Incidence and Treatment Protocol for Maxillofacial Fungal Osteomyelitis: A 12-Year Study

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Purpose: The aim was to retrospectively determine the incidence of fungal osteomyelitis and outcome of the surgical protocol and complications.

Materials and Methods: Data were recorded from the medical records of patients treated from 2006 to 2018. Predictor variables were drawn from demographic characteristics (age and gender), etiology, most common site, associated comorbidities involved, and treatment protocol followed. The outcome variables were the success rate and associated complications.

Results: We identified 50 patients with fungal osteomyelitis out of 153 who were treated for various types of osteomyelitis for 12 years. The incidence was 32.6%; men were affected more than women, at a ratio of 2.5:1; and most common site was the maxilla (56%), followed by the mandible (32%) and other sites (12%). Treatment protocols were dependent on the nature of the lesion, site, and optimization of underlying comorbid conditions. The outcome of our protocol showed that 28 patients (56%) healed well. Patients with complications such as palatal fistula (13 [26%]) underwent revision surgery using a local advancement flap and the buccal fat pad. During the immediate postoperative period, 2 patients (4%) had wound dehiscence; 2 patients (4%) had nasal regurgitation; and 1 patient (2%) had a reduced mouth opening that was managed with a mouth-opening exercise regimen. In 1 patient (2%) with recurrence, secondary correction was performed after 6 months and postoperative antifungal therapy was administered for 3 months.

Conclusions: The incidence of fungal osteomyelitis was high owing to associated comorbidities. The surgical outcome was markedly influenced by a prompt diagnosis based on the clinical presentation and histopathology, identification and optimization of comorbidities, correction of electrolyte imbalances, 2 doses of amphotericin B preoperatively under an intensive care unit setup, intraoperative collection of specimens for fungal culture by a microbiologist, curettage and debridement of the soft tissue and bone, closure of the defect with either a local or regional flap, and postoperative antifungal therapy.

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Osteomyelitis is defined as inflammation of the medullary cavities, haversian system, and adjacent cortex of bone.[1] The incidence ratio of osteomyelitis of the maxilla to the mandible ranges from 1.07:1 to 1:6.5.[2,3] In the present antibiotic era, osteomyelitis of the facial bones is a rare condition. The incidence of osteomyelitis involving the maxilla is 45.1%, as reported by Koorbusch et al,[3] and is quite rare compared with that of the mandible because of the extensive vascularity and compartment-like porous architecture seen in the maxilla, which dissipate the infection.[1,4]

Fungal infection can be pathogenic or opportunistic. A pathogenic infection arises in a host with normal immune function, whereas an opportunistic fungal infection occurs in an immunocompromised, low-virulence host. Pathogenic fungal infections include histoplasmosis, blastomycosis, paracoccidioidomycosis, and coccidioidomycosis. These are infectious but not contagious. Saprophytic opportunistic fungal infections include mucormycosis, candidiasis, aspergillosis, cryptococcosis, and pneumocystis. The incidence of fungal osteomyelitis of the maxilla is 52%, the male-to-female ratio is 2.1:1, and the age group is between 10 and 65 years.[2,5]

Mucormycosis is an uncommon acute opportunistic infection caused by a saprophytic fungus that belongs to the order Mucorales, family Mucoraceae, and class Zygomycetes.[6] It was first described in humans by Paultaufi in 1885, as cited by Marchevsky et al.[7] The genera of Mucorales that are recognized as human pathogens are *Rhizopus*, *Absidia*, *Rhizomucor*, and *Mucor*. These organisms are frequently found to colonize the oral mucosa, nasal mucosa, paranasal sinuses, and pharyngeal mucosa in asymptomatic patients.[8,9]

