ORAL CAVITY- A MAJOR TARGET OF COVID-19: PART 2

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Abstract:
The outbreak of corona virus disease 2019 is posing a severe threat to global health management system since it has been detected in the humans. This disease was characterized by severe acute respiratory syndrome corona viruses 2 (SARS-CoV-2) and rapidly developed into a public emergency worldwide with an alarming increase in cases and deaths. Now after living with the disease for one year may different manifestations have been reported from all over the world by different medical and Dental Professionals. These manifestations range from minor taste changes to devasting findings like necrosis of jaws. This second part of the review aims to shed some light on such manifestations which are clinically relevant for dentists and their prior knowledge is important to combat this vicious pandemic.

Keywords: Osseous manifestations, Mucormycosis, Osteomyelitis, Taste disorders, Ageusia.

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INTRODUCTION:

The doctors of a hospital in New Delhi claimed to have witnessed more than 12 cases of Civid-19 triggered mucormycosis fungus- which causes loss of eyesight, removal of the nose and jaw bone, and 50% mortality in cases where it affects the brain- within 15 days. Black fungus, or mucormycosis, previously called zygomycosis, is a serious but rare fungal infection caused by a group of molds called mucormycetes that exist in the environment. Even though rare, it is a severe fungal infection that mainly affects patients who are highly immunocompromised. Early clinical suspicion noticed by the doctors working at the frontline in this pandemic is- nose obstruction, swelling in the eye or cheeks, and black dry crusts in the nose. (Reported 15/12/2020). If this is true, the repercussions of covid-19 are alarming, and dentists play an essential role in the early detection of these lesions as the jaw bone, and vital structures in its vicinity are involved.

Fig 1: News report of Mucormycosis associated with Covid-19

Part one of this review covered the soft tissue lesions and the taste disorders in relation to the covid-19 pandemic

CLINICAL PRESENTATIONS OF ORAL OSSEOUS LESIONS

The maxilla is one of the primary bones of the face and is involved in the formation of the significant portions of the upper jaw, i.e., palate, nose, and orbit. The maxilla's alveolar process holds the upper set of teeth and plays a vital role in speech and mastication. Maxillary necrosis rarely occurs when compared to mandibular necrosis due to the high vascular supply of the maxilla. If maxillary necrosis does occur, it may be due to bacterial infections such as osteomyelitis, viral infections like herpes zoster, fungal infections like mucormycosis, or secondary to trauma, radiation, etc.

PRESENTATION 1 - OSTEONECROSIS OF JAW (Case Courtesy- Dr. Khimji Gohil)

The pathogenesis of COVID-19 has several repercussions for the patient, such as immunological changes, hypercoagulability, ischemic phenomena, use of high dosage corticosteroids, etc.; these factors can be directly linked to the development of osteonecrosis of the jaw.

Excessive immune responses in intensive care patients lead to fibrosis and lung damage, causing functional disability and reduced life quality. As a specific drug is absent for the treatment of COVID-19, a range of existing host-directed therapies could potentially be repurposed to treat it. Tocilizumab is a humanized anti-interleukin-6-receptor (IL-6R) monoclonal antibody that inhibits interleukin-6 (IL-6) signaling used as a treatment in rheumatoid arthritis (RA). Tocilizumab was administered intravenously in the treatment of COVID-19 in China and Italy with encouraging results. Whether the drug tocilizumab can restore T cell counts in the COVID-19 patients by suppressing IL-6 signaling is still uninvestigated. After literature research, a possible correlation between tocilizumab and medication-related osteonecrosis of the jaws (MRONJ) was highlighted, similar to the complication of antiresorptive and antiangiogenic drugs cancer therapy.[1]

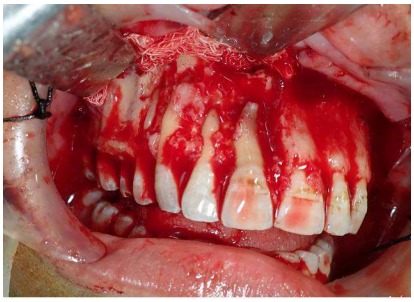
Hence, studies are required to find the possible correlation between tocilizumab and MRONJ, but the dental community should be aware of its potential risk, especially during procedures involving jawbones.

