Review Article

A review on oral manifestations of COVID-19 disease

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Abstract

COVID-19, a multi-system-affecting disease presents with an extensive clinical spectrum, ranging from no symptoms at all to fatal lung involvement. Several orofacial manifestations have also been reported, among which dysgeusia is one of the earliest reported symptoms. Several other manifestations of extensive variety have also been reported by various authors worldwide since the outbreak of the disease. This comprehensive review dispenses a synopsis of the orofacial manifestations of COVID-19 along with a working classification, the knowledge of which is of utmost importance to medical and dental professionals for early detection and prevention of transmission of the disease.

Keywords: Chemosensory dysfunction, COVID 19, dysgeusia, oral manifestations, xerostomia

Introduction

Coronaviruses are a large family of single-stranded RNA viruses. Responsible for the global pandemic is the novel coronavirus disease 2019 which has affected millions of people around the globe with a sizeable mortality rate.[1] The disease shows a myriad of respiratory symptoms including shortness of breath, cough, pneumonia, acute respiratory distress syndrome, and also targets other extra pulmonary organs.[2] Oral manifestations of an extensive variety have also been reported by various authors worldwide since the outbreak of the disease. This comprehensive review dispenses a synopsis of the orofacial manifestations of the coronavirus disease 2019 (COVID-19). Physicians and primary care providers are the first line of contact for the patients; thus, their knowledge of these orofacial manifestations would help them in early detection and intervention. Moreover, diagnosis at an early stage would prevent transmission, reduce morbidity of the patient, and also aid in early recovery.

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Angiotensin-converting enzyme 2 (ACE2) has been recognized as the receptor facilitating the SARS-CoV-2 viral entry into the host cells.[3] These receptors are found in all human organs in varying capacity, with high expressions in lung alveolar epithelial cells, enterocytes of the small intestine, vascular endothelium, myocardial cells, proximal tubule cells of the kidney, and bladder urothelial cells.[4] Comparatively, weaker expressions have been identified in the oral and nasal mucosa, oropharynx, and salivary glands.[5] This ACE2 expression may explain the oral manifestations of the disease. Moreover, expression of ACE2 along with transmembrane serine protease in salivary glands and oral mucosal epithelia in conjunction with positive SARS-CoV-2 infection may also emulate virus transmission via saliva, even in asymptomatic individuals.[6]

Majority of the patients afflicted with the disease reported taste disorders including hypogeusia, dysgeusia, and ageusia along with anosmia to be among the first few symptoms to appear.[7] Oral mucosal manifestations included aphthous-like lesions, herpetiform lesions, ulcers and erosion, white or red plaque formation, xerostomia, salivary gland involvement, erythema multiforme–like lesions, angina bullosa–like lesions, Kawasaki-like lesions, vesicles and pustules, petechiae and

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macular lesions, necrotizing periodontal diseases, non-specific mucositis, and Melkersson–Rosenthal syndrome.[8] Tongue, labial mucosa, and palate were the most commonly afflicted sites in the oral cavity followed by gingiva, buccal mucosa, oropharynx, and tongue.[9]

The oral manifestations of COVID-19 can be broadly classified under the following subheadings: chemosensory debilitation, salivary gland pathologies, oral mucosal lesions, systemic conditions with oral manifestations, opportunistic infections, drug reactions and iatrogenic lesions [Figure 1]. Table 1 provides a concise overview of the various orofacial symptoms of COVID-19.

Chemosensory debilitation

Dysgeusia (taste alterations) with or without anosmia (olfactory alterations), forms of chemosensory dysfunction is one of the most common and earlier occurring symptoms in COVID-19 infection.[8] Various studies have reported prevalence ranging from 68% to 85% for olfactory disturbances and 71% to 88.8% for taste disturbances in patients with COVID-19.[10,11] This altered taste perception is usually temporary and the normal sensations return within 4–6 weeks after recovery from acute illness.[12] Several theories have been put forward to explain this transient phenomenon in COVID-19 patients.

- ACE2 receptors for SARS-CoV-2 present in the tongue's taste bud epithelium and salivary gland make them prompt targets for the virus.[50] The affliction of salivary glands may result in their dysfunction, affecting both the quality and quantity of saliva produced.[51] This, along with the changes made in the taste bud epithelium due to the virus, could explain the resulting dysgeusia, an early manifestation in this disease.