The aforementioned fungus invades the arteries and forms thrombi within the blood vessels that reduce the blood supply and cause necrosis of the hard and soft tissues.[10,11] Once having entered the arteries, the fungus can spread to orbital and intracranial structures.[12,13] Mucormycosis presents as an acute infection and manifests in a rhinocerebral, pulmonary, gastrointestinal, cutaneous, or disseminated form.[10] It is associated with comorbidities such as uncontrolled diabetes mellitus, is acidotic, and occurs in patients with hematologic malignant disease such as leukemia[14] or patients receiving immunosuppressive therapy.[14-16] Symptoms involving the oral and craniofacial tissues account for about 60% of all cases.[10-13,15-18] Intraorally, the hard palate is usually affected because of its proximity to the infection of the nasal fossa, and the paranasal sinuses, alveolar mucosa, tongue, and buccal mucosa of the lips and cheek also may be affected.[19] If left untreated, this condition will cause severe comorbidity with craniofacial deformity and death, which occurs at a rate of 66 to 70%.[20,21] There is no substantial literature available in this regard to optimize the treatment protocol. The main objective of this study was to standardize the approach to the management of this fatal disease occurring in and around the oral cavity.

Materials and Methods

This was a retrospective study involving 50 of 153 patients who were treated for fungal osteomyelitis at our craniofacial center between 2006 and 2018 and underwent surgical treatment such as debridement and sequestrectomy, conservative treatment, debulking, or partial maxillectomy. A review of the medical records of these patients was performed and served as the source of data for the study with the consent of the institutional review board. The age of the included patients with a histopathologic diagnosis ranged from 19 to 70 years, and the minimum follow-up period was 1 year. The data assessed involved the clinical records; imaging ranging from conventional means to computed tomography, magnetic resonance imaging, or a Dentascan and hematologic investigations. The need for surgery for this disease and the associated risks were explained to all patients. Eight patients were excluded because of lack of medical records and follow-up. Important data on preoperative preparation, type of surgical intervention, and postoperative medications were carefully recorded to assess the outcome.

Results

Osteomyelitis was diagnosed in 153 patients, of whom 50 (32.6%) received a diagnosis of fungal origin. Men were affected more than women, at a ratio of 2.5:1; the patients were aged between 19 and 70 years. The most common site was the maxilla (56%), followed by the mandible (32%) and other sites (12%) such as extension into the eye or the frontal and ethmoidal region, which constituted 6 patients. Comorbid conditions included diabetes in 23 patients (24.6%), liver disease in 2 (2%), and renal disease in 1 (1%). A post-extraction etiology was noted in 13 (26%), trauma and sinusitis accounted for 5 patients (10%), and smoking was associated in 2 patients (2%). Of the patients, 22 (44%) were confirmed as having mucormycosis, 1 patient (2%) had aspergillosis, and the remaining 27 patients (54%) were reported as having fungal infections. All the patients underwent optimization for existing comorbidities, received preoperative intravenous antifungal therapy, and were treated by a conservative method (ie, curettage and sequestrectomy), debulking, or a partial maxillectomy (Figs 1A,B) with the following reconstruction options: locoregional flaps with the buccal fat pad in

