Zygomaticomaxillary Osteomyelitis due to COVID-19 Associated Mucormycosis (CAM): A Case Series of 10 Patients

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Abstract

Aim To highlight the incidence of osteomyelitis due to CAM and to elucidate the mode of spread of infection from maxilla to zygomatic bone, to highlight how that is distinct from other cases of zygomatic osteomyelitis due to other etiologies.

Methods A standard protocol of treatment of the cases of CAM with zygomatic involvement based on our own outcomes was furnished. All 10 patients were treated with dual antifungal therapy and aggressive surgical resection via extraoral approach, in conjunction with functional endoscopic sinus surgery (FESS).

Results Ten out of 116 patients of CAM reporting to our institute presented with zygomatic bone involvement with an incidence rate averaging at 8.6%, whereas in previous literature osteomyelitis of zygomatic bone was extremely rare with an incidence pattern of just 1.42%.

Conclusions The treatment protocol followed by the authors gave good outcomes to all patients treated, with no mortalities.

Keywords COVID-19-Associated Mucormycosis (CAM) · Zygomatic osteomyelitis · Rhinomaxillary mucormycosis · Amphotericin B · Posaconazole · Total maxillectomy · Hemi-maxillectomy · Weber Ferguson incision

Introduction

The second wave of the coronavirus disease 2019 caused by the novel Coronavirus or the SARS COV 2 has led to an increase in superinfections which prior to the beginning of the current pandemic were rarely ever reported. There is particularly a surge in cases of COVID-Associated Mucormycosis (CAM) which in common parlance has been termed ‘The black fungus.’ Mucormycosis which in prior times used to be a rare fungal infection is becoming rampant in many regions of India with the state of Maharashtra being one of the worst affected. Yet another curious finding is the involvement of the zygomatic bone in mucormycosis cases which have been reported to our center in these past few months. The maxilla is the most common jaw bone being affected by fungal osteomyelitis and is more commonly associated with diabetes mellitus. Clinically, mucormycosis occurs in one of the four forms: rhinocerebral, pulmonary, gastrointestinal and disseminated. Rhinocerebral form is the most
common, representing one-third to one-half of all cases ofzygomycosis. This is further subdivided into two subtypes:ahighly fatal rhino-orbito-cerebral form which is invasiveand may involve the ophthalmic and internal carotid arteriesand a less fatal rhino-maxillary form which involves thesphenopalatine and greater palatine arteries, resulting inthrombosis of the turbinate and necrosis of the palate[1].The clinical hallmark of mucormycosis is vascular invasionresulting in thrombosis and tissue infarction/necrosis[2]. This tissue infarction has been speculated as the cause ofnecrosis of the bone leading to fungal osteomyelitis. A reviewof the existing literature in the past or in pre-COVID times shows a low incidence of zygomatic bone osteomyelitis. In a survey of 141 cases of osteomyelitis by Adekeye et al. only 2 patients (1.42% of the study population) hadinvolvement of the malar bone. [3] There now is however anoticeable increase in the number of patients presenting withzygomatic osteomyelitis secondary to CAM, a phenomenonwhich is highlighted in the following case series. It should benoted that there are no structured studies in the literaturehighlighting the incidence of CAM infection involving thezygomatic bone.

**Patients and Methods**

A descriptive study was planned at a tertiary care center, involving all patients with CAM of the paranasal sinuses andhaving a history of COVID-19 infection. Patients included inthis study presented to the department of Oral and maxillofacialsurgery over a period of 7 months (January 2021 to July 2021). Ethical approval was obtained from the Institutional Ethics Committee.

A total of 116 patients reported to our center of which 10patients had involvement of zygomatic bone with an incidence rate of 8.6%. Four of the patients were female and 6were male. Mean age of the patients was 56.4 years.

