REVIEW ARTICLE

Oral manifestations, pathogenesis and drug modalities in individuals infected with SARS- CoV-2

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ABSTRACT

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) that causes COVID-19 is a highly contagious disease that has had a significant global impact. A wide range of oral lesions have been reported in these patients. It is controversial whether these oral cavity manifestations are directly linked with the COVID-19 infection or are due to the patient's systemic condition. Oral lesions in COVID-19 patients lead to difficulty in speech, mastication and deglutition. This article's goal is to elaborate the typical oral lesions that people with COVID-19 disease manifest and possible drug modalities to management.

Keywords

Corona virus, COVID-19, Oral lesions, SARS-CoV-2

INTRODUCTION

In the month of December 2019, The new virus that causes viral pneumonia, SARS- CoV-2, has been identified. First, it was identified in an outbreak in a city in China named Wuhan. The virus is known for its high mortality rate. It is highly infectious and primarily causes respiratory illnesses [1]. On 11th February 2020, the illness was dubbed Coronavirus 19 (COVID-19) by the World Health Organization and Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2) by the International Centre for Tropical Diseases (ICTV) [2]. On March 11, 2020, WHO began referring to it as a pandemic.[3] People who suffered from the COVID-19 infection had many common symptoms like pyrexia, pharyngitis, dry cough, pneumonia, and overtiredness. It may cause plenty of other complications in other organs like the kidney, heart among others.[1] Although the exact cause of the pandemic is not completely understood, many researchers believe that the virus has been acquired froman animal and thus having a zoonotic origin.Bats are known to be reservoirs of this particular virus. In the Chinese city of Wuhan in November 2019, this animal and a humanhad a viral leap[4].

This review aims to list the lesions manifested in the oral cavity of a patient when infected with

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Coronavirus 19 and also discuss the treatment aspect of the same.

PATHOGENESIS

The oral cavity is prone to viral infection due to its anatomical structure, mainly because of its soft tissue and salivary glands. There are many viruses known to cause oral lesions likemeasles and oral hairy leukoplakia [5]. At present, The question of whether oral problems arise directly from COVID-19 infection or are a result of it is a contentious one.

Airway proteases such as transmembrane serine protease (TMPRSS) 2, 4, 11D, and others are among the mechanisms that allow SARS-CoV-2 to enter the mouth. Other factors include furin, cathepsin B, cathepsin L, and angiotensin-converting enzyme 2 (ACE2). One of the most important binding sites for ACE2 receptors in humans is the SARS-CoV-2 spike protein, which is present in the single-stranded RNA-positive SARS- CoV-2 virus. Receptors like these may be found on the surface of several human cells in places including the adipose tissue, lungs, pancreas, liver, and salivary glands. When the S protein interacts with the ACE2 receptor found on human epithelial cells, it triggers the viral machinery to multiply inside the host cell and eventually kill the host cell. This destruction of the host cell in turn triggers the activation of innate immunity against the virus, it causes immune cells to infiltrate. This causes the synthesis ofpro-inflammatory cytokines, which leads to the development of oral signs and symptomsin the oral cavity [6].

As the virus develops and matures, Furin locates the S protein's S1/S2 site, also known as the multibasic site, and cleaves it. Then, via interactions that are not covalent, the S1 and S2 subunits are stabilised. Infection causes a conformational shift in the S proteinthat reveals its S2' site when it binds to the target cell membrane's ACE2 receptor. It is possible for TMPRSS2 to cleave the S2' site from the target cell membrane. In what is called "membrane fusion," the virus immediately begins to fuse with the cell membrane of its intended host and secrete viral RNA into the cell's cytoplasm. The virus enters the cell by clathrin-mediated endocytosis and forms an endosome when there is insufficient TMPRSS2 on the target cell membrane or when the viral-ACE2 complex does not come into contact with TMPRSS2. Then, cathepsins (CTSL/CTSB) break the S2' site to start the membrane fusion process, which releases the viral RNAinto the cytoplasm. Furthermore, SARS- CoV-2 has a rate of infection that is greater than SARS-CoV due to the fact that Furin orTMPRSS2 can cleave the S protein, which contains the S1 and S2 domains, speeding upthe fusion of the virus with the cell membrane and increasing its tropism to organs [7]. On the other hand, some experts claim that the lesions in the oral cavity are caused by opportunistic or secondary infections broughton by weakened immunity following coronavirus infection. Additionally, during treatment of illness or due to a declining immune system, oral mucosal ulcers might occur. The host releases a cytokine storm that can result in drug eruptions, drug allergies, and hives during COVID-19 treatment [7].

GENERALISED ORAL MANIFESTATION

Taste disorder:

Loss of taste was a common problem encountered by most of the COVID-19 patients. It can be of varying intensities, like hypogeusia, dysgeusia, or ageusia.[8] It presented mainly as an early indicator of the disease [8].

By occupying taste bud sialic acid binding sites, SARS-CoV-2 speeds up the degradation of flavour particles when it engages with sialic acid receptors. Sialic acidis a salivary component that safeguards the glycoproteins necessary for transporting tasteparticles inside the taste pores. This results inincreased taste threshold and may be connected to taste loss [10,11]. As SARS-CoV-2 targets PNS nerves, it is also possible that direct damage to any cranial nerve involved in transmitting taste sensation could result in dysgeusia [11].

Some researchers believe that taste disorders are related to olfactory disturbances as olfactory and gustatory sensations are interlinked and often occur simultaneously, so when SARS-COV-2 damages the olfactory epithelium, it affects the olfactory sensation along with the gustatory sensation, which also gets disturbed as the brain cannotdistinguish between taste and smell and combines them together [10].

