



# Post-COVID mucormycosis osteomyelitis and its imaging manifestations in the North of Iran: case series

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Received: 24 February 2022 / Accepted: 19 August 2022

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## Abstract

Mucormycosis is an invasive fungal infection that usually affects patients with immunocompromised conditions. In the context of the COVID-19 pandemic and the following corticosteroid therapy, mucormycosis prevalence has increased. The situation may be more complicated with some underlying diseases such as diabetes mellitus. In addition, due to the vicinity of maxillary bone to the nasal cavity and paranasal sinuses, which are the main routes for the infection to spread, dentists, maxillofacial radiologists, and surgeons may be the first to encounter these patients. Post-COVID mucormycosis osteomyelitis is one of the complications of this infection. Bone destruction and the erosion or breach of cortical boundaries of the maxilla and the bone structures in the vicinity of paranasal sinuses are the most critical radiographic findings of post-covid osteomyelitis. Herein, there are some cases of post-covid mucormycosis osteomyelitis involving the maxillary and other facial bones.

**Keywords** Osteomyelitis · Complications · Mucormycosis · Computed tomography

## Introduction

Mucormycosis is the third fungal infection globally after candidiasis and aspergillosis [1]. It is caused by a commensal organism, especially in the human nasal mucosa. Although it is rarely infectious in the healthy immune system, it can infect people with immunocompromised conditions [2, 3]. Tooth extraction, trauma, surgery, radiation, excessive use of vitamins, zinc, and iron and systemic situations such as diabetes mellitus, hematological malignancies,

solid organ transplantation, and osteopetrosis can be potential risk factors for mucormycosis infection [4, 5]. Other risk factors are consumption of corticosteroids and immunosuppressive drugs. Recently, with the Coronavirus disease 2019 (COVID-19) pandemic, the prevalence of these risk factors has risen and resulted in an increased incidence of mucormycosis worldwide [6]. There is a triad of diabetes, steroid therapy, and COVID-19 infection predisposing patients to mucormycosis [7]. In the COVID-19 infection, elevated

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**Table 1** Demographic, clinical, and radiographic information of patients with mucormycosis osteomyelitis of the maxilla after COVID-19 infection

Number	Sex	Age	Clinical findings	Past medical history	CT or CBCT findings
1	Female	53Y	Rt. facial swelling, mucosal discoloration on rt. side of the maxilla, fluctuant swelling in rt. side of the palate, tooth mobility	+ COVID-19, diabetes mellitus	Erosion and breach of cortical borders of the maxilla, palate, base of the nasal cavity, and maxillary sinus on the rt. side, loss of lamina dura, hanging teeth, and opacification of the rt. maxillary sinus
2	Female	34Y	Pain on lt. side of maxilla and tooth mobility	+ COVID-19, consumption of a high dose of corticosteroid	Erosion and breach of cortical borders of maxilla, zygoma, and inferior rim of the orbit
3	Male	61Y	Ulceration of anterior portion of max	+ COVID-19, diabetes mellitus	Mucosal thickening of bilateral max sinuses, erosion of alveolar bone from rt. max canine to lt. tuberosity, breach of buccal and palatal cortical boundaries of the maxilla, erosion of nasal and maxillary sinus floor, bone sequestra detached from lt maxillary alveolar bone
4	Female	62Y	History of post-operation of paranasal sinuses due to mucormycosis discoloration of overlying skin of the upper lip, extensive bone defect in the midline of the maxilla	Dialysis, + COVID-19, corticosteroid therapy	The fullness of paranasal sinuses, destruction of the palate
5	Male	47Y	Headache, swelling of rt. side of the face, fluctuant intraoral swelling in rt. max premolar area	+ COVID-19, corticosteroid therapy, and remdesivir	Ill-defined radiolucency in rt. side of the maxilla, loss of the buccal cortex in lt. maxillary premolar-molar area, the fullness of rt. max sinus
6	Male	53Y	Pain on rt. max canine, premolars, and first molar teeth fistula	+ COVID-19, corticosteroid therapy, and diabetic crisis during the disease	Ill-defined radiolucency from the midline to the posterior portion of maxilla, erosion of cortical plates
7	Female	58Y	Tenderness of rt. side of the maxilla, paresthesia of the skin	+ COVID-19	“Ground glass” appearance in the posterior portion of maxilla, loss of definition of cortical borders of maxilla and max sinus as well as max sinus mucosal thickening
8	Female	24Y	Extensive ulceration of the palate	+ COVID-19, diabetes mellitus type II, hypothyroid, The orbital mucormycosis	Destruction and erosion of palate on lt. side as well as nasal septum involvement
9	Female	60Y	Infraorbital swelling, tenderness, and erythema	+ COVID-19, diabetes mellitus, hypertension	Bone destruction of rt. side of the maxilla, erosion of rt. max sinus walls, rt. pterygoid process, rt. zygomatic bone, opacification of rt. max sinus, and front-ethmoid sinuses
10	Female	57Y	Swelling and tenderness of lt. infraorbital area	+ COVID-19, diabetes mellitus type II, rheumatoid arthritis, hypertension	Unilateral involvement of lt. paranasal sinuses, erosion of cortical border of lt max sinus floor as well as the involvement of posterior maxillary bone in the molar region
11	Female	64Y	Paresthesia, tenderness on lt. zygomatic bone	+ COVID-19, hyperlipidemia	Destruction of lt. side of the maxilla, mucosal thickening of lt. max sinus, erosion of palate
12	Male	66Y	Peri- and infraorbital swelling	+ COVID-19, diabetes mellitus, hypertension	Destruction of the anterior portion of the maxilla on rt. side, erosion and destruction of sinus walls of frontal, maxillary, and ethmoid, bone sequestra in the frontal bone, no gross intracranial abscess

