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Case Series

Unravelling features in post COVID mucormycosis: case series with review of literature

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ABSTRACT

In the midst of the severe acute respiratory syndrome coronavirus 2 (SARS COV-2) pandemic, the victims are acquiring secondary infections like mucormycosis. Rhinocerebral mucormycosis (ROCM), is the most prevalent form and is an invasive, opportunistic fungal infection that typically affects immunocompromised patients. It exhibits a pronounced propensity to invade blood arteries, resulting in tissue thrombosis, necrosis, and infarction. Early conventional and advanced medical imaging like computed tomography (CT) and magnetic resonance imaging (MRI) is helpful in assessing the extent of involvement of this lethal disease which requires prompt and aggressive treatment. Despite of aggressive therapy, which includes disfiguring surgical debridement and frequently adjunctive toxic antifungal therapy, the overall mortality rate is high. The prime objective of present study focuses upon, unravelling the aberrant imaging presentations along with the detailed discussion about existing common features. The current study presents, a case series of 15 patients of rhino-orbital-cerebral mucormycosis (ROCM) including clinical data; common radiographic features like sinusitis, bony erosions, and soft tissue involvement also there were few uncommon features illustrated while evaluating the radiographic imaging. All patients underwent chair side and histopathological investigations. Appropriate treatment modalities were enrolled followed by rehabilitation of the defects after a thorough follow-up over an interval of 6 months. A thorough examination of the imaging findings is necessary since the aggressive nature of the infection can involve any parts of head and neck region illustrating few rare presentations involving uncommon sites. Radiologists must be aware of these unravelling radiographic features to know the precise extension of the infection.

Keywords: Mucormycosis, Unusual, Fungal ball, Pathologic fracture, Septal spur, Treatment, Rehabilitation

INTRODUCTION

COVID-19 has brought a slew of new illnesses and problems to humanity.[1] It's an infection caused by a respiratory virus called coronavirus-2 that causes severe acute respiratory syndrome (SARS-CoV-2). It spreads quickly and widely, causing mild to severe symptoms. Supportive care, corticosteroids, and palliative therapy ware viable modality of choices.[2] Affected patients are given high doses of steroids, which act as immune suppressant making them susceptible to a lethal consequence known as mucormycosis.[3]

Mucormycosis is a serious and uncommon opportunistic fungal infection which was first documented in 1855, that spreads rapidly in immunocompromised individuals and is caused by a group of mould called as mucorales.[3] Inhalation of spores, consumption of contaminated food, and inoculation of the fungus into abrasions or scrapes are the primary contacts for mucorales.[4] Medical co-

morbidities, steroidal use, and malnutrition are some of the factors that contribute to its prevalence. These have high mortality and morbidity rates based on underlying condition.[5]

Medical imaging like computed tomography (CT) and magnetic resonance imaging (MRI) helps in diagnosis thereby help salvage vital organs and bring positive outcome.[6] The main objective of this study is to discuss complete case series of 15 mucormycosis patients in relation to clinical data, detailed imaging features along with early radiographic signs, microbiological and histopathological investigations, treatment plan and rehabilitation. This study also aims at revealing uncommon presentations which were less documented in literature.

CASE SERIES

The current paper showcases a series of 15 cases of post COVID mucormycosis who reported to department of oral medicine and diagnostic radiology, of our institution with the chief complaint of fascial pain, swelling and having a common history of hospitalization due COVID-19 followed by steroid therapy. Thorough medical and dental history were retrieved followed by complete extra and intra-oral examination was executed. Appropriate imaging with extraoral radiography was performed in the form of orthopantomogram (OPG) and para-nasal-sinus (PNS) view in all the patients (n=15). Further, these patients underwent advance medical imaging like multidetector-computed tomography (MDCT) and MRI including axial, coronal and sagittal was performed with and without contrast. An appropriate medical and surgical line of treatment was performed followed by rehabilitation of the defects were executed.

Demographic and clinical data

This study comprised of 15 patients among which 11 were male and four were female patients with a mean age range of 45-70 years with a common chief complaint of swelling and pain involving middle 1/3rd of face (n=15), all patients experienced prodromal symptoms along with headache, seven with nasal discharge. They presented with various clinical presentation like facial swelling (n=15; 100%), facial pain (n=15; 100%), proptosis of eye (n=5; 33%), altered vision (n=4; 26%), chronic palatal and alveolar ulceration with bony exposure (n=14; 93%), palatal swelling (n=1; 6%), generalised periodontitis with exfoliation of teeth (n=7; 46%). Out of 15 patients, five were having orbital involvement (2 with loss of vision) and no patients with cerebral involvement (Figure 1).

