immense counselling of patients as well as relatives. Moreover, opinion from two ophthalmologist is mandatory for orbital exenteration. This was tricky in our experience, as most ophthalmologist deny a consent when perception of light / vision is present. It is our responsibility to discuss and convince, the need in life threatening situations like uncontrolled ROCM where a larger picture must be seen to prevent cranial extension. It has to be emphasised that loss of vision and cranial involvement, may occur in few hours making survival a challenge. Eyeball exenteration should be done the moment the patient shows signs of severe orbital cellulitis, severe proptosis, total ophthalmoplegia, eyelids showing gangrene / necrosis or imaging shows evidence of retrobulbar involvement. It is also indicated as in uncontrolled ROCM where chances of intracranial retro grade dissipation of infection is very high.[27] In such cases it should be performed as lifesaving procedure even if perception of light is present.

We observed that time factor from COVID- 19 to mucor infection seems to have decreased during and after second wave of COVID- 19 in India. Also, during second wave orbital involvement has been seen to be more frequent.

Conclusion:

One must assume presence of fungal osteomyelitis in CMF region unless proved otherwise particularly on background of COVID-19. In early cases where imaging shows no bony involvement it would be wiser to have bone biopsy. Remember though the entry of fungus is through aerodigestive mucosa, it doesn't remain a mucosal disease, but culminates into fungal osteomyelitis, and hence must be treated as osteomyelitis.

One must have high suspicion index of orbital involvement. There should be no hesitation to exenterate eyeball as lifesaving procedure in cases of severe orbital involvement. Aggressive surgical and medical management is core and paramount in treatment of ROCM.

Further studies are required to establish the cause-and-effect relationship of various drugs used to treat COVID-19, various immunocompromised conditions, and mucormycosis infection with COVID-19.

References:

1. Alizargar J: Risk of reactivation or reinfection of novel coronavirus (COVID-19). J Formos Med Assoc. 2020, 119:1123. 10.1016/j.jfma.2020.04.013

2. Rijnders B, Schauwvlieghe A, Wauters J: Influenza-associated pulmonary aspergillosis: a local or global lethal combination?. Clin Infect Dis. 2020, 71:1764-7. 10.1093/cid/ciaa010

3. Cao B, Gao H, Zhou B, et al: Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. Crit Care Med. 2016, 44:318-28. 10.1097/CCM.0000000000001616

4. Salehi M, Ahmadikia K, Mahmoudi S, et al: Oropharyngeal candidiasis in hospitalised COVID-19 patients from Iran: species identification and antifungal susceptibility pattern. Mycoses. 2020, 63:771-8. 10.1111/myc.13137

5. Alhazzani W, Møller MH, Arabi YM, et al: Surviving sepsis campaign: Guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Int Care Med. 2020, 46:854-87. 10.1007/s00134-020-06022-5

6. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al: Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019, 19:405-421. 10.1016/S1473-3099(19)30312-3

7. Hamilos G, Samonis G, Kontoyiannis DP: Pulmonary mucormycosis. PG Seminars in Respiratory and Critical Care Medicine. 2011, 32:693–702. 10.1055/s-0031-1295717

8. Hariprasath P, Arunaloke C: Epidemiology of Mucormycosis in India. Microorganisms. 2021, 9:523-35. 10.3390/microorganisms9030523

9. Sandra Lopez-Leon, Talia Wegman-Ostrosky, Carol Perelman, et al: More than 50 long-term effects of COVID-19: a systematic review and meta-analysis: medRxiv Preprint. 2021, 10.1101/2021.01.27.21250617

10. Dinesh KV, Rishi KB: COVID-19 and Mucormycosis of the craniofacial skeleton: Causal, contributory or coincidental?. J Maxillofac Oral Surg. 2021, 20:165-6. 10.1007/s12663-021-01547-8

11. Swain SK, Behera IC, Mohanty JN: Mucormycosis in head-and-neck region – Our experiences at a tertiary care teaching hospital of Eastern India. Ann Indian Acad Otorhinolaryngol Head Neck Surg. 2019, 3:58-62. 10.4103/aiao.aiao_9_19

12. Ahmadikia K, Hashemi SJ, Khodavaisy S, et al: The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. Mycoses. 2021, 00:1-11. 10.1111/myc.13256

13. World Health Organization (WHO). Coronavirus disease (COVID-2019) situation reports. 2020.Accessed April 25, 2020. https://www.who.int/emergencies/diseases/novel- coronavirus-2019/situation-reports

14. Pasero D, Sanna S, Liperi C, et al: A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. Infection. 2021, 49:1055-60. 10.1007/s15010-020-01561-x

15. Carl Batt, Pradip Patel: Encyclopedia of Food Microbiology. Elsevier, Philadelphia: 2014. 10.1016/B978-0-12-384730-0.00136-1.

16. Skiada A, Lanternier F, Groll AH, et al: Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 2013, 98:492-504. 10.3324/haematol.2012.065110
17. Petrikkos G, Skiada A, Lotholary O, et al: Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012, 54:23-34. 10.1093/cid/cir866
18. Rawson TM, Moore LSP, Zhu N, et al: Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020, 71:2459-68. 10.1093/cid/ciaa530
19. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR: Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med. 2020, 30:100971. 10.1016/j.mycmed.2020.100971
20. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. 2020, https://www.covid19treatmentguidelines.nih.gov/ 2020
21. Song G, Liang G, Liu W: Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. Mycopathologia. 2020, 185:599–606. 10.1007/s11046-020-00462-9
22. Yohai RA, Bullock JD, Aziz AA, et al: Survival factors in rhino-orbital-cerebral mucormycosis: major review. Surv Ophthalmol. 1994, 39:3-22. 10.1016/s0039-6257(05)80041-4
23. Tragiannidis A, Groll AH: Hyperbaric oxygen therapy and other adjunctive treatments for zygomycosis. Clin Microbiol Infect. 2009, 15:82–6. 10.1111/j.1469-0691.2009.02986.x
24. Attanasio J, Wherry EJ: Costimulatory and coinhibitory receptor pathways in infectious disease. Immunity. 2016, 44:1052–68. 10.1016/j.immuni.2016.04.022
25. Campitelli M, Zeineddine N, Samaha G, Maslak S: Combination antifungal therapy: A review of current data. J Clin Med Res. 2017, 9:451-6. 10.14740/jocmr2992w
26. Nikolaos VS, Maria NG, Amalia A, Dimitrios PK: Therapy of mucormycosis. Journal of Fungi. 2018, 4:2-17. 10.3390/jof4030090
27. Roderick NH, Ralph EW: Indications for orbital exenteration in mucormycosis. Ophthalmic Plast Reconstr Surg. 2006, 22:286-91. 10.1097/01.iop.0000225418.50441.ee