**Table 1** (continued)

Number	Sex	Age	Clinical findings	Past medical history	CT or CBCT findings
13	Male	65Y	Severe headache, buccal and periorbital swelling	+ COVID-19, diabetes mellitus	Destruction of the anterior portion of the maxilla and lt. max sinus walls, opacification of lt. max sinus, erosion of inferior rim of lt. orbit

rt right, lt left



**Fig. 1** Periapical radiographies (**a**, **b**) of the rt. side of the maxilla shows significant bone loss on the cervical thirds of rt. maxillary anterior teeth and vertical bone loss in the distal portion of the second premolar

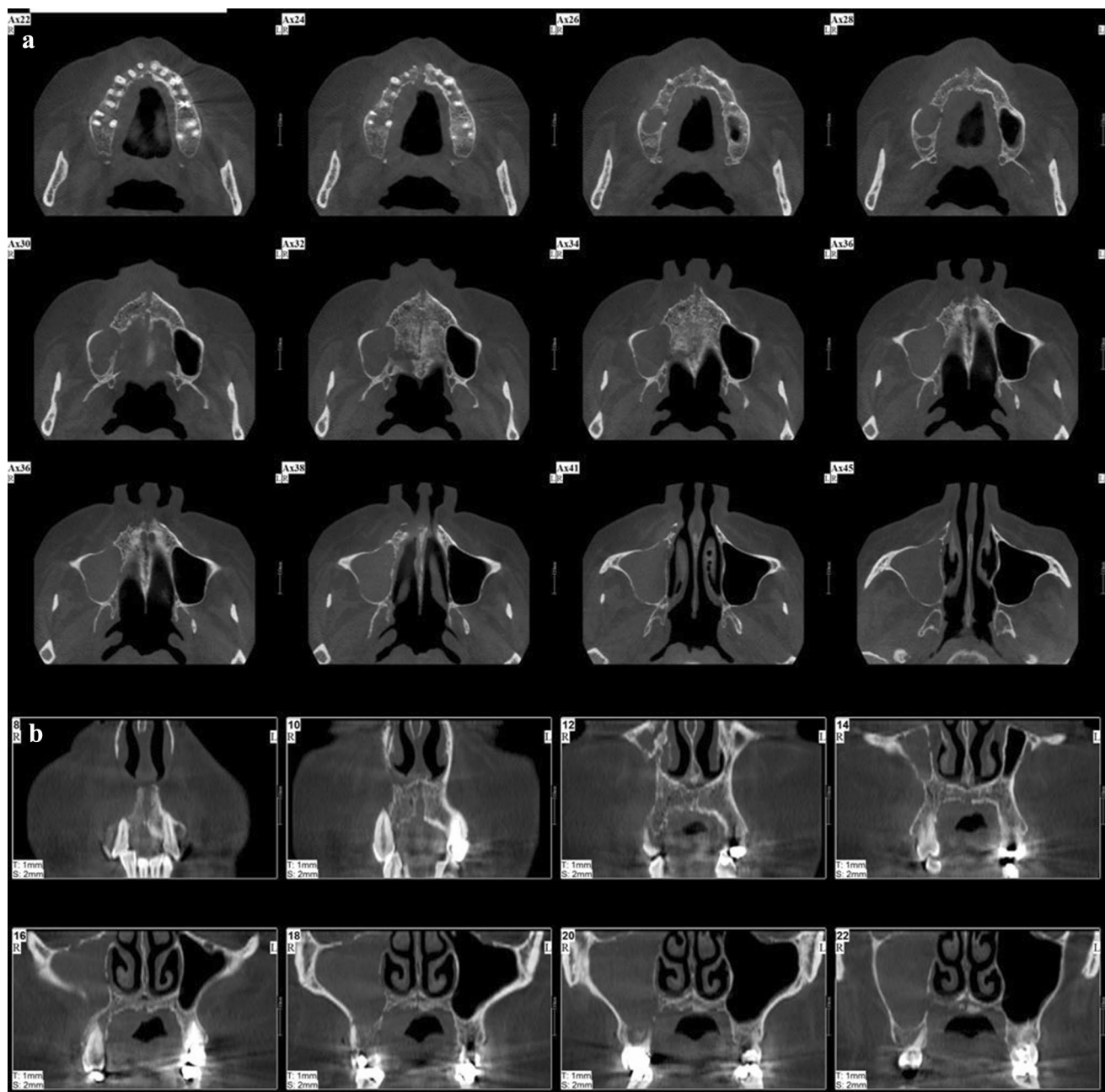
levels of inflammatory cytokines and reduced number of T lymphocytes are related to altered innate immunity [3, 8]