Figure 1: Diagrammatic representation of oral manifestations of COVID-19

- Since gustatory and olfactory functions are inextricably connected, debilitation of the olfactory system as a result of direct damage to the non-neuronal cells in the olfactory epithelium (which show high expression of ACE2 receptors) due to replication and accumulation of SARS-CoV-2 virus could also result in taste disturbances.[52,53] In addition, the peripheral neuronal trajectory of the gustatory tract could also be affected by the viral lytic pathway, especially the chorda tympani nerve.[54]
- SARS-CoV-2 virus when binding to ACE2 receptors of the oral mucosa may set off an inflammatory response, which could result in cellular and genetic changes, which in turn could alter taste.[55] Taste bud cells express cytokine signalling pathways, wherein production of inflammatory cytokines may trigger apoptosis in these cells, resulting in reduction of number of cells or altering the representation of different types of taste bud cells, which, overall, could result in dysgeusia.[51,55]
- Tissue hypoxia in patients with COVID-19 may result in tissue injury, thus causing taste alterations.[56] Literary evidence has shown that anemia, which emanates poor oxygen transport, could also result in dysgeusia.[57]
- Zinc plays a crucial role in taste discernment. Cellular zinc homeostasis of the oral gustatory cells may get altered due to the inflammatory process by SARS-CoV-2 virus, which may result in dysgeusia.[58,59]

Salivary gland pathologies

ACE2-positive salivary gland epithelial cells get affected in the initial stages by SARS-CoV-2 virus, thus resulting in salivary gland dysfunction.[13] Saliva production gets affected both qualitatively and quantitatively, thus resulting in xerostomia or dry mouth. Chronic sialadenitis, including focal lymphocytic sialadenitis, was the most common feature observed in COVID-19 autopsy findings.[14] Sialadenitis was linked with T cell response, and mild-to-moderate sialadenitis was affirmed with focal lymphocytic inflammation and damage to the epithelium. SARS-CoV-2 mRNA was expressed in ducts and acini of parotid glands along with other minor salivary glands.[15] Gherlone *et al.*[16] reported salivary gland ectasia to be common (43%), with oral manifestations being detected in 83.9% of their studied population. Salivary gland ectasia could be attributed to the hyperinflammatory response to the virus, as exhibited by the noteworthy relationship with C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels.

Impaired nasal breathing due to nasal congestion or rhinorrhea brought about by COVID-19 could result in mouth breathing, which in turn may result in oral dryness.[60] Moreover, chronic stress, psychological factors due to fear of the pandemic, medications, nutritional deficiencies, comorbid conditions like diabetes may also result in salivary gland dysfunction.[60,61]

Several possible routes of entry of SARS-CoV-2 into saliva have been postulated. The virus could directly gain entry to the saliva via upper and lower respiratory tract secretions, or enter