Radiographic findings

Extra-oral radiography

Conventional radiography in the form of orthopantomogram and PNS were performed in all patients (n=15) that revealed deviated nasal septum (DNS) opposite to the affected side, diffuse hazy radiopacity seen involving maxillary sinus and other paranasal sinuses. Orthopantomogram showed enlarged inferior turbinate (n=15; 100%), ill-defined radiolucent shadow with ragged borders at the peri-apical portions of teeth involving the affected site with extension to hard palate suggestive of bony erosion (n=6;40%). Chronic generalised periodontitis and pathologic migration of teeth with apical root resorption were seen in 12 patients (n=12;80%) (Figure 2).

Figure 1: Clinical (a) swelling in the right side; (b) drooping of left eye; (c) solitary chronic non healing ulcer; (d) palatal swelling; and (e) chronic generalised periodontitis with exfoliation of teeth.

CT findings

These patients were further subjected to CT plain and contrast which reported as possibility of invasive fungal infection.

Nasal and PNS involvement

A characteristic feature of sinusitis as mucosal thickening with soft tissue enhancement across the walls of maxillary sinus with central hypodense shadow, seen involving bilateral maxillary sinus in 9 (60%) and unilateral maxillary sinus in 5 (33%) patients. A consistent nasal involvement showed DNS (n=7,46%) among which "S" shaped DNS (n=2, 13%) and enlargement of turbinate of involved side (majorly with inferior turbinate) seen in all patients (n=15; 100%). Also, there was obliteration of osteo-meatal seen in 13 (86%) patients among which 4 (30%) were having bilateral involvement (Figure 3). Similar kind of sinusitis features seen involving ethmoidal sinus (n=10; 66%), frontal sinus (n=9; 60%) and sphenoidal sinus (n=7; 46%), with multiple presentations like diffuse hyperattenuating soft tissue shadows involving part or complete sinuses or peripheral mucosal thickening which were enhanced on post contrast study (Figure 3).

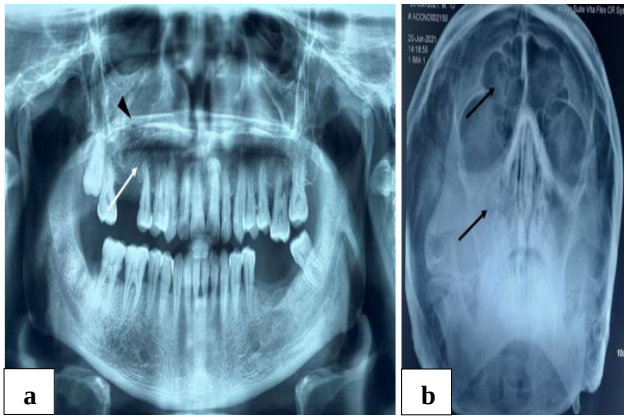

Figure 2: Extra-oral radiography (a) ill-defined radiolucency at the periapical region of tooth (white arrow) with palatal bone erosion on right side (black arrowhead); and (b) complete hazy radiopacity seen involving maxillary sinus, frontal sinus (black arrow).

Bony erosions

Maxillary sinus walls erosions illustrated as discontinuity of cortical bone with irregular cortical plate thinning with respect to medial wall being most common (n=14; 93%), anterior wall (n=11; 73%), postero-lateral wall (n=7; 46%), roof of maxillary sinus (n=4, 26%). Similar cortical plate changes involving adjacent bones majorly seen with hard palate (n=14; 93%) and maxillary alveolar process (n=12; 80%), zygomatic process of maxilla (n=4; 26%), pterygoid plates (n=4; 26%) (Figure 4).

Orbital and cerebral involvement

Dehiscence of the lamina papyracea seen majorly involving unilateral affected side in 5 patients (n=5; 33%). Orbital extension of the lesion illustrated as hyperdense soft tissue shadows involving periorbital space (n=2; 6%), extra and intra conal space (n=4;26%), proptosis of eye (n=2; 13%). Minimal hypoattenuating shadow seen involving superior frontal gyrus (n=1; 6%) (Figure 5).

Miscellaneous

These are some uncommon features which were represented in CT scan. Apart from bony erosions; pathological fractures presented as well-defined hypodense line with discontinuity of cortical bone involving nasal bones (n=4; 26%), anterior wall maxillary sinus of unaffected side running obliquely from right floor of orbit to alveolar process of maxilla corresponding to 17 (n=1; 6%). Osteophytic changes as spur formation involving nasal septum in five patients (n=5; 33%) (Figure 4).

MRI findings

The most concern about the infection is its aggressive nature and spread to adjacent soft tissue, facial spaces and vital organs involvement which can be evaluated precisely by MRI.