According to the site of involvement, mucormycosis can be classified into Rhino-orbito-cerebral mucormycosis (ROCM), pulmonary, cutaneous, gastrointestinal, and disseminated types [8]. The main course of infection in the ROCM type is through inhalation of the organism into the nasal cavity and paranasal sinuses, which may eventually spread to the sphenoid sinuses, palate, and cavernous sinus [9, 10].

A wide range of clinical symptoms has been reported, including fever, headache, sinusitis-like symptoms, nasal blockage, proptosis, facial pain, sudden mobility of maxillary teeth, and abscesses. The major factor for proper prognosis is early diagnosis followed by medical and surgical treatment [5, 11], and in this regard, imaging is crucial for the detection of infection and evaluation of its extension. Computed tomography (CT) is the initial imaging modality for this purpose. Bone erosion and extension beyond the sinus walls are distinct features of mucormycosis osteomyelitis. However, the clinical symptoms also should be considered [4].

To the best of our knowledge, most of the previous studies and case reports discussed ROCM as the most common form of this fungal infection [6, 8–11]. However, Amber- een et al. reported a mandibular mucormycosis following COVID-19 [7].

The present study is a remarkable collection of post-COVID mucormycosis osteomyelitis cases of the maxilla and other facial bones with or without rhino-orbital involvement. Another point is that we faced extensive surgery in most of our presented cases for the removal of the necrotic bone. This presentation would be helpful in the early diagnosis of maxillary infection and the importance of simple to extensive clinical and imaging findings of this fungal infection. We discuss the clinical and imaging findings of these cases in the following section.



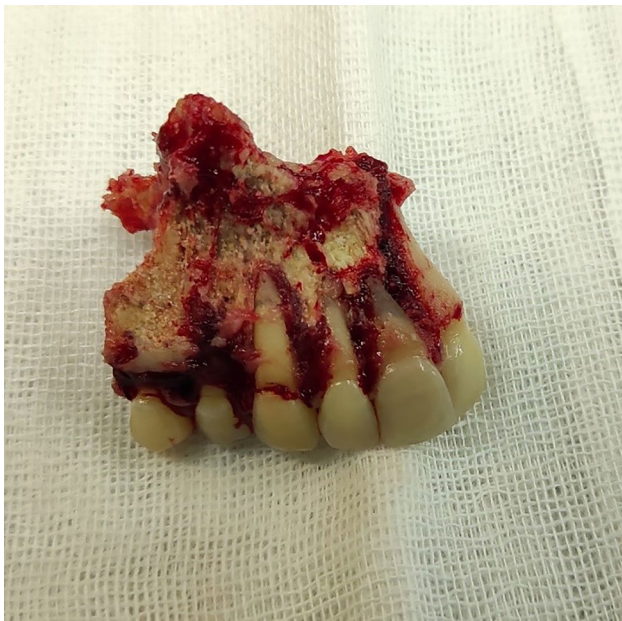
**Fig. 2** CBCT of the maxilla in axial (**a**) and coronal (**b**) views revealing erosion of cortical boundaries in the rt. side of the maxilla, the nasal cavity and maxillary sinus floor in the ipsilateral side, bone hypodensity on the rt. side of the maxilla, and opacification of the rt. maxillary sinus

## Case reports

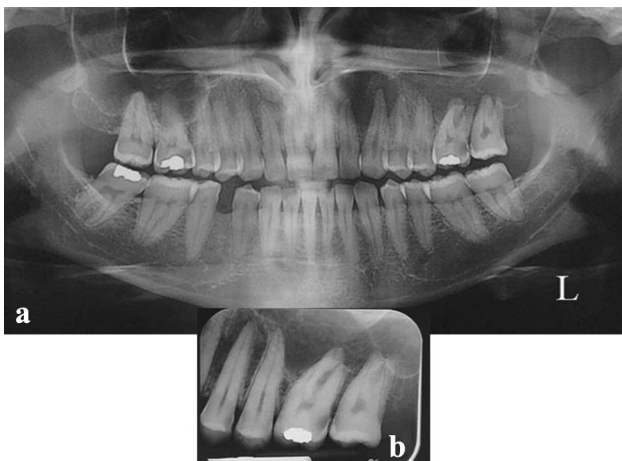
The ethical approval number of this case report is IR.GUMS.REC.1401.052. It was confirmed by the Research Ethics Committee of Guilan University of Medical Sciences. Table 1 shows the details of our case series of mucormycosis osteomyelitis of the maxilla with a history of COVID-19 infection. We explain the first three cases in more detail.

