



Oral Manifestations in Covid-19: A Review

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Received : October 18, 2021

Published : October 29, 2021

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Abstract

COVID-19 is a new disease which mainly presents with respiratory symptoms. However it can present with a multitude of signs and symptoms affecting various body systems. Several oral manifestations related to COVID-19 have also been reported. Different types of oral mucosal lesions have been identified in patients with COVID-19 infection, present at various locations within the oral cavity. Gustatory impairment along with olfactory changes is now listed as a symptom of Covid-19 by the WHO. It is important for healthcare professionals to be aware of the possible link between COVID-19 and oral mucosal lesions. Early diagnosis of the oral lesion along with proper treatment might help to reduce the disease transmission and associated oral complications. This review discusses various oral manifestations of Covid-19 reported in the literature along with possible underlying mechanisms.

Keywords: Covid-19; SARS-CoV-2; Oral manifestation; Oral mucosal lesions; Gustatory impairment

1. Introduction

The COVID-19 pandemic, also known as the corona virus pandemic, is an ongoing global pandemic of corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). On 30 January 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (PHEIC) and a pandemic on 11 March 2020. The global corona virus disease 2019 (COVID-19) pandemic has deranged the recent history of humankind, afflicting more than 232 million individuals to date, and 4.75 million deaths have been confirmed [1], making it one of the deadliest pandemics in history.

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a single chain, plus stranded RNA virus belonging to the family of Corona viridae. SARS-CoV-2 is a β -CoV and mainly infects the respiratory, gastrointestinal, and central nervous systems of humans and mammals. SARS-CoV-2 has been determined to be approximately 80% genetically identical to SARS-CoV-1 and approximately 90% genetically identical to bat CoV 2, which thus led the International Committee for the Classification of Viruses to name the new corona virus as SARS-CoV-2 [2]. It is transmitted through respiratory droplets, aerosols, contact and fomites [3].

The pandemic appears to be far from over with various reports of emerging new variants despite ongoing efforts on worldwide vaccination rollout, suggesting that there is continued need for the medical practitioners to remain up-to-date with their knowledge of signs and symptoms of this condition. The symptoms range from unnoticeable to life-threatening. The most common clinical symptoms are fever, headache, sore throat, dyspnea, dry cough, abdominal pain, vomiting, and diarrhea. People with the same infection may have

Citation: Rajeev R and Rafeek RA. "Oral Manifestations in Covid-19: A Review". *Oral Health and Dentistry* 5.1 (2021): 1-8.

different symptoms, and their symptoms may change over time. Of people who show symptoms, 81% develop only mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging) and 5% of patients suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction) [4]. At least a third of the people who are infected with the virus do not develop noticeable symptoms at any point in time [5-8]. These asymptomatic carriers tend not to get tested and can spread the disease [9-11]. Other infected people will develop symptoms later, called “pre-symptomatic”, or have very mild symptoms and can also spread the virus [11].

2. Oral Manifestations

It is well established that oral lesions of various types are manifestations of several virus illnesses. 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. 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. Furthermore, ACE2 has been found in oral mucosa, especially with more density on dorsum of tongue and salivary glands relative to buccal mucosa or palates. Oral mucosal lesions are presented along with common symptoms of Covid-19 or with other cutaneous manifestations. The lesions appear either before or along with systemic manifestations of Covid-19.

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 [12]. Many oral mucosal lesions are reported in Covid-19 confirmed and suspected individuals. They include ulcers, erosions, blisters, plaque like lesions, reactivation of herpes simplex virus 1 (HSV1), and geographical tongue [13-17]. It is stated in few publications that only oral symptom associated with Covid-19 is taste impairment and other oral lesions arise as a result of decreased immunity due to viral infection, opportunistic or secondary infection or treatment for Covid-19 [18-20]. Oral mucosal lesions are reported to disappear (6 days–2 weeks) or regress in size with time [21-24]. Although the number of studies examining the relationship between the oral cavity and SARS-CoV-2/COVID-19 remains limited, the nature of this interaction is gradually becoming clear. The oral cavity is a key gateway for viral invasion, being one of the first places where the virus interacts with the host. In addition, the oral cavity is home to an abundant and unique microbial flora, such as bacteria and viruses, which can disseminate through the blood stream and salivary flow to the whole body. Therefore, it is important to consider infections caused by the oral flora not only as diseases localized within the oral cavity but also as diseases affecting the whole body. These oral bacteria, such as periodontal pathogens, may accelerate viral infectious diseases such as COVID-19.