Nasal involvement

Post-contrast T1-weighted imaging showed a classical "black turbinate" sign indicative of early MRI finding for mucormycosis seen in nine patients (n=9;60%) among which two patients showed bilateral involvement (n=2; 22%). Turbinates involved were inferior turbinate (n=5; 33%), middle turbinate (n=3; 20%) and superior turbinate (n=1; 6%). Nine patients illustrated choncha bullosa (n=9; 60%) in which three were fluid filled (n=3; 20%). An uncommon feature of "fungal ball" illustrating as T1W hyperintense foci along with dark signal intensities in T2W MR imaging and hyperattenuating shadows in CT involving nasal turbinates and septum (n=4; 26%) (Figure 6).[33]

Paranasal sinus involvement

T1 hypo-intensity or T2/FLAIR heterogeneously hyperintense mucosal thickening seen interspersed with air foci in maxillary sinus (n=15;100%) among which nine patients having bilateral involvement (n=9; 60%). Similar hyperintense area seen involving ethmoidal sinus in 10 patients [n=10, 66%; b/l (n=5, 50%); u/l (n=5, 50%)], frontal sinus in nine patients (n=9; 60%) and sphenoidal sinus in seven patients (n=7; 46%).

Extension of the lesion

Spread of infection into adjacent facial spaces are illustrated by significant inflammatory changes in the form of ill-defined STIR/T2W/FLAIR hyperintense areas and heterogenous enhancement in post gadolinium contrast, most commonly seen involving buccal space (n=15;100%); masticator space (n=10; 66%), infratemporal fossa (n=9; 60%) and pterygopalatine fossa (n=6; 40%). All patients showed unilateral involvement of the affected side with an exception of one patient (case 6) showing bilateral pterygopalatine fossa. Additionally, parapharyngeal space (n=1; 6%) and pterygoid fossa (n=2;13%) were also involved (Figure 7).

Soft tissue involvement

Regional soft tissue involvement seen majorly with peri-antral pad of fat illustrated as T1W heterogenous hyperintense oedematous soft tissue shadow with fat stranding of the affected side (n=15;100%) among which two patients showed bilateral involvement (n=2; 13%). Among the muscles of mastication, lateral pterygoid muscle has major involvement (n=10; 66%); medial pterygoid muscle (n=6; 40%); masseter muscle (n=6; 40%) and temporalis muscle (n=5; 33%). One patient showed inflammatory changes in the form of high STIR signal intensity in antero-superior lobe of left parotid gland (n=1;6%). Cavernous sinus inflammation with

thrombophlebitis of involved internal carotid artery is seen in one patient (n=1;6%) (Figure 7).

Orbital involvement

Five among 15 patients (n=5; 33%) showed peri-orbital inflammatory changes as T2W hyperintense shadow of affected eye (n=5; 100%). Extension of the lesion into orbital space seen in all 5 patients among which three patients having both extra and intraconal spaces (n=3; 60%) and 2 patients individually (n=2; 40%). Regional ocular muscle involvement with bulky rectus and oblique muscles with heterogenous STIR hyperintensities seen in all 5 patients (n=5; 33%).

Optic nerve involvement seen in 2 patients (n=2; 13%) illustrated as abutment of optic nerve (case 5) and optic neuritis (case 6) seen respectively. Global involvement showed tenting of globe seen in 2 patients depicting "guitar pick" sign (n=2; 40%) (Figure 8).

Cerebral involvement

Cerebral ischemic changes leading to infarct of brain seen in 4 patients (n=4; 26%) among which 2 patients had subtle T2/FLAIR hyperintensities noted in bilateral corona radiata, centrum semiovale and deep white matter (n=2; 13%), one patient showed ill-defined hyperintense FLAIR lesion in left basi-frontal region with restricted diffusion on DWI and ADC maps (n=1; 6%) and one patient with acute infarct changes in antero-frontal lobe of brain (n=1;6%). 2 patients (n=2; 13%) showed cerebral sinus changes involving unilateral cavernous sinus inflammation (n=1; 6%) and hypoplastic transverse and sigmoid sinus (n=1; 6%) respectively (Figure 8).

An appropriate staging system for categorising the severity of ROCM disease is not yet recognised, hence a working classification was built in order to categorise the extent of the infection. Honavar S G produced a 4-tiered staging system involving anatomical structures in the path of its progression.[7] Although this staging has several drawbacks, it appears to be a viable and practical staging mechanism. All 15 patients were staged according to this staging system. A difficulty faced in staging three patients as there were no orbital changes but had cerebral changes; as the staging according to Honavar is produced in a sequential manner.

Management of mucormycosis

Management of post COVID-19 mucormycosis patients depends on the stages involved and are broadly divided into medical; surgical and rehabilitation line of treatment. Patients with soft and hard tissue destruction were treated surgically when the affected areas are under accessible locations. Inaccessible areas were treated using medical line of management along with irrigative measures.

Medical line of management

Pro-drug of choice in treating mucormycosis is liposomal-amphotericin B (L-AmB). An initial dose of L-AmB 1000 mg – 1400 mg was given to patients according to their systemic conditions. Posaconazole or isavuconazole were prescribed as an alternative drug for AmB. Intensive surgical care is given to patients with aggressive conditions.

