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Post COVID-19 Mucormycosis of Jaws -An Unusual Clinical and Radiographic Presentation

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Abstract
Mucormycosis is an aggressive, opportunistic, invasive fungal infection which is more prevalent among debilitating and immunocompromised patients with diabetes mellitus, malnutrition, hematological malignancies, neutropenia, burns, long term steroid therapy and immunosuppressive therapy. Many cases have been reported with mucormycosis infection in post COVID-19 patients. Patients with COVID-19 are at high risk of fungal infections, that may result directly from COVID-19 infection and/or as a side effect of the medications used in COVID-19 treatment, such as steroids and antibiotics. Most common sites for the manifestations of mucormycosis infection includes the nasal cavity, orbit and cerebral tissues. Bony involvement specially mandible is extremely rare in mucormycosis. This case report presents an unusual clinical and radiographic manifestations of post COVID- 19 mucormycosis which posed a diagnostic dilemma. Hence this case report focuses on importance of clinical, investigatory and radiographic examination in post COVID oral and maxillofacial infections.

Keywords: *COVID-19 associated Mucormycosis (CAM), mandible, Cone Beam Computed Tomography (CBCT)*

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I. Introduction

Several post COVID opportunistic infections by aspergillus species, candida species, cryptococcus neoformans, pneumocystis carinii, mucormycosis, CMV, HSV, mycobacterium tuberculosis, toxoplasma gonodii, strongyloides stercoralis etc have been reported in literature. Among these infections, most cases have been reported having fungal etiology [1].

Mucormycosis can involve nose, paranasal sinuses, orbit, CNS, lungs, GIT, skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but rhino-orbito-cerebral type is the commonest variety seen worldwide which refers to the entire spectrum ranging from limited sino-nasal disease (sino-nasal tissue invasion), limited rhino-orbital disease (progression to orbits) to rhino-orbital-cerebral disease (CNS involvement) [2].

Attributing factors for mucormycosis are debilitating and immunocompromised patients with diabetes mellitus, malnutrition, hematological malignancies, neutropenia, burns, long term steroid therapy and immunosuppressive therapy.

Mucormycosis can present clinically as facial pain, swelling, orbital cellulitis, proptosis, paraesthesia, loss of vision, ophthalmoplegia, necrosis of nasal turbinates and palate as well as osteomyelitis of facial bones, neurological signs and symptoms if intracranial extension is present [3].

Diagnosing mucormycosis at an early stage is challenging for the clinicians as it has varying clinical presentations. Thorough history taking and clinical examination helps clinician to arrive at diagnosis and proper timely referral. Laboratory investigations are also of prime importance. Culture and sensitivity testing to identify the pathogen plays a crucial role.

Imaging plays a pivotal role in establishing the diagnosis, looking for complications, delineating the extent of the disease, bony involvement and anatomical mapping before surgical intervention. Bony involvement in mucormycosis involves most commonly maxillary complex, mandibular involvement is

extremely rare presentation [4]. This case report presents massive involvement of maxilla and mandible with aggressive nature of mucormycosis within short span of time.

The present case focuses on importance of systematic clinical, investigatory and imaging approaches in diagnosis and management of post COVID-19 infections in oral and maxillo-facial region.

II. Case Report

A fifty years old female patient reported to our institute with a chief complaint of toothache and loose teeth in right upper and left lower back region, noticed for one week duration. History revealed COVID-19 infection a month back and one week hospitalization for the same. History of blackish discharge from nose, paraesthesia of lower lip and pus discharge from gingiva in left lower back tooth region were also elicited. She was diabetic for eight years and was under insulin therapy. She had undergone extraction of right upper second premolar and oral prophylaxis from private clinic but no symptomatic improvement was noted and patient referred to ENT consultation. Computed Tomography (CT) scan was taken and biopsy was performed from right upper back tooth region which showed inflammatory infiltrate but report was inconclusive. She was administered hyperbaric oxygen therapy for the same. Further treatment details are not available.

