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ORAL MANIFESTATION OF COVID-19

Summary

The SARS-CoV-2 virus has shaken the globe with an ongoing pandemic of COVID-19 and has set challenges to every corner of the modern health care setting. The oral mucosa and saliva are high risk sites for higher viral loads and dental health care professionals are considered a high risk group.

Key words: *oral mucous, covid-19, keratinized epithelial, virus, oral lesions*

Pathogenesis of SARS-CoV-2 in Oral Mucosa

Oral viral infections are a common clinical complaint in dentistry, which is often associated with oral mucosal lesions. The herpes virus group (herpes simplex 1–8), human immune deficiency virus (HIV) and Zika virus are capable of infecting and replicating in the oral mucosa, leading to painful oral ulcers (1,11). Viruses like paramyxovirus, HIV, cytomegalovirus and Epstein-Barr virus (EBV) have been found to replicate in salivary glands and negatively affect the normal functioning of the salivary glands (12). Several recent reports have described the oral manifestations of SARS-CoV-2 infection such as vesicular bullous lesions and ulceration (2, 5, 11).

The single cell RNA-seq (scRNA-Seq) studies of ACE2 expression have detected high levels of expression in keratinized epithelial cell surfaces of the oral cavity, such as the dorsum of the tongue and hard palate, rather than buccal or gingival tissues (5). In the human body, the ACE2 receptor is known to be important in regulating blood pressure homeostasis by regulating the renin–angiotensin–aldosterone system (RAAS), where it converts angiotensin I to angiotensin II; this cascades body functions to maintain blood pressure and sodium water retention (6). The S protein is proteolytically cleaved by cellular cathepsin L and the transmembrane protease serine 2 (TMPRSS2) (13). Haga et al. found that SARS-CoV viruses can induce tissue necrosis factor (TNF)-α-converting enzyme (TACE)-dependent shedding of the ectodomain of ACE2, and that process was coupled with TNF-α production (4, 8). TNF-α is an inflammatory cytokine produced by

macrophages/monocytes during acute inflammation and is responsible for a diverse range of signaling events within cells, leading to cell necrosis or apoptosis (9,10). These data suggest that cellular signals triggered by the interaction of SARS-CoV with ACE2 are positively involved in viral entry but lead to tissue damage.

Oral Manifestation of COVID-19

The pathology of viral infections is often associated with either cellular destruction due to viral invasion or the consequence of host immune reaction to the viral antigen (14). Oral vesicles, blisters, macular popular rashes and ulcerations are the common clinical features of viral infections (12). In SARS-CoV-2, epithelial injury causes similar pathogenic features in the oral tissues, such as ulcers, erosions, bullae, vesicles, pustules, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, haemorrhagic crust, necrosis, petechiae, swelling, erythema, Kawasaki-like angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome (9, 11, 14). The most common sites of involvement are the tongue (38%), labial mucosa (26%), and palate (22%) (1, 3). Oral lesions were almost equal in both genders (49% female and 51% male). Patients with an older age and higher severity of COVID-19 disease had more widespread and severe oral lesions (11).

The histological analysis of oral SARS-CoV-2 lesions is associated with defects in the vascular arrangement of the oral mucosa (10). Pathogenesis of oral mucosal lesion of COVID-19 are associated with the accumulation of lymphocytes and Langerhans cells in the vasculature of the subcutaneous junctions and virus induce keratinocyte destruction by the cytotoxic lymphocytes (7).

A lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyper-inflammatory response secondary to COVID-19 were found to be the predisposing factors for the onset of oral lesions in COVID-19 patients (11, 4). Patients have reported changes in sensation in the tongue, plaque-like changes in the tongue and swelling in the palate, tongue and gums (12). Tongue lesions may be associated with the increasing activity of viral events on the epithelial mucosa of the tongue (15). On the other hand, immune suppression can lead to the harboring of opportunistic pathogens like *Candida albicans*, which can lead to the above observed tongue lesions (9). SARS- CoV-2 oral lesions healed between 3 and 28 days after they appeared. COVID-19-induced oro-mucosal lesions can be treated with mouthwashes, topical or systemic corticosteroids, systemic antibiotics and antivirals (13, 15). Increasing evidences are suggested that the antiseptic mouthwashes such as chlorhexidine, sodium hypochlorite and povidone-iodine found to be effective in reducing the SARS- CoV-2 viral load in the oral cavity and can be prescribed to patients with mucosal lesions as first line of therapy (1, 4). The topical or systemic corticosteroids, systemic antibacterial and antiviral needs to be prescribed according to the individual patient needs. Multidisciplinary team approach is important when prescribing or continuing systemic corticosteroids, antibiotics or antivirals to COVID-19-induced oro-mucosal lesions (11).

COVID-19 Induced Taste and Smell Loss

Taste is a special sensation of the human oral mucosa which plays a vital role in the identification of nutrients and regulation of food intake. Humans are capable of detecting five basic tastes: sweet, sour, salt, bitter and umami. Tastes stimulate specialized cells known as taste receptor cells (TRCs), which contain taste signal transduction proteins. Sour and salty tastes modulate the function of TRCs by the direct activation of specialized membrane channels (2, 6).TRCs are locally organized as taste buds (TBs) which are located

in the dorsum of the tongue and extra oral taste buds can be found in the tonsils and oropharynx (figure 1A). TBs are made of receptor cells, support cells and are innervated by branches of the VII (facial), IX (glossopharyngeal), and X (vagal) cranial nerves. Taste information is relayed to the brain and its recognition elicits behavioral responses to the food (8, 9). True loss of taste is extremely rare, and it is usually preceded by the inability to perceive the odor of food due to olfactory dysfunction or the deficiency of saliva to dissolve food molecules to get into the taste receptors (3, 7).