### Case 1

The first case is a 53-year-old female with a history of diabetes type 2 and corticosteroid medication to treat COVID-19 infection. Clinical examination showed facial swelling, mucosal discoloration in the right (rt.) side of the maxilla, and fluctuant swelling in the ipsilateral side of the palate 1 month after recovery from COVID-19 infection. There



**Fig. 3** Resected segment with cheesy-like texture after surgical removal



**Fig. 4** Panoramic (a) and periapical radiographs (b) showed ill-defined radiolucency, loss of definition of lamina dura in the lt. maxillary canine-premolar area

was no history of trismus, fever, or odynophagia, but she complained of slight tenderness and tooth mobility of the anterior and premolar teeth on the right side of the maxilla. She also presented paresthesia of the overlying skin of the cheek on the right side. Nasal endoscopy showed normal nasal mucosa. Radiographic examinations including periapical (PA), and panoramic views reveal significant bone loss on the cervical thirds of the rt. anterior maxillary teeth and vertical bone loss in the distal portion of the rt.

maxillary second premolar tooth (Fig. 1a, b). Cone-beam computed tomography (CBCT) in axial and coronal views, taken for a more accurate regional evaluation, showed erosion and breach of cortical borders of the maxilla, palate, base of the nasal cavity, and maxillary sinus on the rt. side. Bone hypodensity, trabecular bone changes (salt and pepper appearance), and significant widening of bone marrow spaces are compatible with rodent appearance; furthermore, loss of lamina dura, hanging tooth appearance of rt. maxillary teeth, and opacification of the rt. maxillary sinus are observed (Fig. 2a,b).

Based on the medical history and radiographic features, the differential diagnosis was bone changes due to mucormycosis secondary to COVID-19 infection. Therefore, total resection of the necrotic bone of the rt. side of the maxilla was performed (Fig. 3).

