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ORAL MANIFESTATIONS OF COVID-19: EARLY DIAGNOSTIC AID?

Dental Science

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ABSTRACT

The outbreak of coronavirus disease which has rapidly escalated into a global pandemic continues to have disastrous health, economic and social effects on the human population. It has markedly affected the delivery of healthcare services all over the world. Early diagnosis of the disease is imperative to contain the spread of the viral infection. The main clinical signs and symptoms produced by SARS-CoV2 have been well described in the literature. However, there is emerging evidence on the oral lesions that may indicate the presence of COVID-19 infection. Since the virus has affinity for angiotensin converting enzyme (ACE2) receptors present in the respiratory tract, oral mucosa, tongue and salivary glands, the oral cavity serves as a major habitat for invasion of the virus. Thus, COVID-19 infection can affect the functioning of salivary glands, integrity of oral mucosa and can also cause alterations in sense of taste and smell. Good oral hygiene can decrease the incidence and severity of the main complications of COVID-19. The present review analyses the available evidence in relation to oral manifestations which are expressed in the course of the coronavirus disease and how it can aid in diagnosing the disease further.

KEYWORDS

SARS-CoV2, ACE2 receptors, COVID-19, oral manifestations, early diagnosis

INTRODUCTION

The world is facing a significant and urgent threat to global health due to the pandemic caused by the novel coronavirus disease 2019 (COVID-19). Back then, the 21st century has already witnessed severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) and the unfolding of SARS-CoV-2 has been recognised as the third highly pathogenic coronavirus into the human population.[1] Coronaviruses are enveloped viruses with a positive sense single-stranded RNA genome (26-32 kb). Four coronavirus genera (α, β, γ, δ) have been identified till date, with human coronaviruses (HCoVs) detected in the α coronavirus (HCoV-229E and NL63) and β coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera.[2] In December 2019, when patients admitted with pneumonia had undergone virus genome sequencing, it was found that all of them showed presence of a formerly unknown β-CoV strain. 88% of this isolated strain was identical to the sequence of two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, and about 50% showed similarity to MERS-CoV sequence.[3] The novel β-CoV was named "SARSCoV-2" by the International Virus Classification Commission. On 30 January 2020, it was declared by the WHO to represent a public health emergency of international concern and as a global pandemic on 11 March, 2020.

According to the most recent data from the World Health Organisation, the global number of confirmed cases was 3,38,42,281 with 10,10,634 deaths on October 1. Almost 216 nations or territories or regions have been affected so far by the life-threatening virus.

The incubation period of COVID-19 is 1 to 14 days, with most ranging from 3 to 7 days.[4] Patients most commonly present with fever, dry cough, and shortness of breath. Other less frequent symptoms encompass body ache, nasal congestion, headache, conjunctivitis, sore throat, diarrhoea, loss of taste or smell or a rash on skin or discoloration of fingers or toes. Usually these symptoms are mild and have a gradual onset. Though some people become infected, they present with mild symptoms. The lungs are considered as the main site of infection for coronavirus disease. The symptoms vary from mild flu-like symptoms to fulminant pneumonia and potentially fatal respiratory distress.[5] Around 20% people who get infected, develop difficulty in breathing and become critically ill.

Several studies have drawn attention to oral cavity as the primary route of infection.[6] Evidence is rising suggesting that oral signs and symptoms additionally can be regarded as preliminary manifestations of COVID-19. Thus the aim of this article is to provide a brief overview of whether oral manifestations can be considered as inaugural symptoms of COVID-19 and the potential implication of saliva in detection of same.

Expression of ACE2 Receptor of Covid-19 on Oral Mucosa

Angiotensin converting enzyme-2 (ACE2) is a significant receptor for COVID-19.[7] The SARS-CoV-2 gains entry into target cells and replicates using ACE2 receptor. Research indicates that at least partial protection against SARS-CoV-2 infection could be obtained by inhibiting cellular transmembrane serine protease 2 (TMPRSS2), employed in infection for spike protein priming.[8] Additionally, the viral spike protein of SARS-CoV-2 seems to be based on sialic acid-rich proteins and monosialotetrahexosylgangliosides (gangliosides GM1).[9] High ACE2 expression was recognised in type II alveolar cells (AT2) of lung,[10-12] esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon,[12] cholangiocytes,[13] myocardial cells, kidney proximal tubule cells, and bladder urothelial cells.[10] Hence those organs with high expression of ACE2 receptors should be viewed as potential high risk for 2019-nCoV infection.[10]

Some authors confirmed that SARS-CoV and SARS-CoV-2 both used the same receptor to enter the cell. It has been claimed that ACE2-expressing cells in nasal and oral tissues are almost same in number in comparison to the corresponding cells in lung tissue and inside the colon, and the query arises whether or not nasal and oral tissues ought to be the first to be infected by SARS-CoV-2.