On extraoral examination diffuse swelling was present on right middle third of face extending supero-inferiorly from the right infraorbital margin to the right inferior border of mandible and mediolaterally from right nasolabial fold to one cm anterior to the tragus of right ear. Swelling in right peri-orbital region also noted. Eye movements within normal limits. Another diffuse swelling in left lower third of face confined to the mandibular body region (figure 1). Single left level I A and level I B lymph nodes were palpable, tender, soft in consistency and mobile.

On intraoral examination, poor oral hygiene with grade III mobility of right upper first and second molar, left mandibular second premolar, first and second molar were noted. Periodontal pockets were noted in relation to left mandibular posterior teeth. Missing 14,15,46 and multiple root stumps in maxillary left region were noted. Healing extraction socket was noted in relation to 14 (figure 2 and 3).

Provisional diagnosis as chronic generalised periodontitis made and antibiotics were prescribed. Patient reported back after one week with symptomatic improvement but persisting paraesthesia on lower lip. Panoramic radiograph was taken which showed severe generalised periodontal bone loss, multiple round radiolucencies throughout the mandible except right ramus region and altered trabecular pattern in maxilla with haziness in bilateral maxillary sinus (figure 4). Considering positive history of COVID-19 infection and diabetes, microbial culture was done which was reported as sterile. CBCT scan was advised to know extension of the lesion which showed ill-defined lytic lesion involving maxilla, right zygoma, palate, walls of right maxillary sinus, walls of nasal cavity. Ill-defined lytic lesion of mandible involving symphysis-parasymphysis region, left ramus-angle region, with destruction of both buccal and lingual cortical plates and lamellar, discontinuous, interrupted type of periosteal rection throughout the mandible. Internal architecture showed mixed hyperdense hypodense lesion with altered trabecular pattern in mandible (figure 5-10). Considering the frank extension of the lesion radiographic diagnosis was made as malignant neoplasm/metastatic lesion/deep fungal infection. Biopsy from maxilla and mandible and repeat culture was advised. Culture showed presence of bacterial species and histopathology report showed mucormycosis in both maxilla and mandible.

Patient was immediately referred to department of infectious diseases for further management. Systemic antifungal agent (Posaconazole 300mg once daily) was planned to give for six months depending upon patient's condition. Patient followed up after each month. Later repeat culture done which was negative for fungal elements. And surgery of maxilla was performed by ENT department. Patient become symptomatically and clinically better.

III. Discussion

Mucormycosis, a secondary fungal infection, gained much attention in the COVID-19 pandemic. It has a high all-cause mortality rate and imposes a significant economic, epidemiological, and humanistic burden on the patients and healthcare system. A review of published mucormycosis cases found an overall all-cause mortality rate of 54%. A high mortality rate was found among COVID-19 associated Mucormycosis patients with a pooled prevalence rate of 29.6% (95% CI: 17.2–45.9%). The mortality rate varies depending on underlying patient condition, type of fungus, and body site affected ranging from 46% among people with sinus infections, 76% for pulmonary infections, to 96% for disseminated mucormycosis [5].

Evidence from the published epidemiological studies showed the varying prevalence of COVID-19-associated mucormycosis (CAM). The pooled prevalence of CAM was 50 times higher than the highest recorded background of mucormycosis (0.14 cases per 1000 patients). The mean duration of mucormycosis onset was 14.59 ± 6.88 days after the COVID-19 diagnosis [6].

Three studies conducted in India demonstrated rise in annual incidence of mucormycosis from 1990 to 2007 [7-9].

There are six clinical forms of mucormycosis, most common being the rhino-cerebro-orbital form (44–48%) followed by the cutaneous variety (10–19%), then pulmonary (10–11%), disseminated (6–10%) and gastrointestinal form (2–11%) [10].