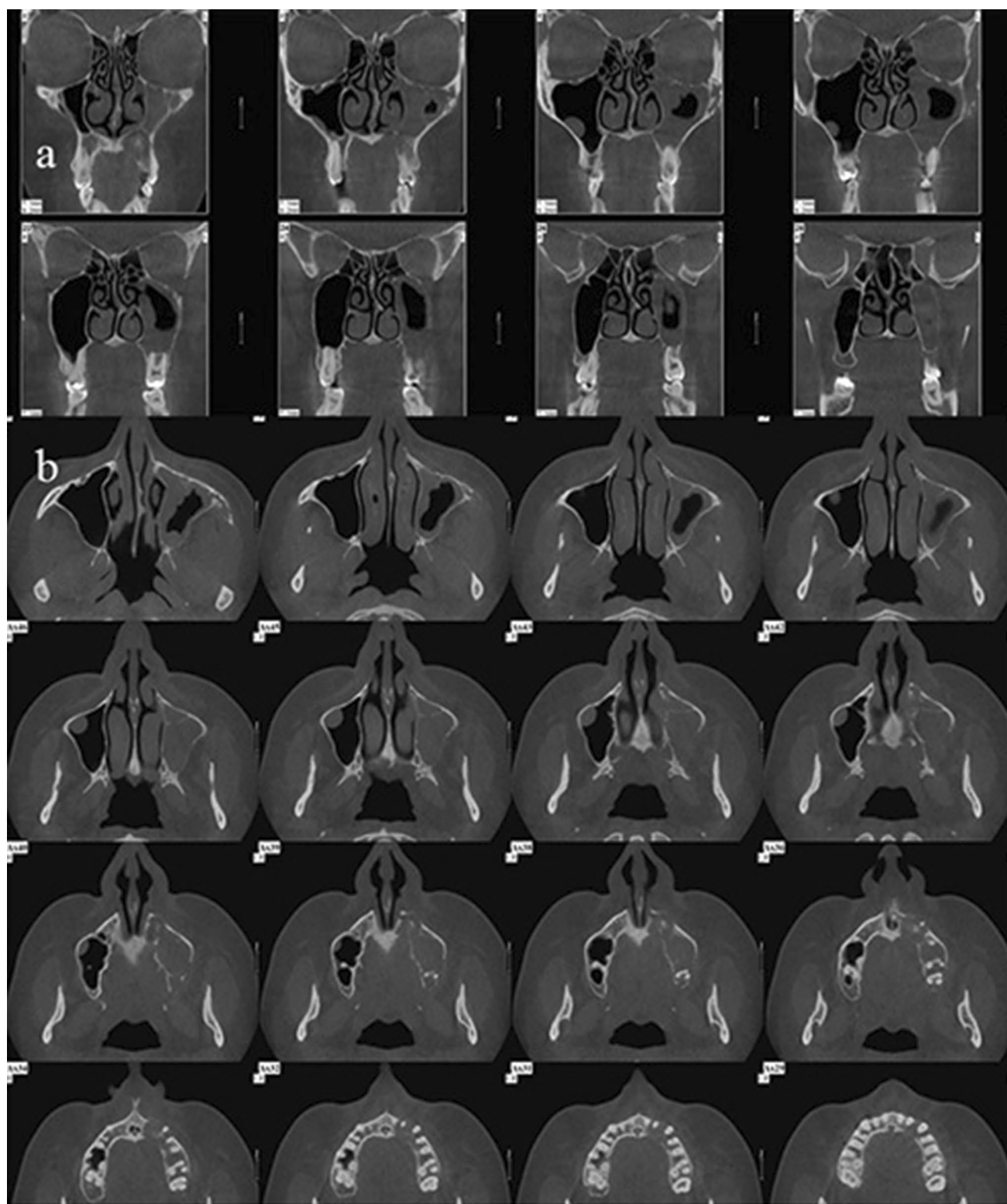
### Case 2

The second patient is a 34-year-old female with a history of COVID-19 infection and high dose corticosteroid therapy. She complained of pain in the left (lt.) side of the maxilla and tooth mobility 3 weeks after COVID-19 infection. Periapical and panoramic views showed ill-defined radiolucency in the left (lt.) maxillary canine-premolar region; loss of definition of lamina dura on the maxillary canine and first premolar teeth was apparent (Fig. 4a, b). CBCT of the maxilla in axial and coronal views reveals extensive bone loss in the lt. side of the maxilla and destruction of the buccal and palatal cortices from the midline to the lt. maxillary second premolar tooth. Erosion of the lt. max sinus walls, orbital floor, and zygomatic bone are other noticeable findings (Fig. 5a, b).

### Case 3

A 61-year-old male with ulceration of the anterior segment of the maxilla and a history of COVID-19 and diabetes mellitus is the third case. The ulceration of the anterior portion of the maxilla happened 1 month after he recovered from COVID-19 infection. The maxillary sinus floor on the lt. side was not correctly visible in the panoramic view (Fig. 6). CBCT of the maxilla and paranasal sinuses in axial and coronal views reveals bilateral maxillary sinus opacification, erosion of alveolar bone from rt. maxillary canine area to the lt. tuberosity, discontinuity of buccal and palatal cortices with involvement of the lt. nasal and maxillary sinus floor. In addition, bone sequestra detached from the left alveolar bone, trapped in the left maxillary sinus mucosa, is visible (Fig. 7). Eventually, mucormycosis was diagnosed based on clinical and imaging findings.





**Fig. 5** CBCT of the maxilla in axial (**a**) and coronal (**b**) views showing significant mucosal thickening in the Lt. maxillary sinus, extensive bone loss in the Lt. side of the maxilla from the midline to the Lt. sec-

ond premolar tooth, and erosion and breach of cortical borders of the maxilla, zygoma and inferior rim of the orbit



**Fig. 6** Maxillary sinus floor on the lt. side is hardly visible in the panoramic view

## Discussion

Recently, COVID-19 has affected millions of people worldwide with a wide range of clinical signs ranging from mild to severe and life-threatening pneumonia [12]. In addition, there is an association between the incidence of secondary fungal infection and COVID-19 [3, 13]. In the last 2 years, many kinds of literature have reported a great number of mucormycosis cases, but we summarized the case reports having erosion of the maxilla or other facial bones [1, 4, 6, 7, 13–23] in Table 2.

Inhalation, ingestion, and open wounds are the major routes of mucormycosis infection [14]. Inhalation of fungal spores into the nasal cavity and its inoculation and germination in hypoxic conditions is the initial stage of ROCM infection. After that, extension into the paranasal sinuses, orbit, erosion of the adjacent bone, and involvement of cavernous sinus and intracranium will occur. Also, Rajasekaran et al. reported mucormycosis in diabetic patients without a history of COVID-19, followed by tooth extraction [24]. In these cases, the socket of extracted teeth plays the role of an open wound and is the primary route of this fungal infection. Unlike them, tooth extraction was not the source of infection spread, but the history of maxillary sinus involvement was noteworthy. The infection of an affected maxillary sinus distributes to the adjacent maxillary bone and nearby soft tissues resulting in maxillary bone osteomyelitis.

