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Invited Article

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Oral Manifestations of Coronavirus Disease 2019 (COVID-19): An Overview

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ABSTRACT

The grim milestone of three million deaths due to the global pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reached a few weeks ago. COVID-19 is a multi-system all-pervasive disease with protean manifestations, and its major signs and symptoms, such as the incessant dry cough, fever, and pneumonia, are well-known. Yet, its mucocutaneous manifestations, particularly those of the oral cavity, appear to be little recognized. This may be due either to the rarity of oral manifestations of COVID-19, or poor detection of such symptoms by attending physicians who may do only a cursory examination of the oral mucosa because of the overwhelming gravity of the other major systemic presentations. Nevertheless, there are now a considerable number of reports, including systematic reviews, on oral manifestations of COVID-19 in the literature. These, apart from the now well-known dysgeusia of COVID-19, range from ulcers, erosions, bullae, vesicles, mucosal pustules, macules, papules and pigmentations, as well as haemorrhagic manifestations including petechiae, crusts and spontaneous bleeding. Unfortunately, the majority of these reports are anecdotal in nature and remain to be substantiated. Here, we provide a brief overview of the reported oral manifestations of COVID-19, and their management protocols.

CPD/Clinical Relevance: To raise awareness of the currently reported major and minor oral manifestations of COVID-19 and their management protocols.

1 INTRODUCTION

The first reports on mucocutaneous manifestations of COVID-19 were by dermatologists,[1,2] who correctly surmised that the skin lesions noted in these patients were very similar to cutaneous manifestations common viral diseases. They also noted that the cutaneous lesions, in particular, could be due to the drug reactions given to these early cohorts of COVID-19 patients and not necessarily due to the viral infection per se.[3] Some of the lesions described in the earliest reports were present on the skin as well as on oral mucosal surfaces.

Apart from these nondescript findings, one of the earliest, virtually pathognomonic oral manifestations was the loss of taste or dysgeusia/ ageusia, and anosmia in a majority of patients. These essentially manifested in the pre-symptomatic or the early symptomatic phase of the disease leading to a rash of reports from many regions of the World where the pandemic was taking root. In the following account, we briefly discuss dysgeusiaand anosmia, followed by salivary gland affections and, finally, the reported oral mucosal lesions.

2 CHEMOSENSORY DYSFUNCTION: DYSGEUSIA

One of the most common, well-recognized oral manifestations of COVID-19 is chemosensory dysfunction, leading to alterations of taste (dysgeusia) either with, or without, olfactory involvement (anosmia). There are now several reports and reviews in the literature on dysgeusia that could be characterized as a pathognomonic symptoms of COVID-19.[4] In a previous COVID-19 commentary, we dealt with this subject in detail,[5] although further data are now available on the condition, including a metanalysis of 31 reports by Dos Santos *et al.*[6] They noted the global prevalence of taste disorders in 45% of COVID-19 patients, with 24% ageusia, 35% hypogeusia, and 38% with dysgeusia. With a moderate certainty of the evidence, they also found that taste disorders are associated with COVID-19 positivity, mild-to-moderate disease severity, and female sex. Some have evaluated the specific loss of different flavours in COVID-19- related dysgeusia, and reported, 77% with changes in their ability to taste spice, 80% for saltiness, 79% for sourness, and 91% for sweetness. However, the veracity of these data are questionable because they were obtained from a web-based questionnaire survey.[7]

The reason/s for the loss of taste in COVID- 19 is/are unclear. Some have speculated that the increasing number of ACE-2 receptors on the tongue keratinocytes and the associated cell death and desquamation may block the taste buds and adversely affect taste perception.[8,9] Whether the dysgeusia is due to direct damage to the taste buds located in the filiform, fungiform and vallate papillae by the SARS-CoV-2 virus is unclear as yet. Dysgeusia is almost always temporary, and normal taste sensation returns by 4–6 weeks after recovery from the acute COVID-19 illness. Additionally, some reports indicate that women experience the condition more than men, although confirmatory evidence is required.[10,11]