ACE2 receptor was expressed on oral mucosa, especially on the epithelial cells of the tongue, followed by minor salivary glands.[6] Besides the high content of sialic acids in salivary mucin, the salivary glands showed the presence of gangliosides GM1[14] and TMPRSS2.[15] Overall, several published reports suggest that SARS-CoV-2 could infect salivary glands.[16] Chen and colleagues, in their study, found that expression of SARS-CoV-2 was higher in seriously ill patients (3/4). This study suggested that the virus invasion due to high viral loads can lead to destruction of salivary glands at later stage of the disease.[16] Additionally SARS-CoV RNA has been frequently detected in saliva earlier than lung lesions appear.[17] This would possibly explain the presence of asymptomatic infections. The salivary glands could be considered as a major source of the coronavirus in saliva.[18] The rate of detection of COVID-19 from patient's saliva is upto 91.7%, and saliva samples can also cultivate the live virus.[19] This indicated that 2019-nCoV transmitted by asymptomatic infection may originate from contaminated saliva.

Oral Manifestations

In patients affected by COVID-19, few oral manifestations have been noticed. However, doubt arises if these oral manifestations could be due to the direct viral infection or they are aggravated by COVID-19

disease, particularly those with autoimmune etiology, linked to immunocompromised system or long term pharmacotherapy. Therefore, the range of oral manifestations of SARS-CoV2 has been considered of broad and modern day interest. Additionally this acute infection, alongside related therapeutic measures, could potentially contribute to undesirable consequences regarding oral health, in all likelihood ensuing in a variety of opportunistic fungal infections, recurrent oral herpes simplex virus (HSV-1) infection, oral unspecific ulcerations, fixed drug eruptions, dysgeusia, xerostomia linked to decreased salivary flow, ulcerations and gingivitis as a result of the impaired immune system and/or susceptible oral mucosa.[20]

The two fundamental oral-related symptoms, dry mouth and amblygeustia, were manifested by a relatively high proportion of SARS-CoV2 patients. In a study conducted by Chen et al., dry mouth (46.3%) and amblygeustia (47.2%), were manifested by a relatively high proportion of 108 COVID-19 patients.[21]

The two genes, namely ACE2 and TMPRSS2 expressed in the olfactory epithelial support cells, stem cells, and nasal respiratory epithelium are mainly involved in the transport of SARS-CoV-2 into the cell, and these may be potential mechanisms whereby this infection can lead to anosmia.[22] On 18 May, it was announced that loss or changed sense of smell or taste were added to National Health Service (NHS) coronavirus symptoms list. Literature suggests that human central nervous system (CNS) may be prone to coronavirus infection.[23] The main routes of penetration of the virus into the CNS are peripheral trigeminal or olfactory nerves following intranasal inoculation.[24,25] Supported by animal studies, it may be hypothesised that the occurrence of dysosmia and dysguesia can be attributed to nerve injuries caused by complications such as demyelination and stimulation of T cell-mediated autoimmune reactions that occur in the path of the infection spreading.[26] Recently, another mechanism has been proposed which states that the sustentacular cells, the supporting cells of olfactory neurons, have the highest number of ACE2 receptors. These cells help transfer odour from air to neurons. The mature olfactory neurons do not express ACE2 while sustentacular cells do. The sense of scent in these patients appears to be lost, due to the fact that these cells aid neurons in sensing odours, possibly by processing odour-binding proteins.

When compared to the buccal or gingival tissues of the oral cavity, the epithelial cells of the tongue show high expression of ACE2 receptor.[6] It has been suggested that xerostomia occurs due to lower salivary rate and disruptions in salivary biomarkers.[27, 28] This may give rise to taste sensorial complaints. Moreover, altered salivary composition induces oral neuropathy or neurological transduction interruption which is responsible for oral sensory complaints and dysguesia.[29,30] Another reason to be considered for taste alteration is direct effect of virus in sensory neurons or other components of the peripheral gustatory system.[31] Lechien *et al*,[32] reported 3 cases for parotitis-like symptoms which could be related to COVID-19. The authors suggested that parotitis-like symptoms might be attributed to intraparotid lymph node enlargement, which is different from a primary parotitis. The adenitis and parotid-related enlargement might block the main gland duct (Stenson's duct), leading to saliva retention and parotid tissue inflammation. Sticky saliva and taste impairment may be due to low salivary flow rate.