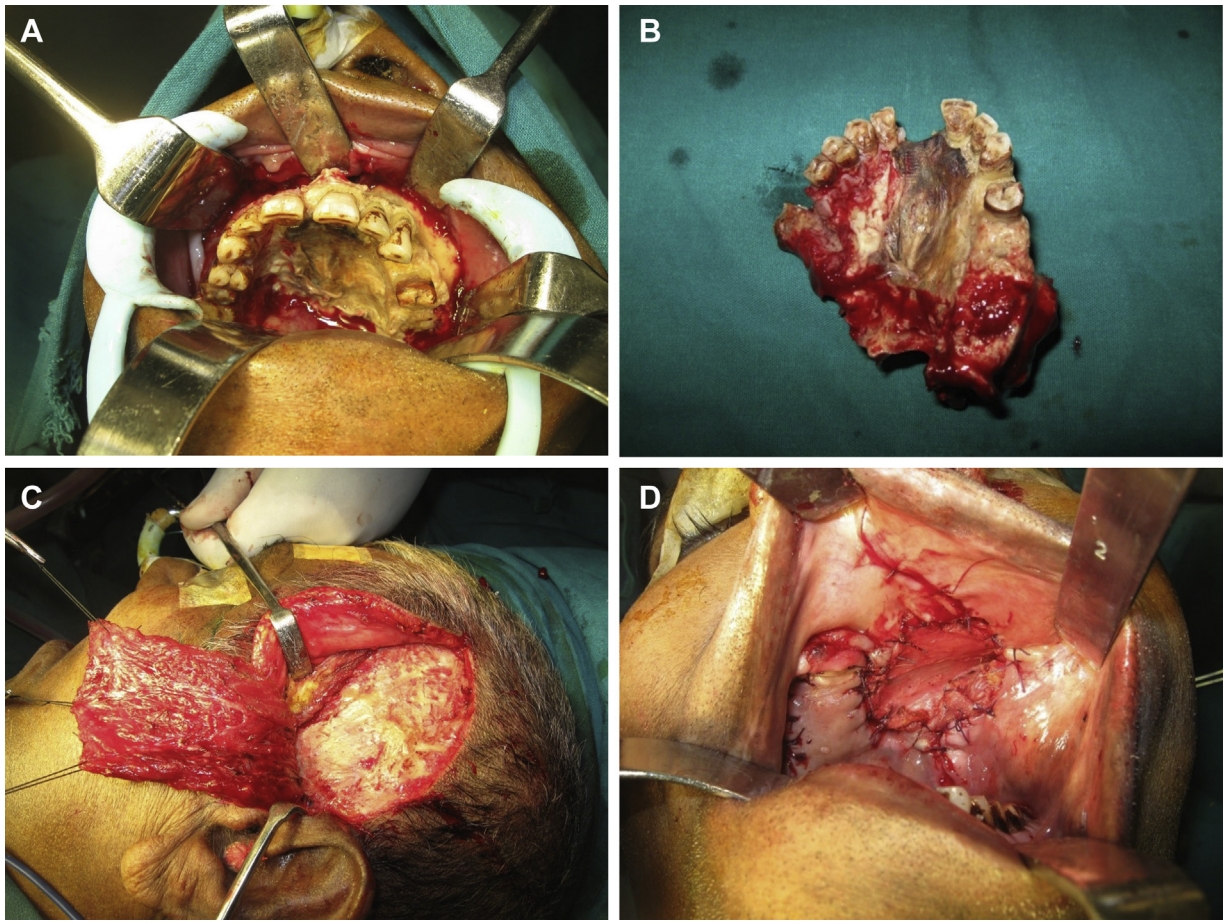

FIGURE 1. *A*, Exposed maxilla using degloving incision. *B*, Excised specimen of maxilla in toto. *C*, Reconstruction of defect using temporalis myofascial flap. *D*, Closure of maxillary defect with temporalis flap.

Anehosur et al. Maxillofacial Fungal Osteomyelitis. J Oral Maxillofac Surg 2019.

26 patients (52%), temporalis myofascial flaps in 5 (10%) (Figs 1C,D), and tongue flaps and obturators in 2 (4%). The outcome of surgery showed that 28 patients (56%) healed well without any complications (Fig 2). Antifungal therapy was continued for a period of 3 months. The complications recorded were palatal fistula in 13 patients (26%), wound dehiscence in 2 (4%), nasal regurgitation in 2 (4%), and a reduced mouth opening in 1 (2%), which was managed with a mouth-opening regimen. In 1 patient (2%) with a recurrence, curettage and debridement were performed after 6 months.