Surgical approach

Functional endoscopic sinus surgery (FESS) was the first line of approach for patients with nasal involvement. Extraction of periodontally compromised teeth along with partial or complete maxillectomy of the involved side. Complete debridement of necrosed soft tissue involving various facial spaces and PNS were performed followed by dressing with amphogel and antibiotic gel foam. Patients with complete orbital extension along with optic nerve involvement underwent enucleation of the affected eye.

Post-surgical and follow up

Post-surgical instructions along with prophylactic drugs were prescribed to prevent the recurrence of the infection with Sodium chloride 0.9% W/V nasal spray, BD for 90 days; xylometazoline 0.1% W/V nasal drops, BD for 5 days; tab immunace forte, OD for 15 days. A periodic follow-up for every 3 months was advised for the evaluation of signs of recurrence. Prosthetic rehabilitation of the post-surgical defects was performed with palatal obturators or with sectional dentures. Extra-oral post-surgical defects were rehabilitated using extra-oral prosthesis (Figure 9).

Histopathological and microbiological evidence

Cytological investigation using KOH staining showed broad aseptate fungal hyphae with right angle branching were seen with clear cytoplasm. LCB staining showed similar mucorale appearances with bluish cytoplasm along with few round blastospores. Histopathological staining with H & E stain showed irregular broad, thick walled, non-septate hyphae branched at right angles with some inflammatory cell infiltration in interstitial tissue. Other stains used were periodic acid Schiff, Grocott methenamine-silver stains that help in highlighting the fungal wall. Sabouraud dextrose agar showed white cotton candy growth (Figure 10).

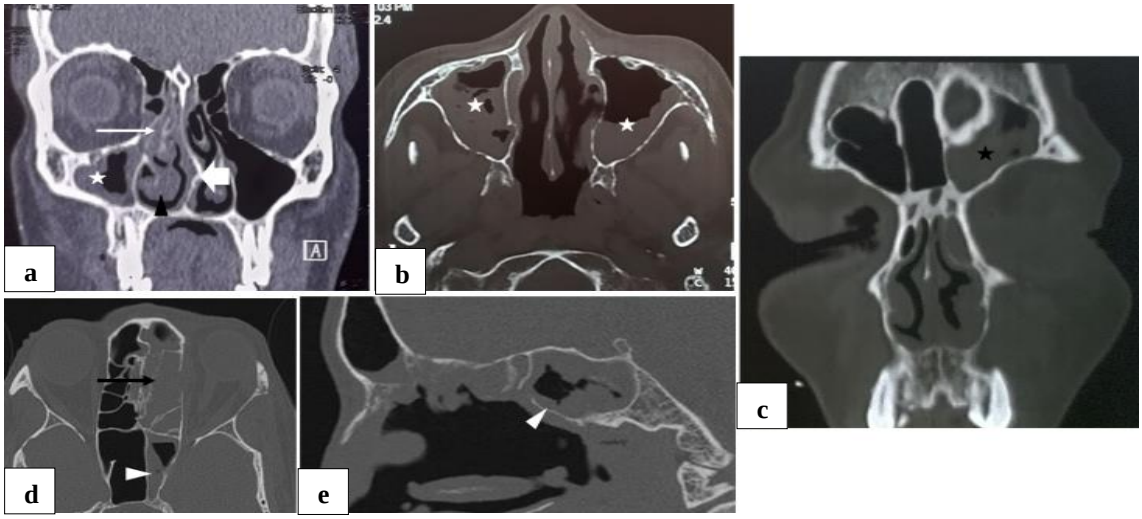

Figure 3: Nasal and PNS involvement; (a) unilateral obliteration of OMC (white-arrow), enlargement of inferior turbinate (black-arrowhead), DNS (thick-white-arrow); (b) sinusitis-maxillary sinus (white-star); (c) frontal sinus (black-star); (d) ethmoidal sinus (black-arrow); and (e) sphenoidal sinus (white-arrowhead).