The list of signs and symptoms that should be considered to be "red flags" includes a cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling, orbital apex syndrome, and ulcers of the palate [11]. Tissue necrosis due to angio-invasion and subsequent thrombosis is the disease's characteristics. The Smith and Krichner criteria (1950) for the clinical diagnosis of mucormycosis are still considered to be gold standard and include: (i) Black, necrotic turbinate's easily mistaken for dried, crusted blood, (ii) Blood-tinged nasal discharge and facial pain, both on the same side, (iii) Soft peri-orbital or peri-nasal swelling with discoloration and induration, (iv) Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and, (v) Multiple cranial nerve palsies unrelated to documented lesions. In case series of 14 diabetic patients conducted by Wael M et al (2019) found that, majority of patients of mucormycosis presented with clinical features of palatal bone exposure, teeth loosening, exposed necrosed bone, extraoral pus discharge, necrosis of premaxilla, palatal perforation [12]. These findings were inconsistent with our case as no oral ulceration or necrosis or palatal perforation was present clinically except presence of tooth mobility. A case of mucormycosis with similar finding as our case has been reported by Deshpande P *et al* (2021), where diabetic patient with history of COVID infection presented with mobility of teeth and mild facial and palatal swelling without ulceration or discharge, with insignificant panoramic findings, so diagnosed as periodontitis initially but involvement of maxilla, maxillary sinus, nasal cavity, zygoma, zygomatic arch was evident on CT [13].

Imaging plays a pivotal role in establishing the diagnosis, looking for complications, delineating the extent of the disease, bony involvement, and anatomical mapping before surgical debridement. Computed tomography (CT), Magnetic Resonance Imaging (MRI) are the imaging modalities of choice. CT is the cornerstone of modern medical radiology to diagnose the extension of the lesion in rhinomaxillary region. But Cone beam CT (CBCT), which is a comparatively recent scanning technology in dentistry, provides images equivalent to medical CT at reduced costs and radiation doses. CBCT characteristics of mucormycosis is rarely been reported.

Case reported by Shastry *et al* (2020), CBCT findings of rhinomaxillary type mucormycosis included haziness in paranasal sinuses, involving nasal septum, perforation of the palate, irregular outline of extraction sockets with disruption in the buccal and palatal cortical plates. Some case reports showed complete opacification of bilateral maxillary sinus, air entrapment within sinus, breach in the floor and walls of sinus, hypertrophied nasal conchae, destruction of lateral wall of nose, irregular destruction of cortices in the alveolar region [14]. These findings were consistent with our case CBCT findings. CBCT findings in case reported by Pagare J *et al* (2019), revealed erosion of the maxillary bone with moth eaten appearance, discontinuity in maxillary sinus walls bilaterally involving nasal concha and septum, bilateral obliteration of maxillary sinus, osteolytic lesions involving the maxillary alveolar bone, perforation of the palate with involvement of the maxillary sinus etc [15]. These CBCT findings were also consistent with our case but involvement of mandible by mucormycosis is rarely been reported in literature which was obvious in our case.

Initial CT scan of our patient showed inflammatory changes in right maxillary antrum and bilateral ethmoidal sinus, apical periodontitis in relation to 15 with doubtful cortical breach and no definite lytic lesions or periosteal reactions or cortical break in relation to mandible, multiple enlarged upper cervical lymph nodes on both sides (figure 11-15).

Isolated involvement of mandibular mucormycosis on CECT was reported by Ambereen A *et al* (2019), as multiple air foci in marrow cavity in the body and ramus of mandible with sub-periosteal thickening and bony erosion without evidence of periosteal reactions [16]. Our case highlights unusual and aggressive nature of mucormycosis, as widespread involvement of maxillo-facial structures noted on CBCT scan in short time span.

Differential diagnosis of mucormycosis include sinusitis, osteomyelitis, bacterial orbital cellulitis, deep fungal infections, intraosseous carcinoma, metastatic jaw lesions. Histopathology still remains "gold standard" for final diagnosis.

Microscopy (direct and on histopathology) and culture are the cornerstones of diagnosis of mucormycosis. During biopsy specimens may be collected and send for both culture and histopathology as culture may come sterile initially as in our case. On histological examination mucormycosis shows non-septate, right-angled branching hyphae. Advanced investigations includes DNA-based detection methods believed to have high analytic sensitivities. To increase the specificity of the assays and reduce the false positivity rate, probes or high-resolution melt (HRM) analysis in qPCR, microarrays or electrospray ionization mass spectrometry (ESI-MS) may be used. Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, in addition to classic culture techniques and PCR with sequencing, can be utilized to identify the pathogenic species. Other investigations such as molecular assays can be used either for detection or identification of mucormycetes, and can be recommended as valuable add-on tools that complement conventional diagnostic procedures [17].