Discussion

Osteomyelitis is a chronic inflammatory condition of bone and its marrow content that originates from chronic infection. The etiopathogenesis includes trauma, surgery, bacteremia, or fungal infection. It is further influenced by the stagnation of blood, which acts as a nidus for the development of infection.[22] Fungal osteomyelitis is very rare and presents in an indolent fashion. It can affect other parts of the body such as the vertebrae and sternum.[23] Involvement of the jaw bones after cytotoxic chemotherapy also has been reported.[14] If fungal infections are invasive in nature, they are devastating to patients. These are

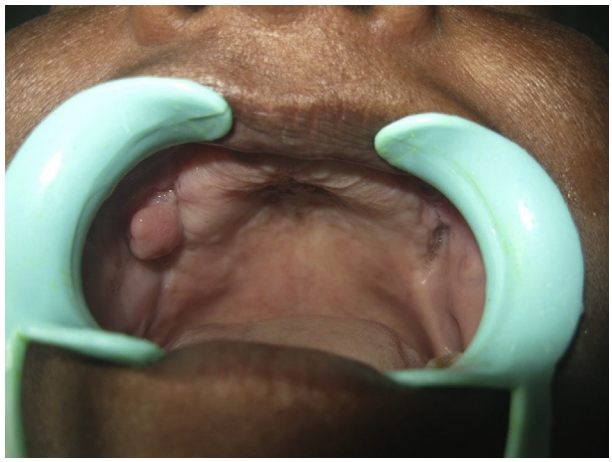

FIGURE 2. Postoperative healing of defect with flap in situ.

Anehosur et al. Maxillofacial Fungal Osteomyelitis. J Oral Maxillofac Surg 2019.

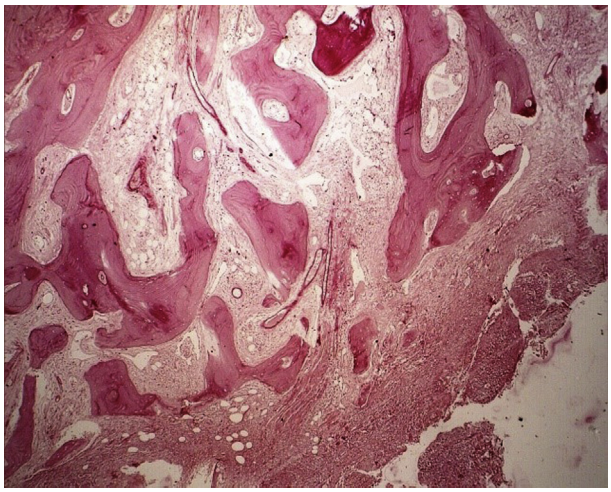

FIGURE 3. Histopathologic slide with periodic acid–Schiff stain showing right-angle branching of aseptate fungal hyphae (original magnification ×100).

Anebosur et al. Maxillofacial Fungal Osteomyelitis. J Oral Maxillofac Surg 2019.

opportunistic infections that enter the body through an invasive gateway, such as a dental extraction, owing to a decrease in host defense. The clinical presentation of fungal osteomyelitis is similar to that of bacterial osteomyelitis. Because fungal infections involving bone occur less frequently, they can pose a diagnostic and therapeutic challenge for clinicians who are not familiar with their clinical presentation, hence leading to compromised treatment or incomplete resolution. On clinical presentation, we found that 45 patients (90%) presented with exposed bare

FIGURE 4. Cotton-candy appearance on Sabouraud agar depicting fungal growth.

Anebosur et al. Maxillofacial Fungal Osteomyelitis. J Oral Maxillofac Surg 2019.

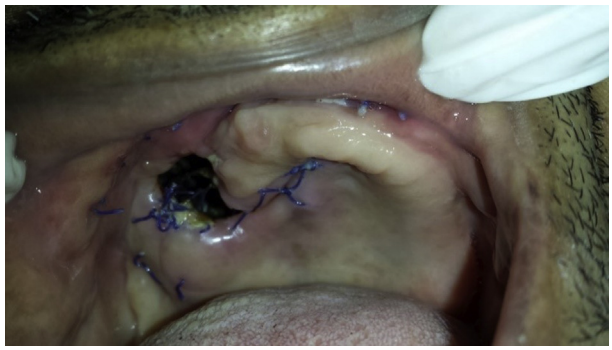

FIGURE 5. Palatal fistula noted on 20th postoperative day.