CASE PRESENTATION-

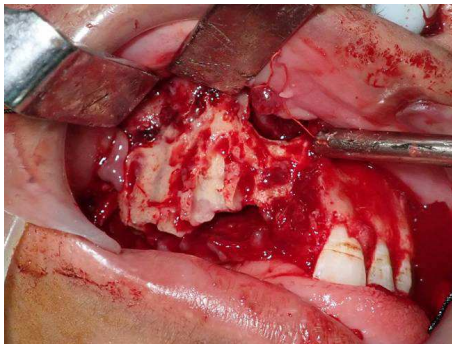
Patients with a recent history of COVID-19 infection and a history of uncontrolled diabetes reported pain and mobility of teeth in the upper jaw during mastication of food. Oral examination showed multiple draining sinuses and mobile teeth in the right upper jaw of the patient. 3D CT scan revealed multiple irregular osteolytic lesions involving a significant part of the maxilla along with the maxillary sinus. The affected teeth were extracted, infected sinus lining was removed, and curettage was done under local anesthesia. Histopathological examinations were done from multiple sites, including bone, granulation tissue, sinus lining, which were suggestive of Avascular Necrosis in Maxilla and ruling out any fungal or malignant lesion.

The final diagnosis was made as a rare and severe complication of post-COVID-19 infection in the maxillofacial region due to impaired vascular supply in the maxillary region's minor blood vessels with supra-added sinus infection associated with uncontrolled diabetes mellitus.

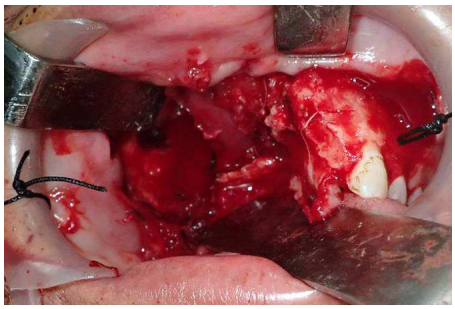
Normal looking maxilla with sinus opening



Bone loss from anterior teeth to molars in the anterior region (Photo courtesy- Dr. Khimji Gohil)

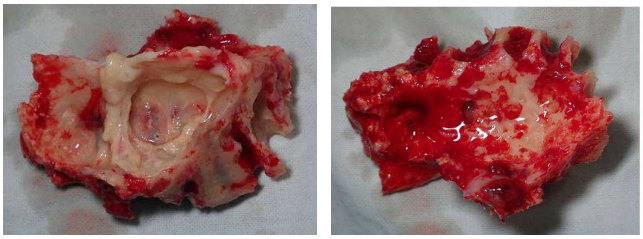


Necrosis of entire right maxilla



Resected Maxilla

(Photo courtesy- Dr. Khimji Gohil)



Completely necrosed maxilla
(Photo courtesy- Dr. Khimji Gohil)

Fig 2: Clinical presentation of Osteonecrosis of Jaw

PRESENTATION 2 - MUCORMYCOTIC OSTEOMYELITIS (Case Courtesy- Dr. Akshay Dhoble)

Osteomyelitis is an inflammation of the bone that begins in the medullary cavity and ends in the periosteum involving the Haversian system. Various factors are involved in developing the disease, such as trauma, surgical therapy, bacteremia, fungal infection, and systemic diseases that decrease host defense mechanisms such as diabetes, malignancy, anemia, radiation, and malnutrition, osteoporosis, osteopetrosis, and Paget's disease. In all of these conditions, the vascular supply is decreased, thereby predisposing the infection. Microbes' entry into cancellous bone causes the compression of blood vessels preceded by the inflammation and edema of marrow. Severe compression of vascular supply leads to ischemia and subsequent necrosis of bone. This immobile and stagnant blood leads to nidus for the development of infection. Osteomyelitis is more commonly seen in males (80.36%) than in females (19.64%), with its peak incidence in 30–39 years of age.[2]