Treatment for mucormycosis include antifungal medications. Antifungal medications inhibit the growth of fungus and destroy fungal infections and are essential in controlling the spread of infection. The most commonly used medication is amphotericin B. If affected individuals do not respond to amphotericin B, or cannot tolerate the medication due to side effects, then salvage therapy using posaconazole or isavuconazole may be given intravenously. Surgery is necessary to remove infected or dead tissue, damaged skin, and involved subcutaneous tissue. Individuals with rhino-cerebral mucormycosis can experience significant changes to facial appearance, so surgical debridement should be done as soon as the infection is confirmed. Some affected individuals may receive adjunctive treatment with hyperbaric oxygen. Controlling underlying conditions is important in the treatment of mucormycosis. This can include medications to increase the levels of white blood cells in people with neutropenia; insulin for people with uncontrolled diabetes, iron chelators that lowers the level of iron in the blood like deferiprone for people with iron overload.

IV. Conclusion

Successful management of mucormycosis is based on early detection, multimodal treatment approach, including reversal or discontinuation of underlying predisposing factor, early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies.

This case report highlights importance of thorough history taking, detailed clinical examination, and role of CBCT to know maxillofacial spread of the mucormycosis and insists histopathology as a gold standard for the final diagnosis of the mucormycosis.

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VI. Legends for photographs

Figure 1. Extraoral photograph
Figure 2. Intraoral photograph maxilla
Figure 3. Intraoral photograph mandible
Figure 4. Panoramic radiograph
Figure 5-10. CBCT scan images as on 31/1/2022
Figure 11-15. CT scan images as on 11/12/2021