Smells or odorants reach the olfactory epithelium, which covers the cribiform plate and the upper part of the nasal septum and the middle/upper turbinates and dissolve in the mucus layer, binding/activating olfactory receptors (figure 1A). Up to 30 million receptor neurons, which express up to 350 different olfactory receptors, can be found in the olfactory epithelium. A complex combinatorial coding, by which each odorant ligand may be recognized by an olfactory receptor combination, enables humans to detect billions of different odors. Smell loss in respiratory infections are multifactorial and are caused by a combination of the mechanical obstruction of odorant transmission in the olfactory cleft due to mucosal type 2 inflammation (oedema or nasal polyps), leading to shedding, and/or degeneration of the olfactory epithelium and the reduction or loss of the sense of smell (10).

FIGURE 1

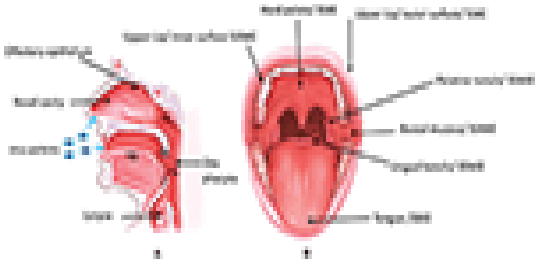

Figure 1*. Modified image indicating the location of the entry points of SARS-CoV-2 and the anterior view of the oral cavity labeling different areas of the oral mucosa.*
(A) *Blue arrows indicate the nasal and oral entrance of the virus. The location of the olfactory epithelium and taste buds (TB). Olfactory epithelium is located on the roof of the nasal cavity. Taste buds can be found in the tongue, tonsils and oropharynx.* ***(B)*** *The specific location of the Stratified squamous keratinized epithelium (SSKE) and Stratified squamous non keratinized epithelium (SSNKE) in the oral cavity.*

The SARS- CoV-2 infection associated sudden loss of taste and smell was reported in several countries in early March, with the rapid increase in COVID-19 patient numbers. Interestingly, a series of sporadic cases, predominantly in health care workers, reporting a sudden, severe, and sometimes isolated loss of smell and/or taste was reported in different countries (11, 12). Nasal congestion was found to be the driving factor for the loss of smell. It is possible that damage to the olfactory neuroepithelium can cause defects in smell detection. Loss of smell is common among females and loss of smell is associated with a loss of taste most of the time (3, 9).

Still, there are a lack of data on a specific loss of different tastants (flavors) (4). In a web-based questionnaire study (n = 128), 67 patients (52%) reported changes in taste sensation. Fifty-two patients reported a change in their spicy taste perception, 54 in salty taste, 53 in sour taste, and 61 in sweet taste. In a comparison between men and women, COVID-19 induce taste changes and changes in taste subgroups were found to be common among women, but this needs further investigations (5, 6). A possible reason for the loss of

taste in COVID-19 might be due to the increasing number of ACE-2 receptors on the tongue keratinocytes and the keratinocyte cell death and slough production can block taste buds which can adversely affect taste perception (3, 7). However, the presence of ACE-2 receptor activity on taste receptor cells is unknown at present, hence the specific role of SARS-CoV-2 on specific taste bud cells (receptor cells and supportive cells) needs to be further investigated (9). It has been shown that GPCR can be found in a diverse range of body tissues, not only in the oral cavity but in the lung epithelial cells, blood brain barrier and blood vessels (1=). It will be interesting to see the specific role of SARS-CoV-2 and GPCR interactions in terms of COVID-19 pathogenesis. On the other hand, COVID-19 induces salivary gland dysfunction, which leads to dry mouth, and can result in the malfunctioning of taste perception (11). Treatment with artificial saliva can improve the xerostomia-induced taste loss (8). Quantitative smell testing demonstrates that decreased smell function is a major marker of SARS-CoV-2 infection, and suggests the possibility that smell testing may help, in some cases, to identify COVID-19 patients in need of early treatment or quarantine (10). Song et al. found that a loss of taste was more frequent (21%) than a loss of smell (11%) in hospitalized patients, with the loss of taste but not smell being associated with severe COVID-19 (12). Most patients recovered their smell and taste dysfunctions within 2 weeks (12, 14).

Overall, there is no real evidence for any specific pharmacological option for the post-viral loss of smell including COVID-19. Some studies report an improvement in olfactory function following topical or systemic corticosteroid therapy (5, 7). Olfactory training is the only current evidence-based therapeutic option for post-viral olfactory loss, with COVID-19 positive patients reporting an improvement in smell (45.6%) and taste (46.1%) at the time of the survey; in 90.6%, this was within 2 weeks of infection (3). Over 90% of COVID-19 patients with a loss of smell may recover that sense within the first month, and olfactory training is strongly recommended if smell has not recovered after that period of time, but can be started earlier (8).

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