The most presented clinical sign and symptoms in the recently published papers summarized in Table 2 are fever, headache, sinusitis, nasal blockage, proptosis, unilateral facial pain, numbness, teeth mobility, blurred vision, and other neurologic symptoms depending on the site of involvement. In our case series, the clinical findings were facial swelling and erythema, mucosal and skin redness, swelling or ulceration in the palate, tooth mobility, tooth pain, headache, denuded bone, fistula, tenderness, and skin paresthesia (Table 1). In addition, all of them suffered from maxillary osteomyelitis with involvement of the other adjacent facial bones in the final stage.

Due to the high mortality rate (up to 70%) [10], early diagnosis and treatment of mucormycosis are essential. Besides clinical signs, imaging result has a critical role in detecting the disease and its extension. In the previous studies, CT and magnetic resonance imaging (MRI) were the modalities of choice used for disease evaluation [4, 6, 8, 9, 12, 25, 26]. We also used CBCT, a highly recommended modality for detecting slight osseous changes because of its high bony resolution.

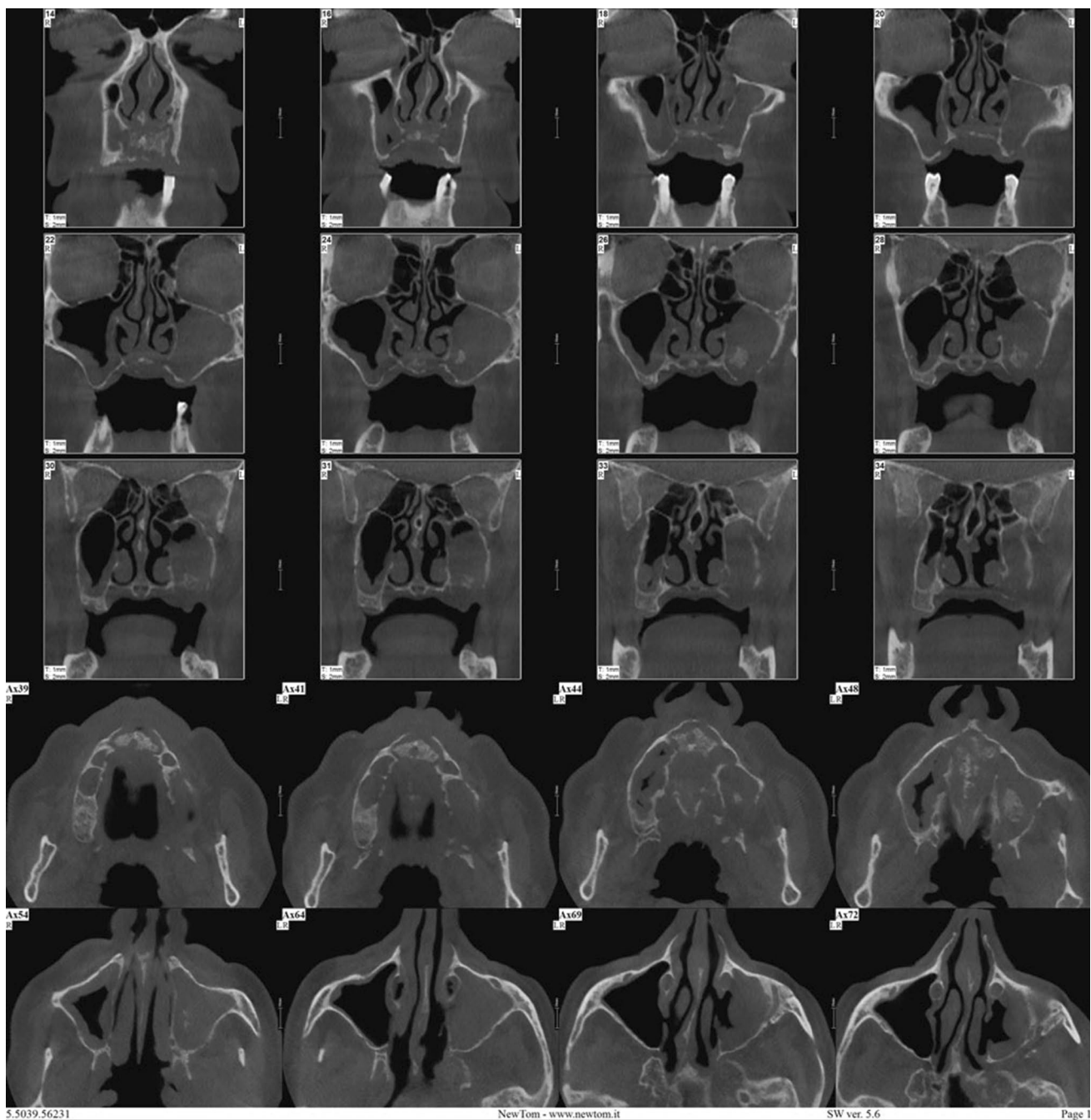
On the other hand, some of our cases in the first step were diagnosed as paranasal sinus mucormycosis, and their treatment strategy focused on these anatomical regions. After a while, some patients referred with the chief complaint of tooth mobility. Hence, in these cases, CBCT was taken for a more accurate investigation of the trabecular and osseous changes in the maxillary and palatal bones. These changes were missed on MRI and soft tissue algorithm of CT images. The maxillary sinus floor may be the first site to be involved, and infection may blow out the maxillary bone and palate following erosion and destruction of the sinus floor. It is interesting to mention that all of these cases had become infected in the Delta peak of the Coronavirus disease, which could indicate that the chance for mucormycosis osteomyelitis may be more in this type of disease.