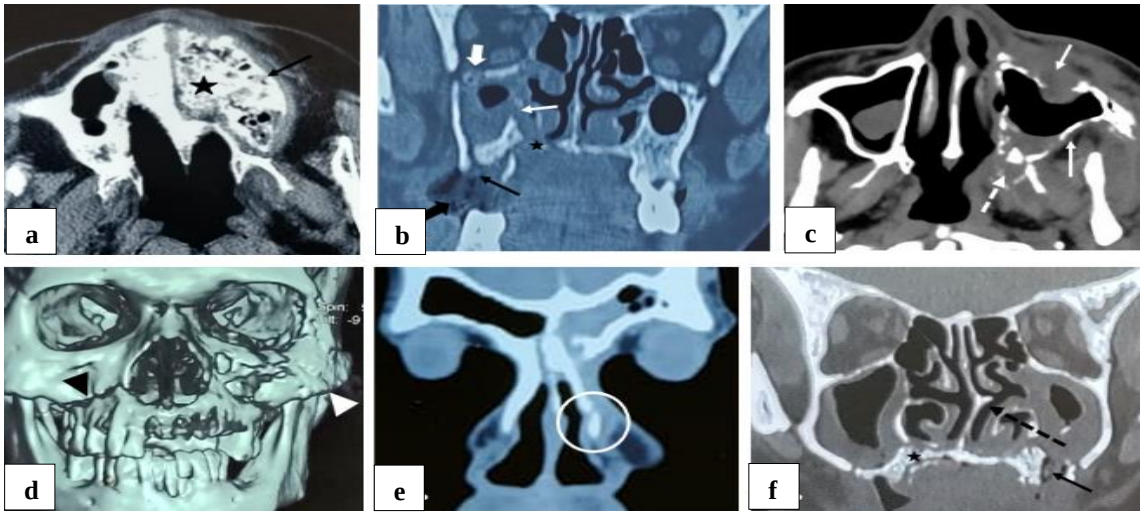

Figure 4: Bony erosions and miscellaneous-palatal bone (star); maxillary sinus walls (white-arrow); alveolar bone (black-arrow); pterygoid plates (white-dashed-arrow); zygomatic arch (white-arrowhead); teeth exfoliation (thick-black-arrow); orbital floor (thick-white-arrow); pathological fracture (black-arrowhead); nasal bone fracture (ring); and septal spur (black-dashed-arrow).

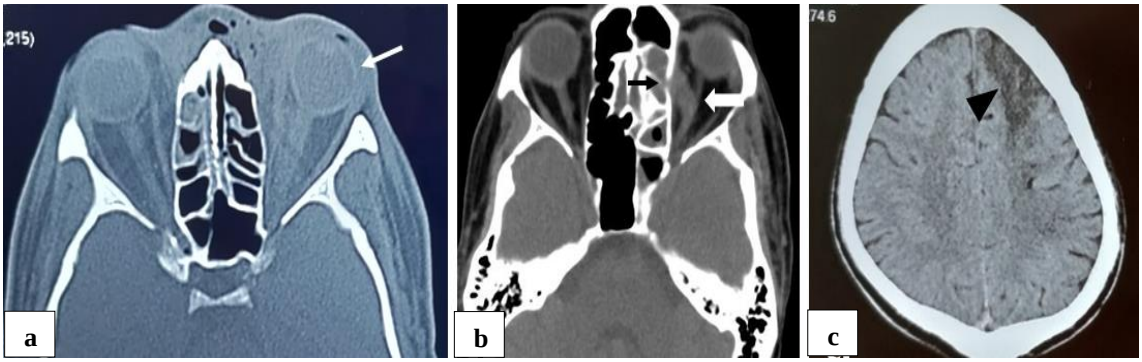

Figure 5: Orbital and cerebral involvement; (a) periorbital edema with proptosis (white-arrow); (b) dehiscence of left lamina papyracea (black-arrow) with extension into extraconal space (thick-white-arrow); and (c) hypodense areas involving left superior frontal gyrus (black-arrow-head).

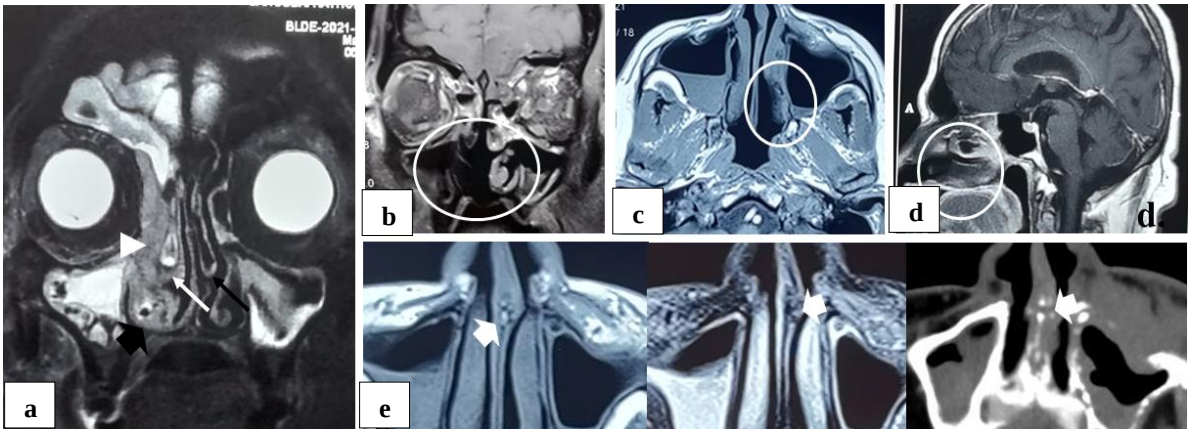

Figure 6: Nasal changes; bilateral concha bullosa (black-arrow) with fluid filled (white-arrow), enlarged inferior turbinate (thick-black-arrow) and obliteration of right OMC (white-arrowhead); "black turbinate" sign (white-circle); T1W, T2W and contrast enhanced CT of fungal mycetoma (thick-white-arrow).