All the patients had a history of previous COVID-19 infection. Eight of the ten patients were admitted in COVID-19 wards and 2 of the patients were under home isolation being treated on an out-patient basis. Supplemental oxygen therapy was required for 6 patients during their COVID-19 infection treatment. Nine of the patients required Inj. Methylprednisolone during their treatments. Four patients were given Inj. Remdesivir treatment. Four of the patients developed type 2 Diabetes Mellitus during their COVID-19 treatment phase and the other 6 patients were known cases of type 2 Diabetes pre-infection. Two of the patients underwent dental extraction of teeth after discharge from COVID-19 hospitals and went on to develop CAM thereafter, incidentally affected on the same side as the dental extraction site. Seven of the ten cases had a longstanding history of hypertension and 1 patient had benign prostatic hyperplasia (BPH). Four of the patients developed type 2 Diabetes Mellitus during their COVID-19 treatment phase and the other 6 patients were known cases of type 2 Diabetes Mellitus. It is of note that all the 10 patients exhibited poor glycemic control which was a significant predisposing factor for the opportunistic infection. The patients did not report any other relevant medical history. Intra oral findings observed in the patients were, mobility of teeth in all of the cases, pain in teeth in 8 cases, multiple draining sinuses in3 cases, palatal fistula was observed in only 2 cases andexposed bone intra-orally was present in 1 patient. Seven ofthe patients had nasal findings such as nasal stuffiness,perinasal edema and pain. Ocular findings which includedpain, periorbital edema and proptosis were encountered in 4patients. Neurologic findings were present in only one of thecases which was headache. Rhino-orbito-maxillary subtype waspresent in 4 patients. The rest of the cases were rhino-maxillary subtype. Rhino-orbito-cerebral subtype was notencountered. Either Contrast Enhanced Computed Tomography (CECT) of PNS + orbit + brain or plain CT HEAD or MRI was advised to the patients in preoperative period.

KOH mount of Pus culture/swab culture of all patients as well as tissue biopsy in all the patients presented with signs and symptoms of CAM showed broad-based, ribbon-like,non-septate hyphae with wide-angle branching (approximately 90°) in the laboratory diagnosis, thus confirming the diagnosis of CAM.

Surgical procedure was tailored according to each patient’s findings and by extension of the infection. Endoscopic, open, and combined approaches were utilized with aggressive resection of the involved bone and sinus debridement (ethmoid, sphenoid, frontal and maxillary) followed by antifungal therapy to eradicate infection. Dual antifungal drug therapy with Amphotericin B and Posaconazole were given in all diagnosed cases of CAM. Tab Posaconazole 300 BD was given as a loading dose followed by 300 mg OD for 3 months and Injection Amphotericin B (Conventional/Lipid complex/Liposomal) was given 3 days pre-operatively and 7–15 days post-operatively. Overall, a protocol of aggressive surgical debridement was followed. All of the 10 patients first underwent Functional Endoscopic Sinus Surgery (FESS). Six out of ten patients had right sided zygomatic bone involvement and the remaining 4 had left sided zygomatic involvement. Treatment given to 4 of the patients was total maxillectomy + zygomatic resection + FESS and the remaining 6 patients underwent hemi-maxillectomy + zygomatic resection + FESS all via extraoral approach taking Weber Ferguson incision with Dieffenbach extension. Zygomatic resection extended till frontozygomatic suture and zygomatic arch in 2 of the cases. All the cases showed bilateral maxillary involvement of varying degrees of severity but it can be observed that the side which showed zygomatic involvement had more advanced progression of disease in
ipsilateral maxilla. Taking note that all 10 cases had unilateral zygomatic involvement, on the side without zygomatic bone involvement, treatment given in 3 of the cases was maxillary sinus debridement via Caldwell-Luc approach and the other 7 underwent hemi-maxillectomies. Seven of the cases underwent inferior nasal turbinectomies. All the cases had concomitant involvement of either unilateral or bilateral ethmoid and/or sphenoid and/or frontal sinuses. Pterygoid plate involvement was present in 1 case and pterygopalatine fossa was involved in one of the cases. Out of the 4 cases with orbital involvement one underwent lateral canthotomy and debridement of pus pouches and infected periorbital tissue. There was complete preservation of ocular movements post-operatively in this case due to meticulous surgical technique. 3DCT head image and intraoperative images of a patient are depicted in Fig. 1a–d. Image of the excised specimen of diseased tissue is depicted in Fig. 2. 3DCT face images of a patient with involvement of left zygomatic bone are depicted in Figs. 3 and 4. The intraoperative images of above-mentioned patient are depicted in Figs. 5 and 6. The 15-days follow-up images of the same patient are depicted in Figs. 7 and 8. Figure 9 depicts the patient at the six-month follow-up. Figure 10 depicts the intraoral view of the patient on the six-month follow-up visit.