The most frequent CBCT findings of our cases were mucosal thickening of the paranasal sinuses, bony alterations such as ill-defined radiolucency (bone hypodensity), loss of definition of lamina dura of involved teeth, erosion, breach, or destruction of bony structures, including cortical borders of the maxilla, the zygoma, the inferior rim of the orbit, the palatal bones, the nasal floor, and maxillary sinus walls and sometimes bony sequestra. Other radiographic appearances of infected bones such as “ground glass” and “salt and pepper” were also observed in our cases. In these cases, the counterpart surgical findings were necrotic, fragile, and cheese-like texture of bone.

Similar radiographic findings could also be found in malignant and metastatic bone lesions, osteoradionecrosis, and bisphosphonate-related osteonecrosis. However, metastasis, radiation- and drug-induced osteomyelitis are more common in the mandible. In addition, the patient history is helpful to differentiate these conditions.

It is essential to know; that all clinical findings in patients with a history of COVID-19 are important and should be considered seriously. In addition, in patients with suspected sinus involvement, bone window CT or CBCT imaging is mandatory to detect any subtle osseous changes in the maxilla and adjacent bony structures in the early stages of the disease, which affects the extent of surgery and final prognosis.

Based on the anatomical extension of the mucormycosis infection, Muley et al. graded the CT findings of mucormycosis: grade (1) involvement of maxillary sinus with or



**Fig. 7** CBCT of the maxilla and paranasal sinuses in axial and coronal views reveal mucosal thickening of bilateral maxillary sinuses, destruction of the alveolar bone from rt. maxillary canine to the lt.

tuberosity, breach of buccal and palatal cortical boundaries of the maxilla, erosion of palate in the anterior portion of maxilla and bone sequestra detached from the lt. maxillary alveolar bone

without alveolar bone changes, grade (2) grade 1 plus osteolytic changes in the maxilla, nasal involvement, opacification of maxillary or ethmoid sinus, and grade (3) advanced osteolytic changes in the maxilla, nasal cavity, sinus walls and zygoma, and opacification of all paranasal sinuses [3]. Although we had all grading forms in our case series, most of the cases were in the first and third stages.

In addition, detection of hyperdense foci within opacified sinuses is noticeable as CT findings of fungal sinusitis [8], but we did not find such foci in our cases.

Ambereen et al. reported multiple air foci in the marrow spaces in the body and ramus of the mandible on contrast-enhanced CT [7] as mandibular mucormycosis findings.



**Table 2** The brief information on mucormycosis cases in the case reports having the erosion of maxilla or other facial bones