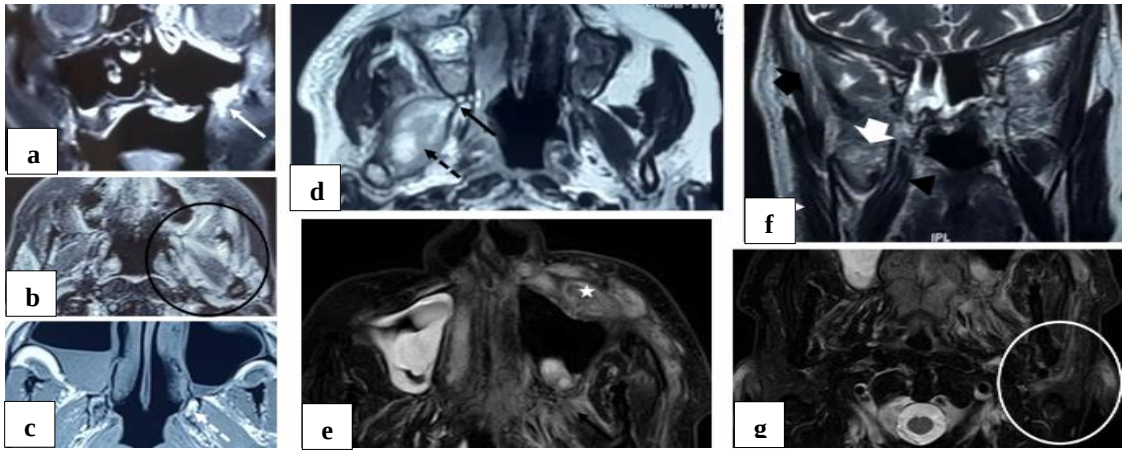

Figure 7: Extension; spaces- buccal (white-arrow), masticator (black ring), pterygoid (white-dashed-arrow), pterygopalatine fossa (black-arrow), infratemporal fossa (thick-white-arrow); muscle involvement- masseter (white-arrow-head), lateral-pterygoid (black-dashed-arrow), medial-pterygoid (black-arrowhead), temporalis (thick-black-arrow); and soft tissue involvement- buccal-pad-fat (star), parotid gland (white ring).

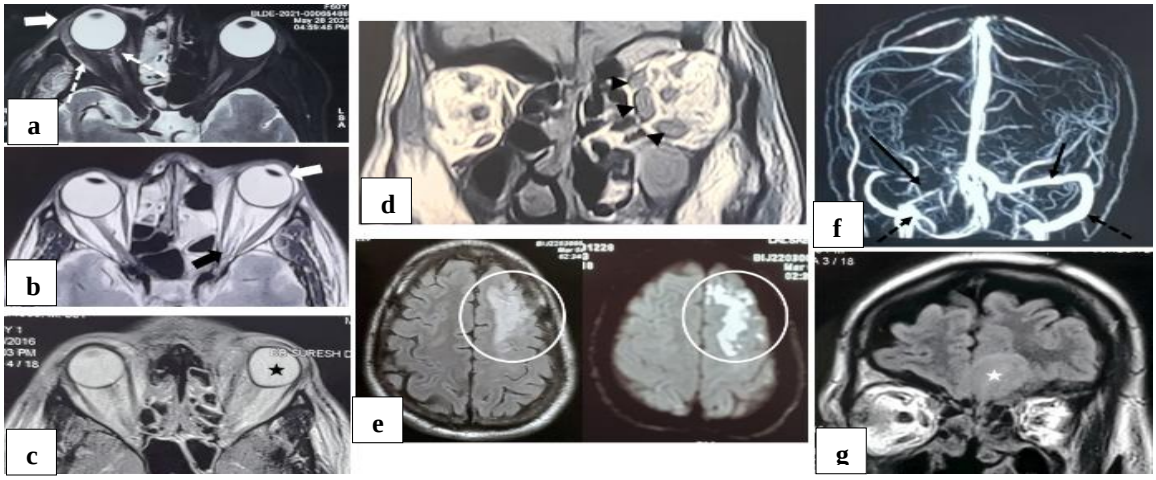

Figure 8: Orbital- ocular-proptosis (thick-white-arrow); extraconal and intraconal space (white-dashed-arrow); optic nerve abutment (thick-black-arrow); guitar-pick sign (black-star); bulky rectus and oblique muscles (black-arrowhead); cerebral- antero-frontal lobe (white-ring); hypoplastic transverse (black-arrows) and sigmoid (black-dashed-arrows) sinuses; and basi-frontal region (star).