2.1. Gustatory Dysfunction

It is well known that the initial symptoms of COVID-19 include taste and smell disorders. In the case of taste disorder, SARS-CoV-2 may infect cells expressing ACE2 in the tongue mucosa and then spread to adjacent taste buds, resulting in impairment of taste cell function. A global search on the public databases of ACE2 mRNA expression level in human tissues shows that its expression level is relatively high in the tongue among oral mucosae, although to a lesser extent in the oral cavity than in the lungs and intestinal tract [25]. Incidentally, a meta-analysis summarizing 40 studies involving 10,228 participants from 19 countries has reported that taste disorder (45%) is the most common oral symptom, with an odds ratio of 12.68 [26]. The degree of taste disorder varies, with 38% of patients having abnormal taste, 35% having blurred taste, and 24% having loss of taste [27]. More importantly, viral load correlates with the loss of taste.

Dysgeusia or ageusia and anosmia is found to be common in COVID-19 patients, and the range varies from 5.6%–88.8% [25,26] of patients. These symptoms are more common in young individuals and females, and these symptoms usually get resolved in three weeks [20]. Ageusia or loss of taste is attributed to the presence of ACE2 expressing cells in higher numbers in the epithelial cells of the oral tissues and nasal mucosa [31,32]. ACE2 expressions is more profound in gustatory receptors of the tongue than the buccal or gingival tissues leading to certain chemosensory changes that led to ageusia [30]. These changes can occur due to the direct damage to the gustatory and olfactory receptors by the SAR-CoV-2 virus, tropism of the SARS-Cov-2 to the olfactory cells and epithelial cells of the

tongue [19], on which ACE2 receptor is highly expressed.

2.2. Salivary Alterations

Oral symptoms may occur due to salivary alterations in patients with COVID-19. ACE2 has been reported, to be expressed in several types of cells in the ducts and acini of the minor salivary glands [35], as well as in the minor salivary gland cells of the lips and epithelial cells in the duct of submandibular glands, and SARS-CoV-2 has been detected in intact saliva directly collected from the opening of the submandibular gland duct [36].

A survey of patients with confirmed COVID-19 in Wuhan found that 46% of the patients reported dry mouth as one of their symptoms [36]. In another study, 32% of patients complained of dry mouth disorders, and, importantly, the onset of symptoms was earlier than the symptoms related to COVID-19 [37]. Thus, the presence of xerostomia (hyposalivation) or other salivary alterations in COVID-19 patients should be evaluated, treated, and monitored in order to prevent the complications associated with the changes in quality and quantity of saliva [38]. Virus penetration into salivary glands affects the function of these glands in the initial stages of the disease causing changes in salivary flow and components. The neuropathic and mucotropic effects of this virus can potentially affect the function of salivary glands and can lead to hypo salivation and xerostomia [39]. Consuming numerous medicines of diverse pharmacological groups is amongst other reasons suggested for xerostomia in Covid-19.

2.3. Oral Mucosal Lesions

Different types of enanthema such as aphthous-like ulcers, Koplik's spots, petechiae, papulovesicular, or maculopapular lesions, white or red patches, gingival and lip swelling have been reported with various viral infections. It is possible that similar lesions can develop on the mucous membranes of COVID-19 patients. Several case reports have been published describing various lesions on the oral mucosa of patients with COVID-19 [40,41].

Oral manifestations reported include ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. These oral manifestations may be associated with an erythematous rash on the face or viral enanthema. Few reports state that along with unexplained ulcers in the oral cavity, desquamative gingivitis, herpetiform ulcers on attached gingiva, blisters/irregular ulcers on the tongue's dorsal surface, [42] enlargements of submandibular glands, and cervical lymph nodes [43].

The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%).

2.3.1. Ulcers and Erosions

The presence of oral ulcer in covid-19 was previously reported by many authors but its etiology remained uncertain [44]. Different factors including drug eruption vasculitis, or thrombotic vasculopathy secondary to COVID-19 were suggested as causes for development of ulcerative and erosive lesions. The site, pattern and presentation vary in different reported papers. Tongue (dorsum and lateral boarder) is the most common reported site followed by hard palate and buccal mucosa.

