



Potential Oral Manifestations of COVID-19. A Review

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ABSTRACT

A new strain of coronavirus (SARS-CoV-2) has been identified and reported as the pathogen causing the global COVID-19 pandemic. This virus proved to induce several clinical manifestations. Recently, It has been suggested that the oral cavity is a perfect habitat for SARS-CoV-2, since this virus has an invasive ability and a special affinity for cells having receptors for the angiotensin converted enzyme (ACE2). These receptors are present in the respiratory tract, oral mucosa, tongue and salivary glands cells, hence, the virus can affect the function of the salivary glands, taste sensations, smell and integrity of the oral mucosa. In addition, this new coronavirus could alter the balance of the oral microbial ecology, which when associated with depressed immune system would allow opportunistic infections colonization. Although the clinical manifestations of this virus have been widely well described in many literatures, yet, the information about oral manifestations is still limited. Thus, this review aims to survey the current state of knowledge about the potential oral manifestations in the context of COVID-19 infection and the mechanism of their incidence as well as the predisposing factors. Consequently, this will highlight the significance of including the dentists in the intensive care unit multi-professional team to improve oral health in managing critical COVID-19 patients.

Keywords: SARS-CoV-2, COVID-19, Oral Manifestations

1. Introduction

At the beginning of 2020, a severe health and life threatening new virus COVID-19 has affected the whole countries all over the world. Several investigators have characterized the clinical manifestations associated with COVID-19 infection including headache, fever and respiratory affection ranging from mild flu-like symptoms to fulminant pneumonia and potentially lethal respiratory distress (Chiotos *et al.*, 2020 and Guan *et al.*, 2020). However, initially, only one systematic review has described oral manifestations of COVID-19 disease that mostly focused on impairment of taste. Dysgeusia is the first recognized oral symptom of COVID-19 reported in 38% of patients, mostly in North Americans and Europeans, females, and patients with mild-moderate disease severity (Seirafianpour *et al.*, 2020). Then, limited research work has recorded some oral manifestations in patients with coronavirus disease (COVID-19) such as recurrent herpes simplex, candidiasis, and geographic tongue (dos Santos and Silva Guerra, 2020). Later, investigators collected data about the presence of other lesions involving ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding (Iranmanesh *et al.*, 2020). They reported the most common sites of involvement in descending order to be the tongue (38%), labial mucosa (26%) and palate (22%). Recently, survivors of COVID-19 who have had the disease for

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weeks to months have also described oral problems including teeth falling out, sensitive gums, teeth turning grey, and teeth cracking (Yan, 2020) . Although many physicians continue to find the direct link between SARS-CoV-2 and oral diseases, studies suggest that the mouth might be the most vulnerable area to this virus due to the abundance of the ACE2 (angiotensin converting enzyme) receptor in oral tissues (Gheblawi *et al.*,2020) .

However, there are still important questions about whether these lesions are new signs induced by coronavirus infection ? or due to secondary manifestations resulting from the patient's deterioration of systemic condition ? or due to treatments for COVID-19 ?. In addition, what is the possible and exact mechanism for the incidence of these oral lesions ?. Moreover, what are the predisposing factors that might exaggerate or increase the severity of such manifestations ?. Thus, the objectives of this review is to survey the available evidence in relation to oral manifestations at the mucosa ,tongue or salivary glands as well as the teeth in context of COVID-19 infection and analyze the mechanism of their incidence and the predisposing factors. Consequently, this could explain the importance of involving the dentists in the intensive care unit multi-professional team to improve oral health in critical patients, not only COVID-19 patients, but also, to contribute in decision-making in managing infectious diseases.

2. The common oral manifestations associated with COVID-19

2.1. Gingival inflammation

Bleeding and inflammation of oral tissues have been recorded as important common oral manifestations of COVID-19 pandemic. These findings could be attributed to the generalized increase in inflammation due to elevated levels of cytokines and interleukins initiated by the SARS CoV-2 virus. COVID-19 disease severity has been linked to an immune dysregulation, leading to a cytokine storm. The periodontal disease can increase levels of circulating cytokines, particularly interleukin-6 (IL-6), which has been implicated as one of the major interleukins leading to the cytokine storm (Tanaka *et al.*,2016). Periodontal disease is currently being examined as a possible contributing disease toward COVID-19 severity.