Table 1: A concise overview of the orofacial manifestations of COVID-19

Orofacial symptoms of COVID-19	Symptoms/Clinical Features	Ref.
Chemosensory debilitation	Dysgeusia (taste alterations) with or without anosmia (olfactory alterations) Usually temporary Normal sensations return within 4 - 6 weeks after recovery from acute illness	[8], [10]-[12]
Salivary gland pathologies	Qualitative and quantitative alteration of saliva flow. Xerostomia/dry mouth Sialadenitis Salivary gland ectasia	[13]-[16]
Oral mucosal lesions		
Aphthous-like lesions	Numerous shallow ulcers with erythematous halo and yellowish white pseudo-membranes. Latency period ranges between 2 and 10 days. Tends to resolve within 5-15 days.	[9], [17]-[21]
Herpetiform lesions	Multiple painful, yellowish grey ulcers with erythematous border Appear unilaterally Can occur before, during, or after appearance of systemic symptoms	[22]-[25]
Ulcers and erosions	Seen primarily on buccal mucosa, tongue, and hard palate Painful ulcerative or erosive areas with irregular borders Recovery ranges between 5 and 21 days	[26]-[29]
White or red lesions	Generally seen on dorsum of tongue, palate, and gingiva. Attributed to candidal infection/immunosuppression/deterioration of general health and inability to maintain oral hygiene	[8], [21], [30]
Necrotizing periodontal diseases	Gingival erythema and edema along with necrosis of inter papillary region Accredited to alteration of oral microflora due to COVID and super added bacterial infection by Prevotella intermedia Recovery after five days of treatment	[31]
Vesicles or pustules	Reported on tongue, buccal mucosa, palate, and oropharynx Resolve within a few days	[24], [32]
Petechiae	Seen on the lower lip and palate region Attributed to thrombocytopenia secondary to COVID-19 infection/drug-induced.	[8], [9], [28]
Angina bullosa-like lesions	Manifests as blood-filled oral bullae and vesicles Lesions reported on tongue and hard palate	[33]
Non-specific mucositis	Presents as erythematous or violaceous macules, papules, patches or plaques Seen on tongue, lip, hard palate, and oropharynx	[8], [9], [34]
Post-inflammatory pigmentation	Reported in attached and interpapillary gingiva Attributed to increased levels of inflammatory cytokines and arachidonic acid metabolites from the keratinocytes	[30]
Systemic conditions with oral manifestations		
Erythema multiforme-like lesions	Target lesions in the extremities along with oral manifestations (desquamative gingivitis, macules, erosions, blisters, cheilitis). Appeared between 7 and 24 days of beginning of systemic symptoms. Recovery within 2-4 weeks.	[35], [36]
Melkersson-Rosenthal syndrome	Recurrent facial nerve paralysis+non-pitting and painless orofacial edema+lingua plicata One patient reported with history of syndrome appearing 4 years back. Patient reported with malaise, swollen lip and was COVID-positive. Symptoms resolved completely after treatment	[37]
Atypical Sweet's syndrome	One case of a 61-year-old female reported with fever, arthralgia, myalgia, fatigue, nodules on cheek, and minor aphthous ulcers on hard palate, buccal mucosa Laboratory workup and skin biopsy were consistent with Sweet's syndrome	[38]
Kawasaki-like disease	Oral manifestations like cheilitis, glossitis, erythematous and swollen tongue may appear.	[36]
Opportunistic infections	Infections may be of fungal, bacterial, viral, protozoal or helminthic origin, with fungal infections accounting for the most occurring infections A plethora of clinical symptoms can be seen, attributable to the pathogen virility and immune status of the patient	[39]-[45]
Drug reactions	Manifests as pancytopenia, eosinophilia, leukocytes in cerebrospinal fluid, hepatitis, pancreatitis, acute kidney injury, rhabdomyolysis, hyponatremia, hyperbilirubinemia, QT prolongation, headaches, drowsiness, gastrointestinal symptoms, hyperglycemia, seizures, oral ulcerations or atrophic changes due to prolonged anemia Adverse reactions like peripheral facial paralysis, facial swelling, swellings of face, lip or tongue associated with anaphylaxis have been associated with COVID-19 vaccines	[46]-[49]
Iatrogenic lesions	Injuries due to intubation. Symptoms due to immunosuppression caused by drugs.	

through contaminated blood or serum.[8] Since plenty of ACE2 receptors are present in the salivary gland epithelium, the virus could directly enter these cells and proliferate, and their secretions would contain huge amount of the virus.[62]

Oral mucosal lesions

A wide variety of mucosal lesions have been reported in COVID-19 patients, ranging from ulcers, erosions, macules, papules, vesicles, bullae, pigmentations to fissured or depapillated tongue, and hemorrhagic manifestations including petechiae, crusts, and spontaneous bleeding. Involvement of both keratinized and non-keratinized mucosa have been reported.[8,9]

Aphthous-like lesions

These appeared as numerous shallow ulcers with erythematous halo and pseudo membranes of yellow-white color.[17,18] These ulcers were seen on both the keratinized and non-keratinized mucosa. Patients belonging to a younger age group with comparatively mild infection showed aphthous-like lesions without necrosis. On the other hand, older individuals with an immunocompromised status and severe infection showed evidence of necrosis and hemorrhage with these aphthous-like lesions.[9,19] Latency period of these ulcers could range between 2–10 days while these tend to resolve after 5–15 days, the regression being directly proportional to amelioration of systemic condition.[9,20] Factors like chemotaxis of neutrophils to oral mucosa due to increased tumor necrosis factor (TNF-α) production, stress and immunosuppression post COVID infection could result in these aphthous-like lesions.[21]

Herpetiform lesions

These manifested as multiple painful, yellowish grey ulcers with an erythematous border, and these ulcers appeared unilaterally on both keratinized and non-keratinized mucosa.[22,23] These lesions have been reported to occur before, during, or after appearance of systemic symptoms.[24,25]

Ulcers and erosions

These lesions appear primarily on the buccal mucosa, tongue, and hard palate as painful ulcerative or erosive areas with irregular borders. Factors including drug-related eruption, vasculitis, and thrombotic vasculopathy post COVID infection have been proposed as the reasons behind the manifestation of these lesions. Recovery from these lesions ranges between 5 and 21 days.[26–29]