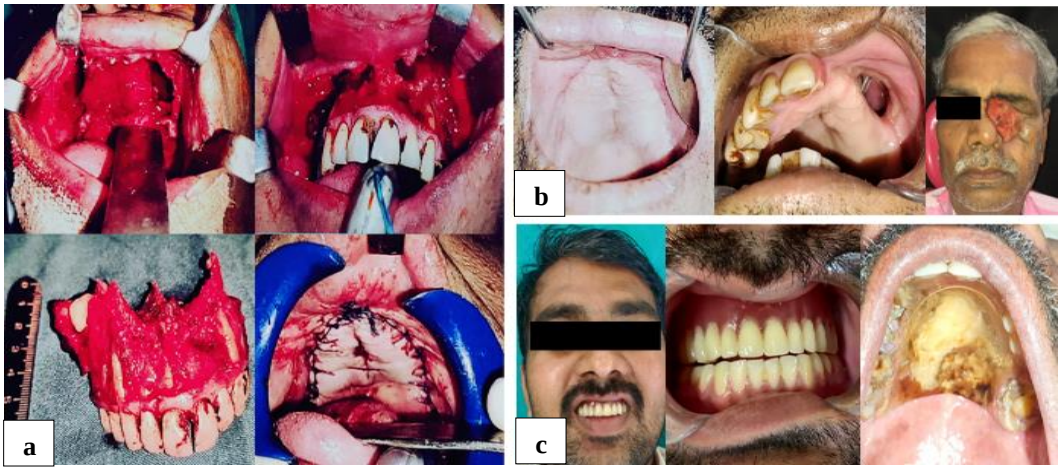

Figure 9: Management of mucormycosis: (a) surgical management with complete maxillectomy along with post operative suturing; (b) post-surgical follow-up after 4-6 months; and (c) prosthetic rehabilitation with complete denture and obturator.

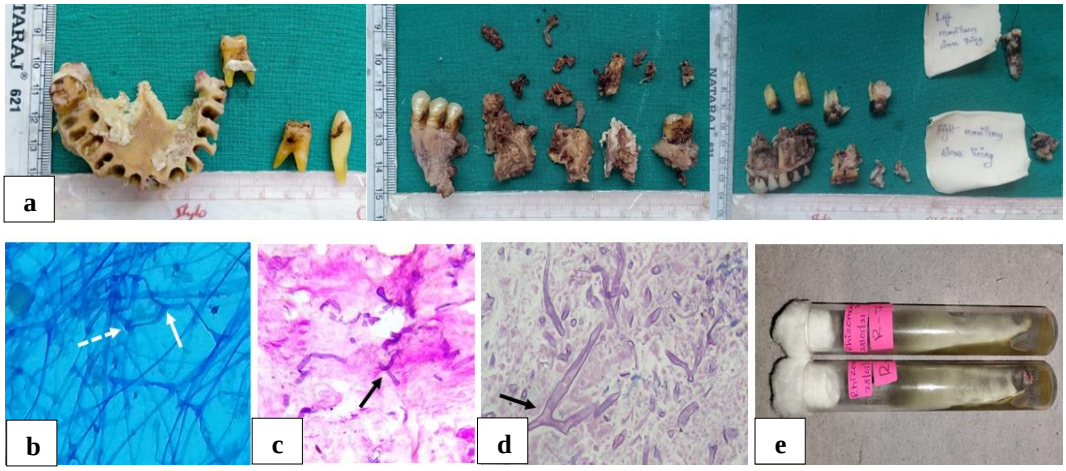

Figure 10: (a) Post-surgical excised specimens; (b) LCB stain- aseptate hyphae with right angled branching (thin-white-arrow) and sporangium (white-dashed-arrow); (c) broad, irregular, thick walled, hyphae in H&E and (d) PAS stain; and (e) culture- fluffy white-brown growth in SDA.