2.2. Xerostomia (dry mouth)

COVID-19 has been suggested to cause dry mouth for several reasons. The most common is mouth breathing by an individual due to mask use with subsequent desiccation of oral tissue especially without frequent hydration. In addition, another biologic mechanism involves the viral entry into the salivary glands, which are known to be abundant in the ACE2 receptor (Xu *et al.*, 2020). It has been reported that novel coronavirus infection of the salivary glands can influence both the quantity and quality of saliva being produced (Lanese, 2020). Additional research work is needed to identify causal effect, but in the meantime, clinicians should note that xerostomia has been linked to an increase in both caries and candida infections.

2.3. Oral ulcerations and gingival tissue breakdown

COVID-19 has been associated with vascularity affection due to viral damage of blood vessels. The virus may gain entry into the endothelial cells that line blood vessels via the ACE2 receptor and damages them, leading to situations of oxygen deprivation. Tissue necrosis, including oral ulcerations, can be the result of vessel damage. Ulceration and tissue damage can be further exacerbated by increased inflammation and the subsequent up-regulation in inflammatory markers due to the SARS-CoV-2 virus (Sampson *et al.*, 2020). Case reports have been cited in the literature that show confirmed COVID-19–positive patients having oral ulcerations that were suspected to be caused by the SARS-CoV-2 virus (Sinadinos and Shelswell,2020) .

2.4. Loss of taste and smell

The sudden onset of two important symptoms including loss of taste (ageusia) and smell (anosmia) can be considered the earliest indicators of COVID-19. An average of 47% (up to 80%) of individuals who test positive for COVID-19 can have subjective complaints of taste and smell loss, particularly in cases of asymptomatic or mild disease (Agyeman *et al.*,2020) . The mechanism of loss of these functions has been suspected to be viral disruption of cranial nerves 1, 7, 9, and 10, as well as

the supporting cells of neural transmission (Brann *et al.*, 2020). In addition, the presence of an abundance of ACE2 receptors in the tongue can allow direct viral entry into the tongue cells.

2.5. Aphthous-like lesions

Collected data presented aphthous-like lesions appearing as multiple shallow ulcers with erythematous halos and yellow-white pseudo-membranes on both keratinized and non-keratinized mucosae. In one case, oral lesions appeared simultaneously with systemic symptoms and in other ones, latency time was between 2 and 10 days (Iranmanesh *et al.*, 2020). One case had positive history of recurrent aphthous stomatitis (RAS) and two cases had positive PCR for herpes simplex virus (HSV) (dos Santos & Silva Guerra, 2020; Malih *et al.*, 2020 and Dominguez-Santas *et al.*, 2020). Aphthous-like lesions without necrosis were observed in younger patients with mild infection, whilst aphthous-like lesions with necrosis and hemorrhagic crusts were observed more frequently in older patients with immunosuppression and severe infection. These lesions healed after 5 to 15 days (Brandão *et al.*, 2020). Regression of oral lesions was in parallel association with improvement of systemic disease. The mechanism of incidence could be related to the increased level of tumor necrosis factor (TNF) - α in COVID-19 patients that can lead to chemotaxis of neutrophils to oral mucosa and development of aphthous-like lesions. Stress and immunosuppression secondary to COVID-19 infection could be other possible reasons for appearance of such lesions in COVID-19 patients (dos Santos and Silva Guerra, 2020).

2.6. Herpetiform/zosteriform lesions

Herpetiform lesions appeared as multiple painful, unilateral, round yellowish-gray ulcers with an erythematous rim on both keratinized and non-keratinized mucosae. Manifestations of these lesions preceded, coincided with, or followed systemic symptoms. In one case, geographic tongue appeared after recovery of herpetiform lesions. Stress and immunosuppression associated with COVID-19 was the suggested cause for appearance of secondary herpetic gingivostomatitis (dos Santos & Silva Guerra, 2020; Aghazadeh *et al.*, 2020; Kämmerer *et al.*, 2020; Martín Carreras-Presas *et al.*, 2020 and Indu 2020).