Anebosur et al. Maxillofacial Fungal Osteomyelitis. J Oral Maxillofac Surg 2019.

necrotic bone of an ashen gray color and 5 patients (10%) had a breach in the continuity of soft tissue without exposure of bone. Other features noted were persistent intense pain, soft tissue swelling, and tenderness to palpation. No suppuration or drainage was noted. Per the history, the length and duration of exposed bone ranged between 45 and 60 days.[2] A specific differentiating feature would be the involvement of the maxillary sinus with a complaint of sinusitis in maxillary fungal osteomyelitis. An associated history of diabetes would be present, and it is usually a propagating factor for maxillary osteomyelitis.[24] Fungal hyphae produce "rhizoferrin," which binds to serum iron. The rhizoferrin-iron complex is important for fungal growth. Hence, patients with diabetic ketoacidosis are more susceptible to mucormycosis as they have elevated levels of serum iron.[25,26] Among patients with uncontrolled diabetes mellitus in a rural Indian population, an incidence of maxillary osteomyelitis of 45.1% has been reported by Koorbusch et al.[3] The collateral blood supply, porous nature of bone, and thin cortices of the maxilla reduce the chance of osteomyelitis in the maxilla compared with the mandible. However, our series showed a slight predominance of fungal osteomyelitis in the maxilla over the mandible. Maxillary involvement was seen in 56% of cases with a male predominance associated with diabetes mellitus. A thorough review of the literature showed that an incidence ratio of maxillary to mandibular osteomyelitis of 1.07:1 was noted by Peravali et al,[2] whereas incidences of 1:6.5 and 1:6 were noted by Koorbusch et al and Rangne and Ruud,[27] respectively.

The diagnostic workup is of paramount importance to differentiate between bacterial and fungal osteomyelitis. Routine blood investigations show leukocytosis in the 12,000/μL to 20,000/μL range and a Schilling shift to the left. The biopsy specimens of bony tissues in decalcified sections show irregular bony trabeculae with empty osteolytic lacunae. The presence of fungal hyphae within the bone suggests the fungal nature.