2.1 Pathophysiology of dysgeusia

The pathophysiology for dysgeusia is somewhat speculative at present. There seem to be at least four possible pathways by which SARS-CoV-2 infection leads to dysgeusia, as outlined below:

- As ACE-2 targeted in the pre-symptomatic phase of the infection, resulting in salivary gland dysfunction. The resultant impairment of the quality and the quantity of salivary flow may be reflected as dysgeusia (see below).
- A neurological pathway, where may have an indirect impact on taste sensation, leading to dysgeusia.
- The infection could directly damage peripheral taste neuro sensory chemo receptors through the cranial nerves responsible for gustation and, in particular, the chorda tympani (CN VII) nerve. It has been posited that the virus could access the chorda tympani, first by travelling from the nasopharynx to the eustachian tube and then colonizing the middle ear from where it could access the chorda tympani, eventually causing dysgeusia.
- Lastly, another inflammatory response pathway has been proposed wherein the SARS-CoV-2 virus enters ACE-2-expressing epithelial cells of the taste buds, triggering an inflammatory response, leading to cellular changes that could alter taste.

3 SALIVARY GLANDS AND SALIVA IN COVID-19

One contributory reason for dysgeusia or ageusia could be the reduction in salivary flow or xerostomia associated with COVID-19. Considering that salivary tissues are replete with ACE-2 receptors, which are portals of cellular entry for SARS-CoV-2,[12] it is not surprising that salivary glands are profoundly affected by COVID-19, leading to a reduction in the salivary secretions. Indeed, it is now known that not only the major, but also the minor salivary glands in the labial and other regions of the oral cavity can be infected by SARS-CoV-2.[12]

Other secondary co-factors for COVID-19- induced xerostomia are thought to be impaired nasal breathing due to nasal congestion and/ or rhinorrhoea due to the disease, which in turn, may induce a feeling of oral dryness and a sense of xerostomia, either apparent or real.[13] Pandemic-induced psychosocial factors and chronic stress may also contribute to the functionality of salivary glands and quantitative reduction in salivary secretions.[13,14]

3.1 Routes of viral entry

In this context, it is salutary to review the possible routes of SARS-CoV-2 viral entry into the saliva, as it is a major vector of virus transmission in the community. Such suggested routes include:

- Direct oral entry from the upper and lower respiratory tract secretions;
- Viral proliferation in the mucosal tissues themselves, as epithelial cells have an abundanceofSARS-CoV-2receptors;
- Through salivary secretions as SARS-CoV-2 salivary gland infections can produce profuse quantities of virus in the glandular tissues that may be released into the secretions.[15] For instance, studies on rhesus macaques found that there is a rapid infection in the salivary gland epithelial cells by SARS-CoV-2, suggesting salivary glands as early proliferating foci for coronaviruses.[16]

4 ORAL MUCOSAL LESIONS (TABLE 1)

Reported oral mucosal manifestations associated with COVID-19 are many and varied, as shown in Table 1. Nevertheless, the vast majority of these are single anecdotal

reports or mini-case series with a handful of patients, and hence their veracity remains to be confirmed. The lesions reported range from ulcers, erosions, bullae, vesicles, mucosal pustules, macules, papules and pigmentations; fissured or de-papillated tongue; and haemorrhagic manifestations, including petechiae, crusts, and spontaneous bleeding (Figure 1).