Fig. 1 3DCT face image and intraoperative images.
Most common complication encountered in the post-operative phase was pain and post-operative edema. None of the cases developed wound site infection or wound dehiscence. Meticulous wound care, multivitamin supplementation and topical intraoral 0.1% Amphotericin B gel application rendered an uneventful post-operative period and patients were discharged on an average after 8 days. The patients reported for follow-up appointments after 3 days, 1 week and 2 weeks post-operatively with healthy healing wounds and were in good general condition.

Discussion and Literature Review

Osteomyelitis of bones in the middle third of the face is rare. A review of the literature shows that the mandible is the most commonly involved facial bone. Osteomyelitis of the maxilla is extremely rare. [3]

Osteomyelitis occurring due to fungal infection was rare and occurs in an indolent manner. Osteomyelitis is more
commonly seen in males (80.36%) than in females (19.64%),
with a peak incidence in 30–39 years of age [4]. The maxilla
is the most common jaw bone being affected by fungal
osteomyelitis and is more commonly associated with
diabetes mellitus. Among fungal osteomyelitis, Candida is
the most commonly encountered followed by Aspergillosis
and Mucormycosis. These organisms are from an original
infection that has not been treated properly, commonly from
dental extraction [5]. Niranjan et al., in their ten-year study
reported that 52% of all the osteomyelitis cases were that of
fungal osteomyelitis, whereas 48% belonged to the nonfungal
category [6].

Adekeye et al. published a review of 141 cases of osteo-
myelitis of the jaws and reported the incidence of malar
bone osteomyelitis to be only 1.42% [3]. The incidence
of zygomatic bone osteomyelitis reported in our study of
cases with CAM is 8.6%.
There are no other existing literature reviews or systematic reviews found in the existing pool of knowledge highlighting the incidence, causes and mode of spread of zygomatric bone osteomyelitis. There have been however isolated case reports and case series of zygomatric bone osteomyelitis. Most of these cases are due to tuberculosis and fungal causes (candidiasis, cryptococcus and aspergillosis). The majority of tuberculous cases of zygomatric osteomyelitis are due to hematologic spread of pulmonary tuberculosis by seeding of bacilli or by direct spread from neighboring structures [7]. There have been rare cases reported caused due to trauma and also idiopathic osteomyelitis of zygoma. An analysis of mode of spread of infection to zygomatic bone in a few rare cases reported in the literature is presented in Table 2.

Mucormycosis is an invasive fungal disease caused primarily by fungi belonging to the order Mucorales. This fungus usually acts as an opportunistic pathogen, seen in soil, decaying organic debris and frequently occurs in the patients with a compromised immune system. The leading predisposing factors for mucormycosis are uncontrolled diabetes mellitus, lymphomas, leukemias, renal failures, organ transplant, long-term intake of corticosteroids, immunosuppressive therapy and AIDS. Iron plays an important role in the growth of mucormycosis. Fungal hyphae produce ‘rhizoferrin,’ which binds iron fervently. This iron–Rhizoferrin complex is then taken up by the fungus and becomes available for its vital functions. In the cases of diabetic ketoacidosis, the patients are at high risk of developing mucormycosis, due to an elevation in the available serum iron [15]. Pertaining to the cases reporting to our institution is of special significance to note that all the 10 patients described exhibited poor glycemic control which was a predisposing factor for the opportunistic infection.