Table 1. DEMOGRAPHIC STATISTICS AND TREATMENT MODALITIES

Patient No.	Age, yr/ Gender	Site	Medical Status	Management	Reconstruction
1	52/M	Max	NRH	Debulking, FLU, AMB	Obturator
2	30/M	Mand	NRH	Deb + Seq, AMB	
3	28/F	Max	Renal disease	Deb + Seq, AMB	Buccal fat pad
4	24/F	Mand	NRH	Deb + Seq, AMB	
5	57/M	Left eye—retrobulbar space	DM	Debulking, FLU + ITRA	Buccal fat pad
6	29/M	Right eye	NRH	Cons, FLU	Buccal fat pad
7	56/M	Mand	Liver disease	Deb + Seq, FLU, AMB	Closure with advancement of local tissue
8	34/M	Frontal bone	NRH	Deb + Seq, AMB	Closure with advancement of local tissue
9	65/M	Max	DM	Deb + Seq, AMB	Buccal fat pad
10	40/M	Max	NRH	Deb + Seq, AMB	Closure with advancement of local tissue
11	65/M	Max	DM	Partial maxillectomy, FLU	Buccal fat pad
12	40/M	Max	NRH	Deb + Seq, FLU	Buccal fat pad
13	35/M	Max	NRH	Deb + Seq, AMB	Obturator
14	33/M	Max	DM	Deb + Seq, FLU	Tongue flap
15	50/F	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
16	45/M	Max	DM	Deb + Seq, AMB	Buccal fat pad
17	52/F	Max	DM	Deb + Seq, AMB	Obturator
18	50/F	Max	DM, HTN	Deb + Seq, AMB	Buccal fat pad
19	48/M	Mand	Extraction	Deb + Seq, AMB	Closure with advancement of local tissue
20	25/F	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
21	28/F	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
22	53/M	Max	DM	Deb + Seq, AMB	Temporalis muscle flap
23	30/M	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
24	38/M	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
25	19/M	Max	DM	Cons, FLU, AMB	Tongue flap
26	32/F	Max	NRH	Deb + Seq, AMB	Buccal fat pad
27	30/M	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
28	36/F	Mand	NRH	Deb + Seq, AMB	Buccal fat pad
29	38/M	Max	DM	Deb + Seq, FLU	Obturator
30	70/M	Mand	DM	Deb + Seq, AMB	Buccal fat pad
31	55/F	Max	DM	Deb + Seq, FLU	Buccal fat pad
32	56/M	Max	DM	Deb + Seq, FLU, AMB	Obturator
33	42/M	Max	NRH	Partial maxillectomy, Deb + Seq, FLU, AMB	Obturator
34	20/F	Max	NRH	Deb + Seq, FLU, AMB	Buccal fat pad
35	37/M	Max	NRH	Deb + Seq, FLU + AMB	Obturator
36	19/F	Max	NRH	Deb + Seq, FLU + AMB	Closure with advancement of local tissue
37	51/F	Max	DM, HTN	Deb + Seq, FLU + AMB	Temporalis muscle flap
38	38/M	Max	DM	Deb + Seq, FLU + AMB	Buccal fat pad
39	48/M	Max	DM, liver cirrhosis	Deb + Seq, AMB + ITRA	Closure with advancement of local tissue
40	70/M	Max	DM	Deb + Seq, FLU + AMB	Buccal fat pad

Table 1. Cont'd

Patient No.	Age, yr/ Gender	Site	Medical Status	Management	Reconstruction
41	58/M	Max	HTN	Deb + Seq, FLU + AMB	Temporalis muscle flap
42	60/F	Max	DM, HTN	Deb + Seq, FLU + AMB	Buccal fat pad
43	40/M	Max	DM	Deb + Seq, FLU + AMB	Buccal fat pad
44	39/M	Left infraorbital region	NRH	Deb + Seq, FLU + AMB	Obturator
45	59/M	Max	DM	Deb + Seq, FLU + AMB	Temporalis muscle flap
46	43/M	Mand	NRH	Deb + Seq, FLU + AMB	Buccal fat pad
47	29/M	Mand	NRH	Deb + Seq, FLU + AMB	Closure with advancement of local tissue
48	50/M	Max	DM	Deb + Seq, FLU + AMB	Buccal fat pad
49	60/M	Max	DM, HTN	Deb + Seq, FLU + AMB	Obturator
50	54/M	Max	DM	Deb + Seq, AMB	Temporalis muscle flap

Abbreviations: AMB, amphotericin B; Cons, conservative; Deb, debridement; DM, diabetes mellitus; F, female; FLU, fluconazole; HTN, hypertension; ITRA, itraconazole; M, male; Mand, mandible; Max, maxilla; NRH, no relevant history; Seq, sequestrectomy.

Anebosur et al. Maxillofacial Fungal Osteomyelitis. J Oral Maxillofac Surg 2019.