White or red lesions

White or red plaques have been reported in patients on the dorsum of the tongue, palate, or gingiva. These lesions have been attributed to candidal infection due to prolonged antibiotic therapy, or immunosuppression or deterioration of general health and inability to maintain oral hygiene.[8,21,30]

Necrotizing periodontal diseases

Patel *et al.*[31] reported a case of COVID-19 with periodontal manifestations wherein erythema and edema of gingiva was seen along with necrosis of inter papillary region. Alteration of oral microflora due to COVID-19 infection and super added bacterial infection by *Prevotella intermedia* was hypothesized to be the reason of necrotizing periodontal disease. The lesions, however, recovered after five days of treatment.

Vesicles or pustules

Vesicular eruptions, erythema and erosions have been reported on the tongue, buccal mucosa, palate and oropharynx. These can be grouped as enanthema due to SARS-CoV-2 virus. The lesions resolve within a few days.[24,32]

Petechiae

Petechial lesions have been reported on the lower lip and palate region, and these lesions have been attributed to thrombocytopenia secondary to COVID-19 infection, or could be drug related.[8,9,28]

Angina bullosa–like lesions

Angina bullosa is a benign subepithelial condition which manifests as blood-filled oral bullae and vesicles, and has no association with any dermatologic, hemostatic, or systemic condition.[63] Cruz Tapia *et al.*[33] reported two cases of COVID-positive patients with similar lesions on the tongue and hard palate.

Non-specific mucositis

Vasculitis, thrombotic vasculopathy, and mucosal hypersensitivity post COVID-19 infection could be the possible causes of mucositis in COVID-19 patients. These lesions have been reported on the tongue, lip, hard palate and oropharynx, and manifest as erythematous or violaceous macules, papules, patches or plaques.[8,9,34]

Post-inflammatory pigmentation

This could be attributed to increased levels of inflammatory cytokines and arachidonic acid metabolites from the keratinocytes of basal layer of the oral mucosa. These pigmented areas have been reported in the attached and interpapillary gingiva.[30]

Systemic conditions with oral manifestations

Erythema multiforme–like lesions

Target lesions (regular rounded lesion with concentric circles and a well-defined margin) were seen in the extremities along with oral manifestations (desquamative gingivitis, macules, erosions, blisters, cheilitis). These appeared between 7 and 24 days of beginning of systemic symptoms. Recovery was noted between two and four weeks.[35,36]

Melkersson–Rosenthal syndrome

This neuro-mucocutaneous syndrome is characterized by the triad of recurrent facial nerve paralysis, non-pitting and painless orofacial edema, and fissuring or furrowing of tongue (referred to as lingua plicata).[64] Taşlidere *et al.*[37] reported a case of a 51-year-old female with malaise and swollen lip. The patient's medical history included Melkersson–Rosenthal syndrome,

with manifestations appearing four years back for which she was treated and had no recurrence since. Her laboratory investigations showed increased CRP and LDH levels, and chest tomography (CT) results showed bilateral, multilobular ground glass radiopacities, which confirmed the diagnosis of COVID-19. The patient was treated accordingly, post which the symptoms resolved completely.

Atypical Sweet's syndrome

Sweet's syndrome is a rare disorder manifesting as acute onset of painful plaques or nodules, fever, arthralgia, ophthalmologic manifestations, headaches, and rarely, oral or genital lesions. The syndrome, also referred to as acute febrile neutrophilic dermatosis, is diagnosed by identification of typical features and histopathology of the erythematous plaques.[65] Taşkın *et al.*[38] reported a case of a 61-year-old female with history of fever, arthralgia, myalgia, fatigue, nodules on cheek and minor aphthous ulcers on hard palate, buccal mucosa. Her laboratory workup showed leukocytosis, elevated erythrocyte sedimentation rate (ESR), CRP, D-dimer, and fibrinogen. CT showed multifocal ground glass opacities. Skin biopsy showed diffuse neutrophilic infiltration in the upper dermis along with vascular proliferation and extravasated erythrocytes, consistent with Sweet's syndrome. The amplified neutrophilic response due to COVID-19 may have triggered the manifestations of Sweet's syndrome.