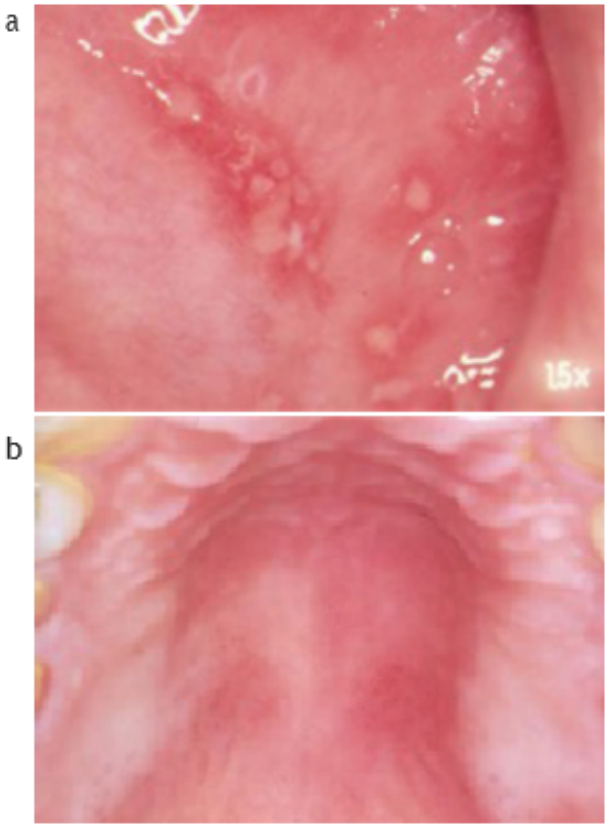

Fig. 1: (a) Non-specific, herpetiformulcers, and (b) erythematous lesions on the keratinized and non-keratinized oral mucosaappear to be relatively common oral manifestations of COVID-19 (see also Table 1).

In a global review of oral manifestations of COVID-19, Iranmesh et al[40] describe over 30 articles, including case reports, letters to the editor, and case series on oral manifestations.

Since their publication, many other reviews have appeared describing similar lesions in COVID-19. However, none of these lesions appears to be specific for the disease, as most are relatively common generalized manifestations of systemic viral infections. For instance, enanthems are common in dengue fever disease, herpangina, human herpes virus infections, measles, and roseola infantum.

In relation to the anatomical site of the described mucosal lesions, the most common sites of presentation appear to be the tongue (38%), followed by the labial mucosa (26%) and the palate (22%). In 68% of the reported cases, oral lesions were symptomatic and almost equal in both genders (51% male and 49% female). Older patients and those with very severe COVID-19 disease had more widespread and more severe oral lesions. The vast majority of oral lesions healed, and appeared to resolve about 4 weeks after their appearance. However, fresh lesions, or crops of lesions, may appear at various stages of the disease, depending on the patient's immune status.

4.1 Histopathology

A few reports are available describing the histopathology of oral lesions associated with COVID-19. In general, the breaches in the oral mucosal epithelium due to viral infections are either due to cellular destruction as a result of viral invasion of the epithelium in the case of epitheliotropic viruses, and/or the consequence of host immune reactions to the viral antigen/s.[33] Indeed, histopathology of oral SARS-CoV-2 lesions indicates the latter to be the case, with an accumulation of lymphocytes and Langerhans cells in the vasculature of the subcutaneous junctions, and virus-induced keratinocyte destruction by the cytotoxic lymphocytes.[41] Furthermore, others have described defects in the vascular arrangement of the oral mucosa.[32] The latter observation concurs with the histopathology of skin-lesion biopsies of COVID-19 patients, which demonstrated profuse vascular ectasia with dilated capillaries, large blood-filled spaces, and perivascular lymphocytic infiltrates with eosinophilia.[32]

4.2 Management

A number of interventional measures have been described for managing COVID-19- induced oral lesions, such as mouthwashes, topical or systemic corticosteroids, systemic antibiotics, and antivirals.[32] There is some evidence to demonstrate that antiseptic mouthwashes, such as low concentrations of chlorhexidine, sodium hypochlorite, or povidone-iodine, effectively ameliorate the severity and the frequency of mucosal lesions,[36,42] but these await controlled trials for confirmation. Topical or systemic corticosteroids, systemic antibacterials and antiviral drugs may also have a place depending on the individual patient's needs. A multidisciplinary team approach is essential when prescribing systemic corticosteroids for oral lesions of COVID-19.