Culture and sensitivity testing should be performed in all cases irrespective of the nature of osteomyelitis. All histopathologic sections should be stained with hematoxylin-eosin on a 10% potassium hydroxide mount, periodic acid–Schiff (Fig 3), and Gomori methenamine silver stain. Gomori methenamine silver stain specifically identifies the nature of hyphae, whether septate or aseptate. Identification can be accurately performed on the histopathologic sections themselves, and the culture on Sabouraud agar will yield a "cotton-candy appearance" (Fig 4) thus confirming the exact species.[28]

Mucormycosis is an opportunistic fungal infection, which infects immunocompromised patients. The fungus invades the arteries, leading to thrombosis that consequently leads to necrosis of the hard and soft tissues.[29] Mucormycosis is frequently seen in patients with diabetes because of the favorable environment created by an excess of ketone bodies. *Rhizopus arrhizus* produces the enzyme ketoreductase, which uses the ketone bodies. Hyperglycemia also stimulates the fungal growth, and there is a reduction in chemotaxis and phagocytic efficiency that permits these innocuous organisms to proliferate. Aspergillosis infection is more common in severely immunocompromised individuals than in patients with poorly controlled diabetes. It presents as a necrotic black skin ulceration on the face or neck or as a sinus infection, resembling mucormycosis.

In this study, a standard protocol was followed wherein the diagnosis of fungal osteomyelitis was based on the clinical presentation and histopathologic diagnosis. Later identification of the patient's comorbidities was performed, with a special emphasis on the glycemic condition. The preoperative preparation included 2 doses of 50 mg of lyophilized amphotericin B under a strict intensive care unit setup with all parameters in place, given its high incidence of nephrotoxicity and allergic reaction potential. All the patients received the antifungal therapy intravenously, which was diluted in 500 mL of normal saline solution at a rate of 50 mL/h initially for 15 minutes and then increased to 250 mL/h. Mild febrile changes developed after the second dose in 6 of 50 patients (12%), which necessitated discontinuation of amphotericin B therapy. Carpopedal spasm developed in 1 patient (2%), which later was related to low levels of calcium and magnesium, for which the patient was shifted to a medical hospital and treated under a medical setup. The outcome of surgery showed that 28 patients (56%) healed well without any complications. Complications such as palatal fistula (Fig 5), which occurred in 13 patients (26%), were subjected to revision surgery using a local advancement flap and the buccal fat pad. During the immediate postoperative period, 2 patients (4%) had wound dehiscence, 2 (4%) had nasal regurgitation, and 1 (2%) had a reduced mouth opening that was managed with a mouth-opening exercise regimen. In 1 patient (2%) with recurrence, curettage and debridement were performed after 6 months, and 3 patients (6%) did not return for follow-up. Even with the extremes of the bone-necrotizing phenomenon, it is seen that the soft tissue blood supply is not compromised, which augments the plan of using local and regional flaps for closure of defects. Reconstruction of maxillary defects was performed using the buccal fat pad (52%), temporalis muscle flap (10%), or tongue flap (4%), and an obturator was placed in 4% of cases. For mandibular defects that were small in size and confined to the alveolar

bone, extraction of the teeth, curettage, and a local advancement flap (15%) were used. In contrast, for larger defects, the literature suggests the use of alloplasts such as titanium plates and demineralized bone matrix or the use of autogenous free vascularized osteocutaneous flaps from the ilium, radius, and fibula. Bone morphogenetic protein therapy also can be used for reconstruction. The role of hyperbaric oxygen is highlighted in the literature as it reduces local tissue necrosis,[1] but in our series, it was not used because of unavailability. Although many case reports have suggested varied treatment options, in this article we present a large series (Table 1) with better outcomes and minimal morbidity. Thus, we recommend our treatment protocol for the management of fungal osteomyelitis of the jaw bone:

1. Early diagnosis based on clinical presentation and histopathology
2. Identification of comorbidities
3. Correction of electrolyte imbalances
4. Two doses of amphotericin B preoperatively under an intensive care unit setup
5. Intraoperative collection of specimens for fungal culture by a microbiologist
6. Curettage and debridement of the soft tissue and bone
7. Closure of the defect with either a local or regional flap
8. Postoperative antifungal therapy for 3 months

To conclude, this study was performed not only to analyze the type of fungal osteomyelitis and its incidence with comorbidities such as diabetes mellitus, as well as the site, but also to evaluate the treatment options for such lesions and to enhance the quality of life of these patients.

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