Author	Type of study	No of cases	No of post covid pts	Clinical findings	Numbers of pts with involvement of jaw bone	Image findings
Kumar et al. 2021 [1]	Case report	1	1	Unilateral pain and swelling, moderate pain aggravated on bending head and chewing food, nasal congestion and headache on the same side, fever, purulent discharge, paresthesia, foul odor, and necrotic bone in the maxillary region. mobility of maxillary molars and edematous soft tissue	1	CT: haziness in right maxillary sinus with erosion in the lateral sinus wall
Prajwal et al. 2021 [4]	Case report	2	2	Sided swelling in the middle third of the face, pus discharge from upper teeth, mild proptosis, ptosis, denuded necrotic alveolar bone, segmental mobility	2	CT: erosion of superior alveolus anterior aspect of hard palate anterior and lateral walls of the maxillary sinus extending to left orbit including zygoma, lesser and greater wings of sphenoid and pterygoid plates
Palou et al. 2021 [6]	Case report	1	1	Headache, diplopia, one-sided decreased visual acuity, amaurosis, peri-orbital cellulitis	1	CT: edema of soft tissues, mucosal thickening, destruction of turbinates, occupation of sinus, destruction of maxillary bone and floor of the orbit, inflammatory changes involving the orbit
Ambereen et al. 2021 [7]	Case report and review of literature	1	1	Pain in lower back teeth, diffuse edema and tenderness on the mandibular body and submandibular region, reduced mouth opening, multiple draining sinuses, and inflamed gingival	1	CT: bone erosion with multiple air foci and hypodense collection in the marrow cavity of mandibular ramus and body
Saidha et al. [13] 2021	Case series	6	6	Pus discharge from gums, loose teeth, facial pain and swelling, headache, numbness, foul odor	6	Non-contrast CT: hyper dense mass and heterogeneous opacification, erosion of the medial wall of the maxillary sinus, involvement of ethmoid sinus, obliteration of PNS sinuses, regarding bone destruction
Bayram et al. 2021 [14]	Case series	19	19	Orbital pain, ptosis, ophthalmoplegia, decreased vision	19	CT: opacification of ethmoidal and maxillary sinuses, mucosal thickening in the maxillary sinus
Ahmadikia et al. 2021 [15]	Case report	1	0	Toothache, headache, earache, nasal congestion, unilateral facial swelling	0	
Misra et al. [16] 2021	Case report	1	1	Ulcer in the palate, exposure of bone, orotracheal communication, febrile, dyspnea, nasal stiffness, exposure of maxillary bone, covered with necrotic slough, indurated and not tender in palpation	1	CT: non-enhancing soft tissue density in sphenoidal, ethmoidal and frontal sinuses, obliteration of osteomeatal openings
Joshi et al. 2021 [17]	Case series	25	25			CT: maxillary sinus involvement, involvement of ethmoid air cells, frontal sinus, sphenoidal sinus, bony erosion of walls of sinus, air foci in bony structures
Krishna et al. 2021 [18]	Case report	2	2	Pain and swelling in the midface area, facial asymmetry	2	CT: aggressive fungal osteolytic lesion

Table 2 (continued)

Author	Type of study	No of cases	No of post covid pts	Clinical findings	Numbers of pts with involvement of jaw bone	Image findings
Eswaran et al. 2021 [19]	Case report	2	2	Facial paresthesia, bilateral ptosis, and chemosis	2	CT: invasive fungal sinusitis, mixed lytic/sclerotic areas in frontal, sphenoid, and ethmoid sinuses, mild thickening of recti muscles, subtle
Gupta et al. 2021 [20]	Case report	2	2	Throbbing and radiating pain, facial swelling, mobility of teeth, palatal gingival inflammation	2	CBC: scattered hypodense areas of the palatal and buccal wall of alveolar bone, discernible haziness and bone destruction, hazy soft tissue component in maxillary, sphenoid, and ethmoid sinuses
Shirke et al. 2021 [21]	Case series	4	4	Peri-orbital swelling, pain, nasal regurgitation of fluids on intake, sinonasal discharge, teeth mobility	4	CT: patchy bone destruction, hypertrophy of turbinates, septal deviation, maxillary and ethmoid sinusitis
Pathak et al. 2021 [22]	Case report	1	1	Ulcerative growth on the hard palate with no pain, headache, vomiting, blackish-gray slough	1	–
Roopa et al. 2021 [23]	Case report	1	1	Sharp radiating pain, headache, fever	1	CT and panoramic: mucosal thickening and opacification in the nasal cavity and paranasal sinuses, ill-defined bony erosion of walls of the maxillary sinus

No number, *pts* patients, *PNS* paranasal sinuses

Mucormycosis is diagnosed definitively through tissue biopsy, which demonstrates large size, non-septate, and thin wall hyphae in right-angle branching [24], but fungal culture is a time-consuming process and may lead to delay in initiation of treatment and thus disease progression [7]. However, the mentioned radiographic findings are non-specific, but the patient's history, clinical signs, imaging findings, and surgical findings could be helpful in the diagnosis of mucormycosis.

Early recognition and proper treatment, including medical management and aggressive surgical procedure depending on the extension of the involvement, can improve the prognosis and reduce morbidity and mortality rates.

In conclusion, since osteomyelitis is less common in the maxilla because of its high vascularity, radiographic findings, including bony erosion and extra sinus extension, especially in patients with a history of COVID-19 and underlying disease, must be considered as mucormycosis unless otherwise proven. In addition, dentists, maxillofacial radiologists, and surgeons may be the first ones who encounter these patients, so it is essential to know the critical radiographic findings and face this kind of osteomyelitis seriously.

**Acknowledgements** We would like to thank the Department of Maxillofacial surgery, of Ear, Nose and Throat, and of Infectious diseases, Guilan University of Medical Sciences, Rasht, Iran.

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