Irregular and painful ulcers either appear alone (single ulcers) or in the form of multiple tiny ulcers. Clusters of ulcers either resemble herpetiform ulcers or multiple aphthoid ulcers with diffuse erythematous base. Herpetiform lesions presented as multiple painful, unilateral, round yellowish-gray ulcers with an erythematous rim on both the keratinized and nonkeratinized mucosae. Manifestations of these lesions preceded, coincided with, or followed systemic symptoms. The presentation of oral ulcer may be due to the infection itself or because of anxiety and stress due to the restrictions of social life during confinement causing development of aphthoid ulcers or herpetic recurrences. Increased level of tumor necrosis factor (TNF)- α in COVID-19 patients can lead to chemotaxis of neutrophils to oral mucosa and development of aphthous like lesions. Tissue necrosis including oral ulcerations can also occur due to vessel damage. Ulceration and tissue damage can be further intensified by increased inflammation and up- regulation in inflammatory markers due to

the SARS-CoV-2 virus [45]. Regression of oral lesions was in parallel association with improvement of systemic disease. Several authors reported coexistence between the presence or the suspicion of covid-19 and oral ulcers. It is therefore important to carry out a SARS-CoV-2 RT-PCR in patient presenting oral ulcers of unknown origin.



Figure 1: Geographic Tongue

2.3.2. Vesicles, bullae and Pustules

These lesions mostly appear in association with cutaneous manifestations and show a range of presentation such as blisters, petechiae, erythematous lesions and erythema multiform-like lesions. EM-like lesions appeared as blisters, desquamative gingivitis, erythematous macules, 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 [46]. Angina bullosa-like lesions presented as asymptomatic erythematous purple blisters without spontaneous bleeding on the tongue and hard palate in two confirmed cases of COVID-19 [47].



Figure 2: Erythematous bulla on the palate

2.3.3. Plaques (White or Red)

White and red patches or plaques were reported on dorsum of tongue, gingiva, and palate of patients with confirmed or suspected COVID-19 [48]. They were also observed along with multiple tiny ulcers, taste changes, tongue and masticatory muscles pain [48]. Candidal plaque-like lesions are also observed. Immune system suppression as a result of antibiotic therapy, deteriorating general health and neglected oral hygiene can be possible causes of these plaques



Figure 3: Plaque on the dorsum of tongue & Nodular lesion on the lower lip

2. 4. Gingival Changes and Necrotizing Periodontal Disease

Gingival changes such as generalized erythematous and edematous gingivae, gingival bleeding, necrotic interdental papillae and desquamative gingivitis are reported. They are reported in critically ill patients with neglected oral hygiene. Case report was presented as oral lesions with a painful, diffuse erythematous and edematous gingiva with necrosis of inter-papillary areas. The suggested diagnosis was necrotizing periodontal disease due to bacterial co- infections (especially *Prevotella intermedia*) along with COVID-19 [50].

2. 5. Other Manifestations

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. Oral lesions including cheilitis, glossitis, and erythematous and swollen tongue (red strawberry tongue) appeared in COVID-19 patients with Kawasaki-like disease (Kawa-COVID) [51]. Petechiae were reported on the lower lip, palate, and oropharynx mucosa. Thrombocytopenia due to COVID-19 infection or the prescribed drugs were suggested as possible causes of petechiae [52]. Symptoms such as halitosis, tongue and masticatory muscle pain and swelling, geographical tongue, hyperplasia of papilla associated and macroglossia are also reported along with fatigue and major symptoms of Covid-19 [53].



Figure 4: Erythematous macules on the hard palate

3. Conclusion

In COVID-19 patients, there is a range of oral manifestations such as, mucosal lesions, ulcerative lesions (aphthous-like ulceration, herpetic stomatitis, non-specific ulcers and erythema multiforme), tongue changes (geographic tongue, strawberry tongue, fissured tongue, macroglossia and coated tongue), hemorrhagic lesions (angina bullosa, mucosal vasculitis, thrombosis, petechiae, haemorrhagic ulcer, focal erythema and spontaneous oral haemorrhage), candidal lesions, oral lichenoid lesions, non-specific blisters, gingival lesions (desquamative gingivitis, necrotic gingivitis and papillary hyperplasia) and necrotizing periodontal disease. Gustatory impairment along with olfactory changes is now listed as a symptom of Covid-19 by the WHO. However, it remains unclear whether these manifestations are caused by SARS-CoV-2 infection, a secondary phenomenon due to immune dysfunction associated with SARS-CoV-2 infection, or a super infection with other microorganisms. 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. Early diagnosis of the oral lesion along with proper treatment might help to reduce the disease transmission and associated oral complications. Timely identification and proper treatment of oral manifestation might help to reduce the further complications. More studies need to be conducted on a larger scale to better understand the relationship between SARS-CoV-2 and its oral manifestation.

4. Conflict of Interest

None reported

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