2.7. White/red patches

White and red patches were demonstrated on the dorsum of tongue, gingiva, and palate of patients with confirmed or suspected COVID-19. Candidiasis due to long-term antibiotic therapy, deterioration of general status, and decline in oral hygiene can be the cause of white or red patches or plaques (Díaz Rodríguez *et al.*, 2020 and Corchuelo & Ulloa, 2020).

2.8. Kawasaki-like disease

Oral lesions including cheilitis, glossitis, and erythematous and swollen tongue (red strawberry tongue) appeared in COVID-19 patients with Kawasaki-like disease (Kawa COVID)(Cherif *et al.*, 2020; Jons *et al.*, 2020; Pouletty *et al.*, 2020 and Verdoni *et al.*, 2020). The long duration of latency between appearance of systemic symptoms (respiratory or gastrointestinal) and onset of oral or cutaneous symptoms could be due to a delayed hyper activation response of the immune system and secondary release of acute inflammatory cytokines rather than direct effects of virus on the skin and oral mucosa (Labé *et al.*, 2020; Mazzotta *et al.*, 2020 and Chiu *et al.*, 2020).

2.9. Dental Manifestations

In a recent *New York Times* article, survivors of COVID-19 who have had the disease for weeks to months- termed “long haulers”-describe oral problems they’re experiencing such as “teeth falling out, sensitive gums, teeth turning grey, and teeth cracking (Yan, 2020).

An article published in September 2020 in the *New York Times* discussed the phenomena of dentists seeing a tremendous increase in patients presenting to their practices with fractured teeth during the coronavirus pandemic (Chen, 2020). The article cited an increase in bruxism (teeth grinding and clenching) as the mostly likely culprit.

The article specifically examined three COVID-19 pandemic-related factors that could cause an increase in tooth fracture from bruxism. First, psychological stress from the pandemic could have a

major role in stress-related tooth fracture. Second, poor orthopedic posture from makeshift at-home workstations could lead to bruxism. Finally, sleep deprivation and/or obstructive sleep apnea could result in bruxism and cracked teeth.

3. Other less common oral lesions associated with COVID-19

3.1. Ulcer and erosion

Ulcerative or erosive lesions presented as painful lesions with irregular borders on the tongue, hard palate, and labial mucosa. These lesions appeared after a latency time of 4 to 7 days and in one case, lesions appeared 3 days before the onset of systemic symptoms and recovered after 5 to 21 days. In two cases, PCR for HSV-1 and HSV-2 was performed and was negative (Iranmanesh *et al.*, 2020). The suggested mechanism for the development of these lesions involved different factors including drug eruption (to NSAID in one case), vasculitis, or thrombotic vasculopathy secondary to COVID-19 (Chaux-Bodard *et al.*, 2020 and Singh *et al.*, 2020).

3.2. Erythematous Macules (EM)-like lesions

EM-like lesions appeared as blisters, desquamative gingivitis, erosions, and painful cheilitis with hemorrhagic crust in patients with cutaneous target lesions in the extremities. Lesions appeared between 7 and 24 days after the onset of systemic symptoms and recovered after 2 to 4 weeks (Martín Carreras-Presas *et al.*, 2020; Jimenez-Cauhe *et al.*, 2020 and Labé *et al.*, 2020).

3.3. Angina bullosa-like lesions

Angina bullosa-like lesions were detected as asymptomatic erythematous-purple blisters without spontaneous bleeding on the tongue and hard palate in two confirmed cases of COVID-19 (Cruz Tapia *et al.*, 2020).