The infection develops after inhalation of fungal sporan-giospores into the paranasal sinuses. The infection may then rapidly extend into adjacent tissues. Upon germination, the invading fungus may spread inferiorly to invade the palate, posteriorly to invade the sphenoid sinus, laterally into the cavernous sinus to involve the orbits, or cranially to invade the brain. The fungus invades the cranium through either the orbital apex or cribiform plate of the ethmoid bone and ultimately kills the host. Occasionally, cerebral vascular invasion can lead to hematogenous dissemination of the infection with or without development of mycotic aneurysms [16]. Upon visual inspection, infected tissue may appear normal during the earliest stages of spread of the fungus. Infected tissue then progresses through an erythematous phase, with or without edema, before onset of a violaceous appearance, and finally the development of a black, necrotic eschar as the blood vessels become thrombosed and tissue infarction occurs. Infection can sometimes extend from the sinuses into the mouth and produce painful, necrotic ulcerations of the hard palate [2].

In the present case series, the authors are of the opinion that the fungal spores enter via the nasal cavities and then spread to the paranasal sinuses. The maxillary sinus is thus invariably involved. The fungus erodes through the posterior aspect of the maxillary sinus gaining access to the infratemporal fossa. From the infratemporal fossa the infection directly invades into the body of the zygoma from the posterior aspect and in some cases also the arch of the zygoma. This has been deduced by the characteristic pattern observed in the CT imaging of each case which shows erosion of the posterolateral wall of the maxillary sinus with obvious haziness in the area of the infratemporal fossa. Retrospectively to co-relate with this clinically, at time of maxillectomy the posterior aspect of the maxilla and the pterygoid bone i.e., the infratemporal fossa and the structures therein were invariably diseased and required thorough debride-ment in all of the cases. This does indicate that spread to the zygoma from the maxilla could well be by way of the ipsilateral infratemporal fossa. According to the existing literature the zygomatic bone can be approached for resection intra-orally or extra-orally. For the cases in this series an open approach was preferred via Weber Ferguson incision to provide unhindered access to this posterior aspect and to be able to thoroughly debride the involved tissues of the infratemporal fossa. Although theoretically access to the zygoma can be achieved intraorally as well, it was deemed prudent by the surgical team to approach extra-orally for a more thorough, aggressive and definitive resection. The pathway of spread is elucidated by the flowchart in Fig. 11.

The incidence of zygomatic osteomyelitis in the literature is rare. Although a definitive cause for this has not been empirically stated in any of the past studies it can be speculated that it is due to the fact that the bone has a rich vascular supply and that there are no direct potential sources of infection such as teeth present in the bone. Additionally, the bone is not in any direct contact with the oral microflora nor is it in communication with the environment, it being a
Table 1 Table describing clinical features, treatment given and outcomes of patients involved in the study