Osteomyelitis due to fungal organisms is rare and is seen more in immunocompromised patients. Fungal microorganisms that are usually causing osteomyelitis are *Candida parapsilosis* and *Aspergillus*. These organisms are from the initial infection that has not been appropriately treated, commonly from dental extraction. Among fungal osteomyelitis, Candida is the most frequently encountered, followed by aspergillosis and mucormycosis. Mucormycosis is an opportunistic fulminant fungal infection usually seen in immunocompromised patients; It is also commonly seen in diabetic patients as the ketone bodies favour the organism's favourable environment's growth. Clinical features of fungal osteomyelitis are similar to bacterial osteomyelitis, exposed bone, and pain with varying intensity. If not diagnosed and treated earlier, fungal osteomyelitis is more invasive than bacterial. The diagnosis of mucormycosis is challenging. Hence it has to be treated as early as possible; otherwise, it may be fatal. There is no recommendation to guide the diagnosis and management of mucormycosis despite the affected patient's infection morbidity and mortality. The American Infectious Disease Society has presented specific guidelines to be used on evidence criteria.[3]

The guidelines, in brief, are as follows:

(1) The diagnosis of mucormycosis relies on histology and detection of the organism by culture from the involved sites to identify and isolate the species level.

(2) Antifungal chemotherapy should be able to control the underlying predisposing condition after surgical debridement.

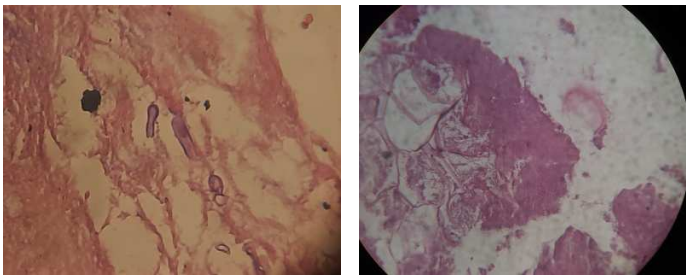
Computed tomography and magnetic resonance imaging techniques were used as early diagnostic tools. Bone scintigraphy is more accurate than a CT scan because bone erosion and remodeling in CT may be confused with osteomyelitis. Hyphae were microscopically identified with stains like H&E (hematoxylin and eosin), PAS (periodic Schiff), and GMS (Grocott's methenamine silver), and in particular, the type of hyphae, whether septate (or) nonseptate is seen by GMS staining. Identification of hyphae was made through histological sections, but the exact species were identified only through culture.

CASE PRESENTATION:

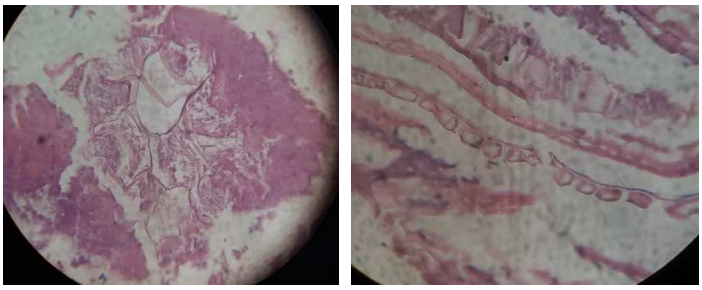
A patient with a recent history of COVID-19 reported a large lesion on the left side of the oral cavity. The patient has a history of uncontrolled diabetes.

The lesion was excised and examined microscopically.