Kawasaki-like disease

A new syndrome resembling Kawasaki disease has been reported in pediatric patients since the beginning of the COVID-19 pandemic, referred to as pediatric multi-system inflammatory syndrome or multi-system Inflammatory syndrome in children (MIS-C).[66] The disease is characterized by high fever, rash, hypotension, gastrointestinal symptoms, small pleural pericardial, and ascitic effusions and organ dysfunction. Respiratory symptoms are uncommon.[67] Though the syndrome bears resemblance to Kawasaki disease in several aspects, the hallmark signs of Kawasaki disease, like bilateral conjunctival injection, strawberry tongue and rash, are not always seen.[68] Orally, manifestations like cheilitis, glossitis, erythematous and swollen tongue may appear.[36]

Opportunistic infections

A wide variety of opportunistic infections have been reported in COVID-19 patients with underlying systemic diseases or among individuals on immunosuppressive drug therapy, which increases the morbidity and mortality. These reported infections are of fungal, bacterial, viral, protozoal, and helminthic origin with fungal infections accounting for the most occurring infections. Most commonly reported fungal infections were candidiasis, aspergillosis, mucormycosis, cryptococcosis, and pneumocystis pneumonia. Less reported endemic fungal infections were histoplasmosis, pulmonary coccidiomycosis, and paracoccidioidomycosis.[39]

According to a study, bacterial co-infection and secondary bacterial infections were detected in 3.5% and 14.3% of COVID-19 patients, respectively.[40] Russell *et al.*[41] analyzed data from 48,902 patients, and reported *Staphylococcus aureus* and *Haemophilus influenzae* to be the most common pathogens causing respiratory co-infections. *S. aureus* and Enterobacteriaceae accounted for the most common secondary respiratory infections. Another study reported infections caused by *Streptococcus pneumoniae, Klebsiella pneumoniae*, and *Haemophilus influenzae* were the most common bacterial co-infections.[42] *Mycoplasma pneumoniae, Pseudomonas aeruginosa*, and *Legionella pneumophila* were among other important bacterial pathogens detected in COVID-19 patients.[43]

Viral infections in COVID-19 patients have been reported to be caused by pathogens like influenza, parainfluenza, metapneumovirus, and rhinovirus. Moreover, opportunistic infections have been reported by cytomegalovirus (CMV) and herpes simplex virus (HSV) in immunocompromised individuals.[44] Intestinal protozoa and toxoplasmosis are opportunistic infections which could result in severe complications in immunocompromised patients.[39] Strongyloidiasis, a helminthic infection, has been reported in COVID patients receiving immunosuppressive drugs.[45]

Drug reactions

Medications used in the management of COVID-19 have been reported to have adverse reactions, most of which affect the gastrointestinal tract, hepatobiliary and cardiac systems. Drugs most commonly associated with adverse reactions were monoclonal antibodies like tocilizumab, anti-viral drugs like atazanavir, chloroquine (anti-malaria drug), azithromycin (antibiotic), and dexamethasone (steroids).[46] Adverse drug reactions could manifest as neutropenia, pancytopenia, thrombocytopenia, anemia, eosinophilia, leukocytes in cerebrospinal fluid, hepatitis, pancreatitis, acute kidney injury, rhabdomyolysis, hyponatremia, hyperbilirubinemia, QT prolongation, headaches, drowsiness, gastrointestinal symptoms, hyperglycemia, and seizures.[47,48] Prolonged pancytopenia, anemia, or any of the above listed drug reactions could directly or indirectly affect the oral health. Moreover, adverse reactions like peripheral facial paralysis, facial swelling, swellings of face, lip, or tongue associated with anaphylaxis have been associated with COVID-19 vaccines.[49]

Iatrogenic lesions

These include injuries caused due to intubation, symptoms due to immunosuppression caused by drugs or any other illness, or symptom brought about due to treatment of the disease.

Conclusion

COVID-19 is a fairly new, continuously evolving domain with lots of avenues for potential research. Like several other viral infections, the orofacial manifestations may be the earliest symptoms to present in COVID-19 disease too. Thus, the knowledge of these symptoms and ability to identify them would be instrumental in providing better health care in the pandemic situation. Since, the physicians and primary care providers

are the first line of contact for the patients, their knowledge of these orofacial manifestations would aid in early diagnosis and intervention, thus facilitating early recovery and reducing the morbidity of patients. Studies on a larger scale should be undertaken to develop a worldwide database for all aspects of this disease, which would help in better understanding the various facets of the disease like etiopathogenesis, clinical features, variations in symptoms amongst patients, severity of disease in different individuals, treatment modalities, and varied response of different patients to the treatment.

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Conflicts of interest

There are no conflicts of interest.

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