DISCUSSION

Mucormycosis is an opportunistic invasive fungal sinusitis that can be either acute or chronic based on the nature of spread. These have high mortality and morbidity rates based on underlying patient's condition.[3] Based on the present study, we found that the presence of SARS-COV-2 infection does not initiate mucormycosis but the steroidal therapy given to COVID-19 patients along with the contaminated environment triggers the incidence of mucormycosis. Also, there is evidence of immune impairment due to COVID-19 infection preventing the polymorphonuclear phagocytes from attacking the fungal spores upon entry.[8]

Mucormycosis is caused by a group of moulds belonging to the *Mucoromycotina subphylum* and order Mucorales.[9] These organisms are present in various parts of the environment but mainly found in soil, decayed food products, and plants. The main route of entry of the infection is by inhaling the spores or fungal hyphae or by consuming the contaminated edibles.[10] Mucorales have a characteristic trait of spreading across the blood vessels causing necrosis and thrombosis.[11] Different host conditions like high iron level (ferritin), high blood glucose levels, ketoacidosis provides favourable conditions for the growth of the organisms.[12]

The present study showed many patients have developed post diabetic conditions (n=9; 60%) as a complication of the steroidal therapy which were more susceptible for the infection. All patients experienced prodromal symptoms like fever, headache, nausea, diarrhoea facial pain.[13] Clinical features include swelling of the affected secondary to accumulation of inflammatory exudate in the subcutaneous region, chronic solitary non-healing ulcer of alveolar and palatal mucosa leading to exfoliation of teeth secondary to angio-invasive nature of the disease leading to necrosis and infarction of the involved tissues. Necrotic degeneration and cellular debris of the tissues by fungal

species causes black coloured nasal discharge. Accumulation of inflammatory exudate in peri-orbital region causes compression of optic nerve leading to altered vision and blindness of the infected eye.[14]

The common imaging features according to literature using advanced medical imaging like CT and MRI involving craniofacial structures were evaluated.[15] Nasal changes in CT scan consists mainly of enlarged turbinates due to invasion fungal foci causing destruction and oedematous accumulation leading to DNS towards opposite side. Irregular hypo-attenuating shadows involving various bony structures like alveolar bone, hard palate, walls of maxillary sinus, zygomatic bone, orbital walls, pterygoid plates etc. suggestive of bony perforations creating an entry to the adjacent areas.[16-19] An early MRI sign of disease manifested as typical "black turbinate" sign of the involved turbinate seen as hypo-intense shadow in post gadolinium contrast imaging due to lack of uptake of the dye secondary to its destruction.[20-22] Extra sinus fat stranding into premaxillary region, fascial and orbital spaces were illustrated as altered signal intensities in T1W and T2W images.[23] Regional muscular involvement presented with various illustrations like ill-defined STIR hyperintensities, heterogeneously enhanced post contrast T1W and T2W imaging and bulkier regional muscles.[24] Inflammatory extension into orbital space can lead to optic nerve abutment and optic neuritis which manifest as altered vision. Orbital inflammatory response manifest as periorbital cellulitis causing to proptosis of eye and leading to deformity involving dorsal part of globe demonstrating classical "guitar pick sign".[25,26] Cerebral involvement is minimal in the initial stages of the infection. Extension to brain tissue demonstrates as heterogeneously hypo-intense T1W and T2W/DWI hyperintensity of infarct grey or white matter and dural structures. Cerebral sinuses and carotid artery are well illustrated in MR venography as hypo-intense discontinuity of flow suggestive of thrombotic changes.[27,28]

Apart from these common features, few rare presentations involving uncommon sites were also illustrated in this present study which are less documented in literature. CT imaging showed a rare entity of pathological fracture of normal bone adjacent to diseased bone due to its weakening secondary to mucormycosis involving maxilla and nasal bones.[29,30] Individuals having good immunity showed host response against infection in the form of irregular hyperdense sclerosis of cortical bone of sinus walls and zygomatic bone. In our case series similar presentations were shown involving nasal septum associated with mucormycosis is a rare phenomenon.[31,32] Fungal mycetoma is an extra-mucosal accumulation of fungal species which is most commonly associated with aspergillosis and less with mucormycosis.[15] As per literature, maxillary sinus is a common site of occurrence but in present study, these were seen involving affected turbinates and nasal septum.[33,34] Mucormycosis involving parotid gland still remains an uncommon extension. In previous literature only few cases have been documented with various levels of tissue involvement. A mild extension to anterior aspect of superficial lobe was noted in one patient which was well illustrated in STIR MRI.[35,36]

Management of mucormycosis at an early stage is necessary to preserve vital structures. Early diagnosis using appropriate imaging modalities can guide for precise treatment plan and can reduce the mortality rates of the patients. Complete debridement with surgical resection should be performed for extensive lesion followed by prophylactic doses of antifungal drugs to prevent the recurrence rate of mucormycosis.[37]

CONCLUSION

The current study sheds light on multiple findings of various maxillofacial imaging modalities that correlates with clinical data of 15 patients. Mucormycosis is an aggressive disease that can involve various soft and hard tissues producing different presentations. Imaging played a crucial role and revealed some unseen features affecting peculiar sites. Radiologist must be aware of unusual presentations of mucormycosis in uncommon sites that helps in early diagnosis leading to better prognostic outcome A routine post-surgical follow-up with advanced imaging was done to ensure remission and complete absence of recurrence before moving to rehabilitation.

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