(Photo courtesy- Dr. Akshay Dhoble)



(Photo courtesy- Dr. Akshay Dhoble)



(Photo courtesy- Dr. Akshay Dhoble)

Fig 3: Clinical presentation of Mucormycotic Osteomyelitis

The microscopic examination revealed the bony trabeculae consisting of empty lacunae intermixed with broad and septate hyphae, branching greater than 90°. These features are suggestive of mucormycotic osteomyelitis. Further, the specimen is stained with the PAS stain, which shows the fungal hyphae in magenta color.

TASTE DISORDERS

While the most prevalent signs/symptoms in COVID-19 patients like cough, fever, and fatigue, as mentioned in a recent meta-analysis, have been used as cardinal clinical diagnostic criteria since the beginning of the outbreak, and the new olfactory and taste disorder(s) were not initially linked to SARS-CoV-2 infection and have not been used for case identification and testing prioritization by the US Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) until August 2020.[4]

The first systematic assessments of the evidence available up to March 2020 failed to identify associations between signs like anosmia/ageusia and COVID-19.[5] For example, none of the studies included in an early systematic review reported features like olfactory or gustative dysfunctions.[6] In sharp contrast, the most recent meta-analysis analyzing smell and taste alterations not only reported that almost half of COVID-19 patients had these symptoms but also that 15% of patients had

olfactory and gustatory abnormalities as their initial clinical manifestations.[7] Now, due to the growing body of evidence, sudden onset of signs like anosmia, ageusia, or dysgeusia have now started to be recognized as major clinical characteristics of the disease and have been included in the list of key clinical criteria for case definition of COVID-19 by the European Centre for Disease Prevention and Control as well as other Public Health surveillance organizations across the world such as CDC, WHO, and Public Health England.[8] Taste disorders were relevant symptoms as compared amongst the data on overall signs and symptoms in patients with COVID-19.[9]

Taste disorders can be-

1. Dysgeusia - characterized by an altered or impaired sense of taste.
2. Hypogeusia – characterized by partially reduced ability to taste things.
3. Ageusia – characterized by complete loss of taste function.

A systematic review aimed to summarize evidence on the prevalence of oral signs and symptoms in patients with COVID-19 was reviewed.[10] Systematic review was reported as per the PRISMA checklist, and their literature search was conducted in 6 databases and grey literature. Studies published in any language mentioning oral symptoms and signs in patients with COVID-19 were included by them. After a 2-step selection, 40 studies were included: 33 cross-sectional and 7 case reports, and overall, 10,228 patients (4,288 males, 5,770 females, and 170 unknown) from 19 countries were assessed. Gustatory impairment was the most common oral manifestation reported, with a prevalence of 45%. The data for different taste disorders were 38% for dysgeusia and 35% for hypogeusia, while ageusia had a prevalence of 24%. Almost all studies diagnosed taste disorders through in-person, online, or phone call questionnaires, except the study by Vaira, Hopkins, Salzano, et al. (2020), who conducted a standardized and validated study. (Table 1)

Table 1: Taste disorder characterization in pateints with Covid-19 (n=33 cross sectional studies)[10]