3.4. Melkersson-Rosenthal syndrome

One report presented a 51-year-old woman presenting with complaint of malaise and unilateral lip swelling, fissured tongue and right facial paralysis. She had past history of Melkersson-Rosenthal syndrome since 4 years ago that was spontaneously cured with no relapse. Laboratory data demonstrated an increased level of CRP and computed tomography scan showed ground-glass opacities in both lungs. The patient cured completely after treatment of COVID-19 disease (Taşlıdere *et al.*, 2020).

3.5. Atypical Sweet syndrome

A case report presented a 61-year-old female complaining of fever, fatigue, arthralgia, myalgia, several erythematous nodules on the scalp, trunk and extremities, and minor aphthous ulcers on the hard palate and buccal mucosa. RT-PCR for COVID-19 was positive. Skin biopsy showed diffuse neutrophilic infiltration in the upper dermis with granulomatous infiltration in the lower dermis and subcutaneous area that was compatible with erythema nodosum-like Sweet syndrome (Taşkın *et al.*, 2020).

3.6. Necrotizing periodontal disease

There was a report of a 35-year-old female suspicious for COVID-19 who presented with fever, submandibular lymphadenopathy, halitosis, and oral lesions. Oral lesions included a painful, diffuse erythematous and edematous gingiva with necrosis of interpapillary areas. The suggested diagnosis was necrotizing periodontal disease due to bacterial co-infections (especially *Prevotella intermedia*) along with COVID-19. The lesions recovered after 5 days (Patel and Woolley, 2020).

3.7. Vesicles and pustules

A case of a 9-year-old female presenting with fever, weakness, abdominal pain, and diarrhea that coincided with oral and acral erythematous papular exanthema was reported. Oral lesions included vesicular eruptions and erosions on the tongue and buccal mucosa. PCR test for COVID-19 was positive. Lesions cured after 1 week (Aghazadeh *et al.*, 2020).

There was also another report of a 51-year-old male presented with fever, fatigue, dry cough, dysgeusia, anosmia, and a positive serology for COVID-19. After 10 days, widespread erythema appeared on hard palate and oropharynx with petechiae and pustules on soft palate border. The suggested diagnosis was enanthema due to COVID-19 and the lesions cured after a few days (Cebeci Kahraman and ÇaŞkurlu,2009) .

3.8. Petechiae

Few studies reported the presence of petechiae on the lower lip, palate, and oropharynx mucosa (Ciccarese *et al.*,2020). Latency time for patients with petechiae was shorter compared to the patients with both petechiae and macular lesions. Thrombocytopenia due to COVID-19 infection or the prescribed drug were suggested as possible causes of petechiae (Corchuelo & Ulloa,2020; Cebeci Kahraman & ÇaŞkurlu,2009 and Jimenez-Cauhe *et al.*,2020).

3.9. Nonspecific lesions (mucositis)

Nonspecific lesions including erythematous-violaceous macules, patches, papules and plaques on the tongue, lip mucosa, hard palate, and oropharynx were reported in several studies. Thrombotic vasculopathy, vasculitis, hypersensitivity associated to COVID-19 could be the causes of mucositis in patients with COVID-19. Mucosal hypersensitivity secondary to COVID-19, thrombotic vasculopathy, and vasculitis might be the possible causes of mucositis in COVID-19 (Malih *et al.*,2020; Soares *et al.*,2020; Jimenez-Cauhe *et al.*,2020; Cruz Tapia *et al.*,2020; Cebeci Kahraman & ÇaŞkurlu,2009 and Tomo *et al.*,2020) .

3.10. Post inflammatory pigmentation

Pigmentation has been reported in the attached and interpapillary gingiva in a 40-year-old female. The increased levels of inflammatory cytokines (including interleukin-1 [IL-1], tumor necrosis factor [TNF]- α) and arachidonic acid metabolites (prostaglandins) secondary to production of stem cell factor (SCF) and basic-fibroblast growth factor (bFGF) from keratinocytes of basal layer lead to post-inflammatory pigmentations (Corchuelo & Ulloa , 2020) .