5 PERSPECTIVES

Referral to Table 1 indicates the many and varied oral manifestations of COVID-19 described in the literature thus far. At this stage, without a prospective, standardized audit of these patients, it is difficult to state with certainty the most prevalent oral lesions associated with COVID-19, apart from dysgeusia, which is generally accepted as a hallmark of

Table 1: Oral mucosal manifestations of COVID-19 (data from various sources)

Lesions	Appearance / location / healing pattern	Comments	References
Aphthous-like lesions (ALL)	-Several shallow ulcers with erythematous halos and yellow white pseudomembrane -On both keratinized and non-keratinized mucosae -Lesions healed after 5–15 days	Latency: 2–10 days; ALL without necrosis was noted in younger patients with a mild infection, while ALL with necrosis and haemorrhagic crusts frequent in older patients with severe infection	(13)
Herpetiform/zosteriform lesions (Figure 1)	-Multiple painful, unilateral, round yellowish-grey ulcers with an erythematous rim -Present on both keratinized and non-keratinized mucosae	Manifestations of these lesions preceded, corresponded with or followed systemic symptoms	(17–21)
Ulcer and erosions	-Ulcerative or erosive painful with irregular borders -Mainly on the tongue, hard palate and labial mucosa	Factors including drug eruption, vasculitis and thrombotic vasculopathy secondary to COVID-19 were suggested as causes	(22–27)
White/red plaques (Figure 1)	-Dorsum of tongue, gingiva and palate -Some white patches were diagnosed as pseudomembranous candidiasis	Candidiasis due to long-term antibiotics, decline of general status, and deterioration in oral hygiene could be the cause of white or red patches or plaques seen in COVID-19	(17,28,29)
Erythema multiforme (EM)-like lesions	-Target-like lesions on skin, lips, buccal mucosa -Appeared as blisters, erythematous macules, desquamative gingivitis, erosions and painful cheilitis, some with haemorrhagic crusts -Simultaneously with cutaneous target lesions in the extremities	Appeared between 7 and 24 days following the onset of systemic symptoms and recovered after 2–4 weeks	(18,30,31)
Angina bullosa- like lesions	-The tongue and hard palate -Erythematous-purple blisters without spontaneous bleeding	Two confirmed cases of COVID-19	(32)
Necrotizing periodontal disease	-Painful, diffuse erythematous and oedematous gingiva with necrosis of interpapillary areas -The lesions resolved after 5 days	A female with suspicion of COVID-19 presented with fever, submandibular lymphadenopathy, and halitosis	(33)
Vesicles and pustules	-Oral and acral erythematous papular exanthema -Vesicular eruptions and erosions on the buccal mucosa and tongue -Erythema on hard palate and oropharynx with petechiae and pustules on soft palate border -Lesions resolved after a week	Two reports of a 9-year-old girl and a 51-year-old male presenting with fever and positive serology for COVID-19	(19,34)
Petechiae and macular lesions	-Lower lip, palate, and oropharynx mucosa	The latency time for patients with petechiae was shorter compared to the patients with both petechiae and macular lesions	(29,30,35)
Post-inflammatory pigmentation	-Attached and interpapillary gingiva	One case of a 40-year-old female.	(29)
Non-specific lesions (mucositis)	-Erythematous-violaceous macules, patches	Mucosal hypersensitivity secondary to COVID-19, thrombotic vasculopathy, and vasculitis might be the possible causes of mucositis in COVID-19	(23,30,35–38)
Melkerson–Rosenthal syndrome	-Malaise and unilateral lip swelling, fissured tongue -Right facial paralysis	A single report of a woman with a history of Melkerson–Rosenthal syndrome; cured, with no relapse, after treatment of COVID-19	(39)

the disease in many. Nevertheless, it is likely that ulcerated lesions such as herpetiform and aphthous-like lesions and white patches resembling candidiasis are more common than the others. Clearly, the presentation and frequency of oral manifestations appear to be higher in older, hospitalized cohorts, with severe COVID- 19 due to a multiplicity of factors, such as immune impairment, underlying diseases (eg diabetes mellitus), poor oral hygiene, adverse drug reactions, stress, hyper-inflammatory responses secondary to COVID-19, and iatrogenic trauma (secondary to intubation).

Whether the currently emerging new viral variants will impact the oral manifestations of the disease is another unknown. Highly controlled and standardized, multicentre, prospective studies are required to yield not only definitive data on the subject, but also the optimal interventional procedures to improve the quality of life in these patients.

6 COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that they have no conflict of interest.

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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