Study	Taste Disorders, %			Period of Appearance	Duration, d, Mean±SD (Range)	TD Diagnosis Method
	Dysgeusia	Hypogeusia	Ageusia			
Aggarwal (2020), United States	19					
Beltran-Corbellini (2020), Spain	10.1	8.8	17.7	First symptoms in 11 (35.5%)	7.1 ± 3.1	Questionnaire applied by phone
Bénézit (2020), France		62				Questionnaire applied online
Carignan (2020), Canada	63.4		50.7			Questionnaire applied by phone
Chary (2020), France		31.3	31.3		15 (4 to 27)	Questionnaire applied by phone
de Maria (2020), Italy		50.5		Occurred early (within 5 d from onset of fever)		Questionnaire applied in personal
Dell'Era (2020), Italy		66.4		First symptoms in 31 (13.3%)	10 (2 to 25)	Questionnaire applied in person or by phone
Gelardi (2020), Italy	72.2			Mean 2.8 d (range, 1 to 4) before the respiratory symptoms	16.1 (7 to 22)	
Giacomelli (2020), Italy	15.2		13.55	Before hospitalization in 91% of patients		Questionnaire applied in person
Kim (2020), South Korea		33.7		First symptom in 44 (28.6%)		Questionnaire applied in person
Klopfenstein (2020), France	85.1					Recorded medical files
Kluytmans-van den Bergh (2020), Netherlands		7				Questionnaire applied in person
Lapostolle (2020), France			28			Questionnaire applied by phone
Lechien (2020), Belgium,	21.1	78.9				Questionnaire applied in person or by phone
Lee, Lockwood, (2020), Canada		57.1		First symptoms in 26 patients (46.4%)		Questionnaire applied online
Lee, Min, (2020), South Korea			13.05		6.0 (3.0 to 10.0)	Questionnaire applied by phone
Levinson (2020), Israel	33.3			Mean 3.3 d after illness onset (range, 0 to 7 d)	7.1 (0 to 7)	Questionnaire applied online or by phone
Liguori (2020), Italy	46.6			More frequent on patients interviewed after the 7th day of hospitalization		Questionnaire applied in person
Mao (2020), China		5.6		Median onset until hospital admission: 2 d (range, 1 to 5)		Recorded medical files
Meini (2020), Italy		41			32	Questionnaire applied by phone
Mercante (2020), Italy		55.4				Questionnaire applied by phone
Merza (2020), Iraq		26.7				
Noh (2020), South Korea			22.6		7.5 ± 5.6	Questionnaire applied in person
Pademo (2020), Italy and Sweden		63.1		First symptom in 57 (11.22%), delayed symptom in 451 (88.7%)	Complete resolution: Questionnaire applied in person 9.2 ± 5.4; ongoing disorder, 12.4 ± 6.8	
Patel (2020), United Kingdom			63.1		Questionnaire applied by phone	
Romero-Sánchez (2020), Spain	6.2			Fist symptom in 31 (60%)	Recorded medical files	
Sayin (2020), Turkey	25	56.3	12.5	First symptom in 14 (30.4%)	Questionnaire applied in person	
Sierpinski (2020), Poland		47.5			Questionnaire applied by phone	
Speth (2020), Switzerland and United States		25.2	39.8		Questionnaire applied by phone	
Sultan (2020), United States		10				
Vaira, Hopkins, Salzano (2020), Italy		34.5	10.4	Taste disorders were more frequent on days 0 to 4 of the disease	191 of 256 (74.6%) Standardized and validated test followed up presentedusing prepared solutions≤7 d of chemosensitive symptoms duration	

The Odds Ratio (OR) analysis showed a positive association between taste disorder symptoms and COVID-19, with an OR of 12.68; $P < 0.00001$. These results confirm that taste disorders may be a significant and specific symptom of mild/moderate COVID-19 cases. Taste disorders, as easily and early detectable symptoms would allow mild/moderate case identification and self-isolation orientation; thus, they can directly contribute to contain the quick spreading of the disease, especially in countries having reduced testing capability.[10]