| Patient no | Age/sex | Co-morbidities | Findings | Zygoma involved | Treatment | Outcomes |
|------------|---------|----------------|----------|-----------------|-----------|----------|
| 1          | 43/M    | DM, HTN        | Clinical CT (sinuses affected) | Left maxilla++ | Surgical | Left maxillary resection, left sided hemi-maxillectomy, right maxillary sinus debridement via Caldwell-Luc approach |
|            |         |                |          | Right maxilla+ | Antifungal | AmB      |
|            |         |                |          | Nasal septum,  |           | Tab. posaconazole Recovered |
|            |         |                |          | Right ethmoid, |           |          |
|            |         |                |          | Left zygoma    |           |          |
| 2          | 61/M    | DM, HTN        | Clinical CT (sinuses affected) | Right maxilla++ | Surgical | Right maxillary sinus debridement via Caldwell-Luc approach |
|            |         |                |          | Left maxilla+  | Antifungal | AmB      |
|            |         |                |          | Ethmoid,       |           | Tab. posaconazole Recovered |
|            |         |                |          | Sphenoid,      |           |          |
|            |         |                |          | Frontal,       |           |          |
|            |         |                |          | Zygoma         |           |          |
| 3          | 54/F    | DM             | Clinical CT (sinuses affected) | Right maxilla++ | Surgical | Right maxillary sinus resection, bilateral hemi-maxillectomy |
|            |         |                |          | Left maxilla+  | Antifungal | AmB      |
|            |         |                |          | Ethmoid,       |           | Tab. posaconazole Recovered |
|            |         |                |          | Frontal,       |           |          |
| 4          | 73/F    | DM, HTN        | Clinical CT (sinuses affected) | Bilateral maxillae++ | Surgical | Right maxillary sinus debridement, right maxillary sinus resection, bilateral hemi-maxillectomy |
|            |         |                |          | Sphenoid,      | Antifungal | AmB      |
|            |         |                |          | Ethmoid,       |           | Tab. posaconazole Recovered |
|            |         |                |          | Frontal,       |           |          |
|            |         |                |          | Zygoma,        |           |          |
|            |         |                |          | Inflammatory edema of retrobulbar soft tissue | | | |
| 5          | 62/F    | DM             | Clinical CT (sinuses affected) | Right maxilla++ | Surgical | Right maxillary sinus debridement, left inferior turbinectomy |
|            |         |                |          | Left maxilla+  | Antifungal | AmB      |
|            |         |                |          | Ethmoid,       |           | Tab. posaconazole Recovered |
|            |         |                |          | Zygoma         |           |          |
| 6          | 65/F    | DM, HTN        | Clinical CT (sinuses affected) | Bilateral maxillae++ | Surgical | Right maxillary sinus debridement, right lateral antrotomy, right maxillary sinus debridement, left inferior turbinectomy |
|            |         |                |          | Zygoma         | Antifungal | AmB      |
|            |         |                |          | Ethmoid,       |           | Tab. posaconazole Recovered |
|            |         |                |          | Sphenoid,      |           |          |
|            |         |                |          | Pterygoid bone |           |          |
|            |         |                |          | Inferior, lateral and medial orbital walls | | | |
| Patient no | Age/sex | Co-morbidities | Findings | Zygoma involved | Treatment | Outcomes |
|------------|---------|----------------|----------|----------------|-----------|----------|
| 7          | 59/M    | DM, HTN, BPH   | Left sided facial swelling and pain, Restricted eye movements with left eye, Nasal stuffiness | Bilateral maxillae++, Left zygoma body and arch, Bilateral ethmoids, Pterygopalatine fossa, Left Inferior rectus thickening, Inferior and medial and lateral walls of orbit | LEFT | L- AmB Tab. Posaconazole | Recovered |
| 8          | 52/M    | DM, HTN        | Left sided facial pain and swelling, | Left maxilla++, Right maxilla+ Left zygoma body and arch and frontozygomatic process, Bilateral ethmoid, Bilateral sphenoid | LEFT | L- AmB Tab. Posaconazole | Recovered |
| 9          | 46/M    | DM             | Right sided facial pain and swelling, Nasal stuffiness | Right maxilla++, Left maxilla+ Right zygoma, Bilateral ethmoid, Bilateral sphenoid | RIGHT | L- AmB Tab. Posaconazole | Recovered |
| 10         | 50/M    | DM, HTN        | Left sided pain and swelling, Nasal stuffiness, Bloody red nasal discharge | Left maxilla++, Right maxilla+ Left zygoma Left ethmoid Bilateral sphenoids | LEFT | L- AmB Tab. Posaconazole | Recovered |