4. Mechanism of COVID-19 oral infection

At the beginning of COVID-19 pandemic, it was assumed that lack of oral involvement is a differentiating feature of COVID-19 exanthema relative to other viral exanthemas (Putra *et al.*, 2020 and Rocha *et al.*, 2020). However, later on, it has been suggested that the oral cavity is a perfect habitat for SARS-CoV-2, since this virus has an invasive ability and a special affinity for cells having receptors for the angiotensin converted enzyme (ACE2). Recently, SARS-CoV-2 has been detected from saliva of the patients and it has been demonstrated that reverse transcriptase-polymerase chain reaction (RT-PCR) from saliva can even be a more sensitive test in comparison with nasopharyngeal test. Although many physicians continue to find the direct link between SARS-CoV-2 and oral diseases, studies suggest that the mouth might be the most vulnerable area to this virus due to the abundance of the ACE2 (angiotensin converting enzyme) receptor in oral tissues (Gheblawi *et al.*,2020).

Moreover, ACE2 receptor has been well-documented to be the target receptor of the SARS-CoV-2 virus and the portal of entry into the human cell (Gheblawi *et al.*, 2020). A new preprint study found that, compared with other oral tissues, cells of the salivary glands relative to buccal mucosa or palate, dorsum of the tongue, and tonsils carry the most RNA linked to proteins that the SARS-CoV-2 virus needs to infect cells (Huang *et al.*, 2020) . Namely, these include the ACE2 receptor and an enzyme called TMPRSS (transmembrane protease, serine 2), which allows the virus to fuse its membrane with that of the host cell and slip inside.

5. Predisposing Factors of Oral Manifestations

It has been reported that, oral lesions associated with COVID-19 were nearly equal in both genders (49% female and 51% male) (Biadsee *et al.*, 2020. Patients with older age and higher severity of COVID-19 disease had more widespread and severe oral lesions. Lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyper-inflammatory response

secondary to COVID-19 are the most important predisposing factors for onset of oral lesions in COVID-19 patients. Latency time between appearance of systemic symptoms and oral lesions was between 4 days before up to 12 weeks after onset of systemic symptoms. In three cases, oral lesions preceded systemic symptoms and in four cases oral and systemic symptoms appeared simultaneously. The longest latency period belonged to Kawasaki-like lesions. Oral lesions healed between 3 and 28 days after appearance. Different types of therapies including chlorhexine mouthwash, nystatin, oral fluconazole, topical or systemic corticosteroids, systemic antibiotics, systemic acyclovir, artificial saliva, and photobio modulation therapy (PBMT) were prescribed for oral lesions depends on the etiology (Biadsee *et al.*,2020 and Dominguez-Santas *et al.*,2020) .

6. Conclusions

COVID-19 can affect the oral mucosa and can directly or indirectly induce oral manifestations. There is latency time between appearance of oral and systemic lesions. However, oral lesions may sometimes precede the systemic symptoms or may appear with the systemic symptoms simultaneously. Gingival inflammation, xerostomia, ulceration, loss of taste, teeth crack, aphthous-like lesions, herpetiform lesions, candidiasis, and oral lesions of Kawasaki-like disease are the most common oral manifestations of COVID-19 disease. An older age and severity of COVID-19 disease seem to be the most common factors that predict severity of oral lesions in these patients. Lack of oral hygiene, opportunistic infections, stress, underlying diseases (diabetes mellitus, immunosuppression), trauma (secondary to intubation), vascular compromise, and hyper-inflammatory response secondary to COVID-19 are the most important predisposing factors for the development of oral lesions in COVID-19 patients. Hence, this review supports the argument that some oral conditions might be primary to COVID-19 infection, while others could be secondary to the deterioration of systemic health or due to treatments and drug therapy for COVID-19. In addition, this review highlights the importance of including the dentists in the intensive care unit multi-professional team to improve oral health in critical patients, not only COVID-19 patients, but also, to contribute decision-making in managing infectious diseases .

Further investigations and research work are needed to identify and survey the incidence of any new oral manifestations and their mechanisms in the context of COVID-19 infection.

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