DISCUSSION

Although the pathogenesis of taste disorder in patients with COVID-19 is not entirely understood, several hypotheses have been formed (Finsterer and Stollberger 2020; Mariz et al. 2020; Vaira, Salzano, Fois, et al. 2020). Finsterer and Stollberger (2020) highlighted the possibility of a local inflammatory response resulting from rhinitis triggers, which could hamper taste buds' normal function. However, the occurrence of signs and symptoms of nasal mucosal inflammation is unnecessary for taste impairment in patients with COVID-19. Nonetheless, patients with COVID- 19 present taste disorders even without smell dysfunction since the prevalence of taste disorders are frequently higher. Another questionable hypothesis of taste disorder as a side effect of certain drugs for COVID-19 treatment is analyzed. The association between taste disorders and mild to moderate cases corroborates Finsterer and Stollberger's (2020) conclusion that these symptoms also occur in patients with COVID-19 who did not use the drug. The interaction of SARS-CoV-2 and gustatory components and ACE2 receptors supports a direct effect in COVID-19– related taste disorders, and as cranial nerves innervate gustatory buds, related functions may be impaired, resulting in taste disorders.[11] The SARS-CoV-2 may bind essential salivary mucin components, such as sialic acid, consequently accelerating taste particle degradation and disturbing gustatory sensation.[12] The tongue presents a high expression of ACE2[13], and its interaction with SARS-CoV- 2 might affect normal gustatory functions through the dopamine and serotonin synthesis pathway coregulation.[14] Besides, ACE inhibitors and ACE2 blockers are associated with impairment of taste sensation.[15] These drugs play a role in taste disorders by G protein-coupled and sodium channel inactivation.[16] Similar to patients with COVID-19 experience after infection recovery, there is a regression of the gustatory sense effect by ACE inhibitors a few weeks after discontinuation. Furthermore, ACE2 high expression was demonstrated in rats' taste buds associated with the production of angiotensin II in mice taste buds. The disorderly taste responses are suggested to be a result of the inability of ACE2 to degrade this protein during COVID-19 infection .[17,18]

COVID-19- A PERIODONTAL VIEWPOINT…

The SARS-CoV, with its spike mediated entry into target cell through ACE-2 receptors, affecting lungs is the etiopathogenesis for COVID-19. Pascolo et al. (2020) demonstrated that the associated expression of ACE-2 and trans-membrane serine protease TMPRSS2 in salivary glands are required to facilitate the virus into the cell. Saliva lodges numerous SARS-Co Viruses, and a periodontal pocket is in its close vicinity. Breach of the pocket epithelium results in direct contact of the virus and activation of the host immune response with the release of pro-inflammatory cytokines like CL8, CXCL10, C3a, C5a stimulating macrophages, granulocytes, and natural killer cells, which releases IL-1β, IL-6, IL-8, TNF-α, IFN-γ. These aggravate the pocket formation by downward displacement of the junctional epithelium. "Focal infection theory" by William Hunter states that oral foci of infections spread through the bloodstream and affect systemic organs. In SARS-CoV-2 infection, the primary pathology behind the lung damage is "Cytokine storm" or "Macrophage activated syndrome," which is auto-amplifying cascades of host immune response. ACE-2 receptors in the lungs aggravate the entry of SARS-CoV-2 and activate cytokines damaging the respiratory epithelium and lung parenchyma. Cytokine storm, in turn, suppresses the innate and adaptive immunity against SARS-CoV-2. IL-6 and TNF-α] are noticed to increase excessively in severely ill hospitalized individuals. Thus, a hypothesis based on this is a relationship of COVID-19 to periodontal pocket wherein the cytokine responses happen to be common. The increased cytokines in the periodontal

pocket could further aggravate the COVID-induced destruction of the lungs. Future research focusing on this issue could prove the hypothesis's authenticity and highlight the importance of a periodontists managing the deadly virus.[12]

CONCLUSION

Even in a small number of reported studies, taste alterations are the most prevalent reported oral manifestation. These findings have highlighted the possible development of dysgeusia and anosmia early in the course of SARS-CoV-2 infection; therefore, these manifestations should be considered a disease marker by dentists working in the frontlines of the pandemic. Taste disorders like ageusia, even though not life threatening, may have a severe psychological impact on the patient.

The osseous lesions associated with Covid-19 have a very fast spread and grievous after-effects. Resection of a major part of the jaw can create high levels of psychological and physical trauma for the patients. This additional trauma in these already testing times can cause an overall burden on the patient's day-to-day life. Hence along with treatment of the oral lesions, the patients should be provided with psychological support associated with the disability. In these challenging times, it is pertinent for dental professionals to consider the patient's overall physical and mental health.

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