*L-AmB, Liposomal Amphotericin B; +AmB, Amphotericin B Deoxycholate

++Extensive sinus involvement, +intermediate sinus involvement
### Table 2  Review of literature describing zygomatic bone osteomyelitis with etiology, clinical features, mode of spread and treatment

| Sr. no | References          | Etiology                  | Clinical presentation                                                                                           | Likely mode of spread                                                                 |
|--------|---------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 1      | Sethi et al. [7]    | Secondary Tuberculosis    | Erosion and sclerosis of left zygomatic bone with a soft-tissue abscess suggestive of osteomyelitis                | Direct spread of infection from neighboring structures such as the orbit, paranasal sinuses, face and nasal mucosa |
| 2      | Rama et al. [8]     | Primary tuberculosis      | A sinus measuring 3x4 cm having undermined edges and yellowish pus discharge over the right zygomatic region       | Primary extra-pulmonary zygomatic tuberculosis                                         |
| 3      | Virendra Singh et al. [9, 9] | Secondary to pulmonary TB | Fluctuant swelling on the right zygomatic prominence                                                             | Hematologic seeding of bacilli                                                       |
| 4      | Takashi Matsuki et al. [11] | Cryptococcus             | A tender swelling in the right zygomatic region and trismus                                                       | Isolated cryptococcal osteomyelitis of zygomatic bone                                 |
| 5      | Arranz-Caso et al. [12] | Candidiasis              | Tenderness of right zygomatic region                                                                             | Self-inoculation of spores from muguet plaques on the oral mucosa to the exposed bone tissue (due to topical 5-fluorouracil treatment of the right malar region for actinic keratosis) by hand contact |
| 6      | Noroy et al. [13]   | Aspergillus necrotizing otitis externa (NOE) | Blocked right ear for several months, associated with pain on mastication, without earache                     | Severe otitis externa with a foreign body in the external auditory canal, corresponding to cotton bud debris causing rare complication of Aspergillus NOE with temporomandibular arthritis and temporozygomatic osteomyelitis |
| 7      | Borle et al. [14]   | Secondary infection due to trauma | Pus discharge from the cheek, infraorbital area, and lateral canthus region of the eye on the left side for 2 months | Incomplete immobilization despite direct fixation of zygomatic fracture                |

Treatment given:
- Anti-tubercular chemotherapy [7]
- Anti-tubercular chemotherapy [8]
- Surgical curettage and 4-drug antitubercular therapy [9, 10]
- Fluconazole therapy for 6 months [11]
- Oral fluconazole, 200 mg/12 h, intravenous amphotericin B (0.5 mg/Kg/day, 40 days), a skin flap mobilized from the temporal region was implanted over the exposed bone [12]
- Surgical curettage and 3 months of antifungal therapy [13]
- Sequestrectomy and debridement with sinus curettage [14]
solid, non-pneumatized bone, not bearing a sinus. With this in consideration an open approach was preferred via Weber Ferguson incision to provide unhindered access to this posterior aspect and to be able to thoroughly debride the involved tissues of the infratemporal fossa.

This case series attempts to highlight the unique nature of the mode of zygomatic involvement of the patients affected with CAM as compared to case reports and series presented in the past such as those due to tuberculosis, other fungi, trauma, etc. In our experience with cases of zygomatic bone osteomyelitis due to CAM, an aggressive surgical resection of bone and thorough debridement of diseased tissues combined with a dual antifungal drug therapy was the key to successful recovery. The authors recommend this treatment regimen for similar cases encountered.

**Conclusion**

The incidence of zygomatic bone osteomyelitis reported in our study of cases with CAM was found to be 8.6%. The mode of spread of infection to the zygomatic bone in cases of CAM is distinct from that of the other etiologies of zygomatic osteomyelitis reported in the past. The pattern of spread follows a distinct route and this should be kept in mind during the treatment planning and decision making for these cases. As the pattern of spread follows this predictable path the landmarks along the path of spread can serve as prognostic indicators for such cases and also serve as red flags for immediate intervention to prevent further spread and to reduce morbidity and to render a less challenging prosthetic rehabilitation. Considering the favorable outcome of the treatment protocol followed in this series, similar standard operating procedure can be employed in these cases encountered in the future.

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**Declarations**

**Conflict of interest**  The authors declare that they have no conflict of interest.

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