VII. Figures

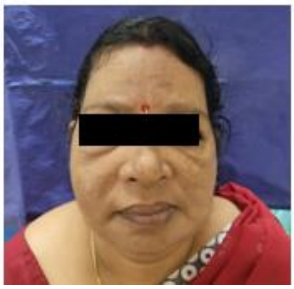

figure 1 Extraoral photograph

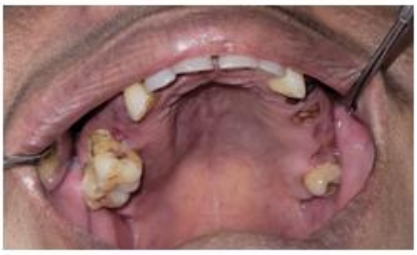

figure 2. Intraoral photograph maxilla

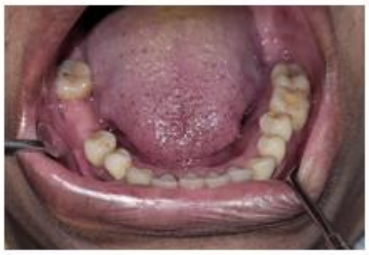

figure 3. Intraoral photograph mandible

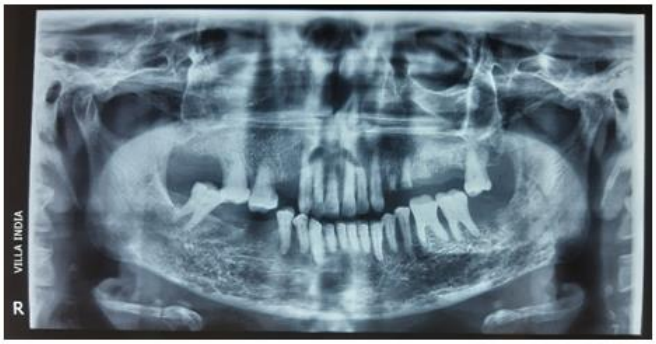

figure 4 Panoramic radiograph

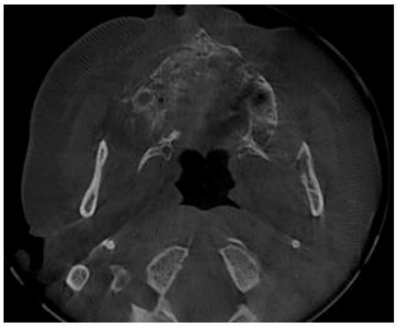

Figure 5

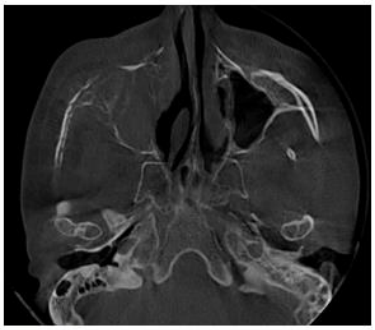

Figure 6

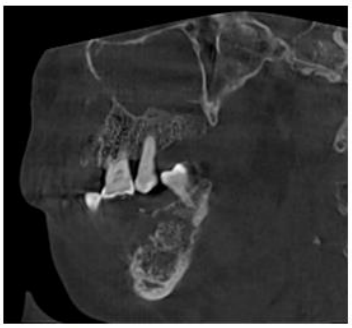

Figure 7

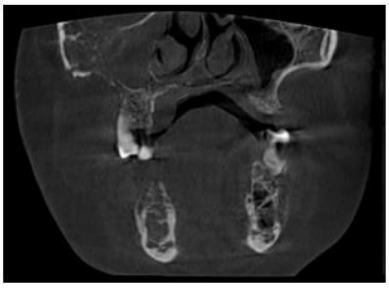

Figure 8

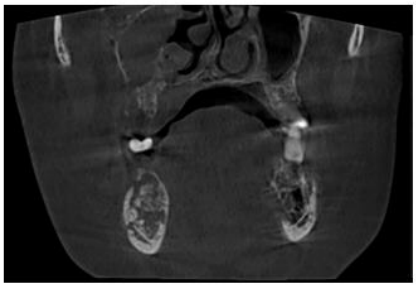

Figure 9

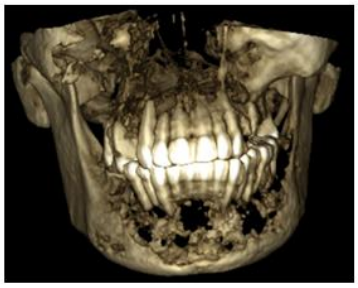

Figure 10

CBCT scan images (figure 5 to 10) as on 31/1/2022

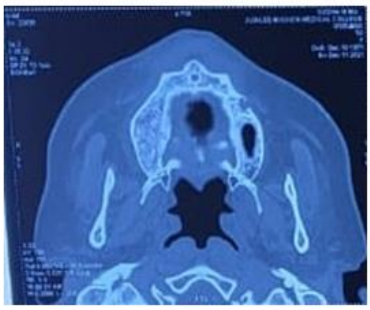

Figure 11

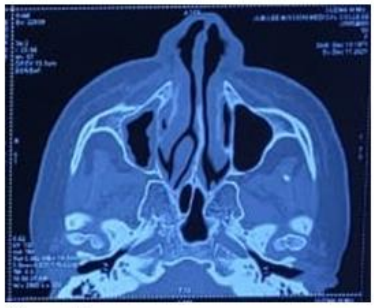

Figure 12

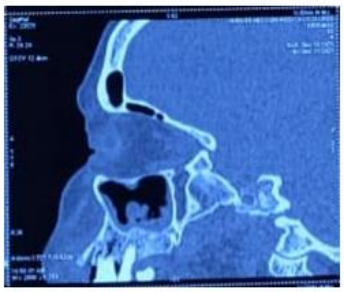

figure 13

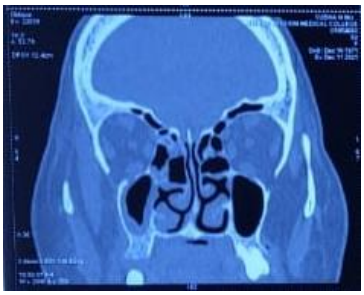

Figure 14

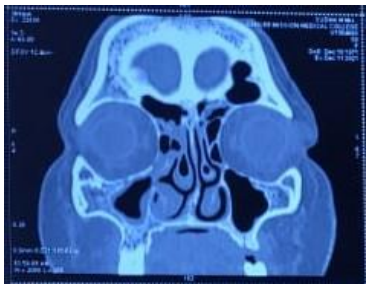

Figure 15

CT scan images (figure 11 to 15) as on 11/12/2021

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