There have been some COVID-19 cases reporting oral manifestations[32-36] such as blisters in labial mucosa, recurrent herpetic stomatitis, small multiple painful ulcers in palate and desquamative gingivitis. In addition to this, other findings include geographic tongue, petechiae, recurrent oral herpes simplex (HSV-1), candidiasis, traumatic ulcers and thrush-like ulcers.

Bodard *et al*,[33] reported a case of a 45 year old female patient who reported with an irregular ulcer on the dorsal side of the tongue. At third day, after occurrence of oral lesion, an erythematous plane lesion appeared on the big toe. Further on day 8, the patient tested positive for COVID-19. The irregular ulcer observed occurred after a short time of macular erythematous lesion, which could be explained by vasculitis. COVID-19 is associated with a variable inflammatory response that can induce vascular inflammation. Erythematous rash which occurred could also be explained by an inflammatory reaction.[33] Another case report suggested that recurrent oral ulcers could be an inaugural symptom of COVID-19.[33] In addition, three case reports (two suspicious and one confirmed) revealed that pain and intraoral findings such as oral ulcers or blisters before seeking medical advice were a common finding in COVID-19.[35] The treatment of these oral lesions most commonly includes hyaluronic acid and chlorhexidine mouthwash. Topical application of hyaluronic acid is advised three times a day and patient is advised not to eat or drink for at least 1 hour following use. The main advantage of hyaluronic acid is that is coats the oral mucosa, enhances tissue hydration and accelerates healing. It should be used only in patients above 6 years of age. Chlorhexidine mouthwash may also help ulcers to heal more quickly. It helps to prevent ulcers from becoming infected and may reduce pain. Thus, it was encouraged to perform intraoral examinations in patients suspected of SARS-CoV-2.[35] As the oral findings are still new in the literature, their occurrence may vary significantly among COVID-19 patients and, thus, the associated systemic diseases and/or poor oral health may be a contributory factor to the oral presentations.

Recent research suggests that saliva can be used as a viable diagnostic fluid for the detection of COVID-19. Saliva was observed to be even more sensitive for SARS-CoV-2 detection in COVID-19 patients in comparison to nasopharyngeal swabs. Due to abundance in disease biomarkers, saliva is considered as a potential diagnostic tool for monitoring general health and disease. It has added advantages of being an easy, safe, economic and non-invasive diagnostic approach.[37, 38] Greater than 90% of nasopharyngeal specimens detected respiratory viruses, including coronaviruses genera. The ACE2 expressing-cells were higher in number in minor salivary glands than that in lungs.

It has been proposed that there are minimal of three exceptional pathways for COVID-19 to be existing in saliva: firstly, from the lower and upper respiratory tract[39,40] the virus enters the oral cavity alongside the liquid droplets often exchanged by way of these organs. Secondly, the virus present inside the blood can enter the oral cavity through gingival crevicular fluid, an oral cavity-specific exudate that includes local proteins derived from extracellular matrix and serum-derived proteins.[41] Finally, another way for the virus to reach the oral cavity is by major and minor salivary gland infection, with subsequent release of particles in saliva through the way of salivary ducts. Added advantage of saliva over nasopharyngeal and oropharyngeal collection is that latter promotes discomfort and may induce bleeding especially in infected patients with platelet disorders like thrombocytopenia. Saliva collection being a non-invasive procedure, it extensively minimizes the exposure of healthcare workers to COVID-19. Considering that COVID-19 was recently identified in saliva of infected patients,[19] the COVID-19 outbreak is additionally a reminder that dental/oral and other health professionals must always be diligent in protecting against the unfold of infectious disease, and it gives a chance to determine if a non-invasive saliva diagnostic for COVID-19 could aid in detecting such viruses and minimising the spread.

CONCLUSION

COVID-19 represents with various combination of signs and symptoms. It can cause partial impairment of oral tissues, thus providing a new perception to the clinical prevention, diagnosis and treatment of SARS-CoV2. Also, saliva can have a pivotal role in the human-to-human transmission, and salivary diagnostics may provide economic and appropriate point-of-care platform for COVID-19 infection. More in vitro and in vivo evidence and in-depth histological data from a clinical and pathogenic point of view are needed to confirm the above mentioned findings. Thus the relevance of the oral healthcare professional as a part of the multi-disciplinary team in diagnosing COVID-19 patients should be emphasized.

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