Most COVID-19 sufferers regain their sense of taste without needing any specific medical treatment. Neurostimulants like steroids, vitamin B, and ATP are proven to be useful in treating taste related issues in COVID-19 individuals. In addition, zinc supplementation can help with taste issues. The amount of zinc used differs fromindividual to individual, and a few people with taste issues do not benefit from taking zinc supplements, even when utilizing very high zinc concentrations [8]. Minocycline and doxycycline, types

of second-generation tetracycline are anticipated to treat dysgeusiaand ageusia in relation to COVID-19 [12].

Xerostomia:

Inadequate salivary secretion causes xerostomia. However, in many cases, changes in saliva quality rather than quantitycause this condition. Medications are a common cause of xerostomia. The most commonly used medications in treatingCOVID-19 disease are antiviral agents (e.g., Remdesivir), hydrochloroquine, anti-HIV medications, and interferons. After the COVID-19 pandemic, xerostomia became a common finding in most of the COVID-19 patients. Researchers have shown that salivary glands have an abundance of ACE2 receptors, which they think are important for SARS-CoV-2 entrance. Therefore, it is clear that viruses can easily invade the salivary glands, resulting in dryness of the mouth [13].

There is evidence that SARS-CoV-2 infection may have induced lesions in the salivary glands, since ACE2 and TMPRSS2 were expressed in the ductal epithelium, serous acini, and mucous acini of these glands. When SARS-CoV-2 attaches to the ACE2 port, it causes acute sialadenitis. which allows it to assault salivary glands. The production of fibrous connective tissue and fibroblast proliferation may then result in thehealing of the salivary glands. This will leadto a decrease in saliva production and a clogging of the salivary gland ducts due to fibrosis of the acinar cells. This notion provided a possible explanation for the salivary gland lesions seen in COVID-19 patients[7].

Corticosteroid, zinc supplementation, antiviral drug, malic acid sialagogue, chewing gum are found useful in treating COVID-19 related xerostomia [14].

Burning mouth:

Burning mouth is known to be common in most patients with dysgeusia and/or xerostomia. However, a wide variety of diseases and disorders may cause burning feelings in the mouth, such as psychological disorders, candidiasis, diabetes, differentmedications and vitamin and/or mineral deficiencies [9]. According to reports, triamcinolone acetonide 0.05% is therecommended for treating mouth burning sensations [15].

OCCASIONAL ORAL MUCOSAL LESIONS

Herpetiform Lesions:

Herpetiform Lesions were seen in COVID-

19 patients, which appeared yellowish in color and were unilaterally present with an erythematous border on the oral mucosa. The ulcers seen in COVID-19 patients haddifferent clinical presentations, resembling varied types of Lesions like aphthous stomatitis, generalized ulcerations with necrosis or lesions with herpetiform pattern, but when tested for herpes simplex virus, the results were negative. It is believed that immunosuppression and stress due to COVID-19 disease are the causes for theappearance of secondary herpetic gingivostomatitis [6]. Two individuals in a case series of three COVID-19 patients in the United Kingdom who had Herpetic recurrent stomatitis were described by Sinadinos et al, shows 67% chances of getting it [16]. Herpetiform lesions can be treated with systemic acyclovir and various local antiseptics like nystatin or panthenol [17].

Erosive or ulcerative lesions:

Ulcers seen in these patients were tender withan irregular border on the oral mucosa like the tongue,hard palate, etc. These ulcers had a latency period of 4–7 days. It was proposed that several factors were responsible for the appearance of ulcerative lesions. For example, it can be due to any drug reaction that the patient takes for the therapeutic purpose of COVID-19, thrombotic vasculopathy secondary to COVID-19, or vasculitis like cutaneous lesions [6]. In a cross-sectional study performed by Favia in 2021 on 123 COVID-19 patients in Italy, 65 had developed ulcerative lesions, thus showing a 53% chance of getting it [1].

Two reports, used hyaluronic acid gel with chlorhexidine to treat ulcero-erosive lesions. The former also utilized tranexamic acid to stop ulcer bleeding [1,18].

Oral Lichen Planus:

Lichen planus is an inflammatory reaction ofunknown origin. It was reported to be observed in some COVID-19 patients, but no same patient presented with both oral and cutaneous lesions of lichen planus [19]. A retrospective study was performed by Fidan et al. on 58 COVID-19 patients with oral lesions, of who 12 manifested oral lichen planus, but in the study the author has not mentioned if they performed any biopsy to confirm the same [20].

W. Saleh et al. reported a case of 63 year old male patient with oral lichen planus was treated with topical corticosteroids prescribed thrice daily for 10 days after mealsand gradually the dosage was reduced as thelesion healedand after 4 weeks the patient had a significant

decrease in the pain scores and size of the lesion [19]. Anil et al. reported a caseof 28 yearold male patient with oral lichen planuswas prescribed with an anti-oxidant(Cap. BEVON) and combination of topical corticosteroid (Tacroz ointment®) and retinoid (Isotretinoin cream 0.05%) for 12 weeks and within 2-3 months the lesion healed completely [21].

Erythema-Multiforme-like Lesion:

Erythema multiforme (EM) mainly appears on the skin and less often in the oral mucosa.It appears as a papular, bullous, and erythematous lesion. The causative agent of EM involves several factors like viral infections, drugs, etc. EM is associated with infectious agents, and the primary infectious agents are the herpes simplex virus and Mycoplasma pneumoniae [22]. A case series presented by Sinadinos in 2020 on 3 COVID-

19 patients, of whom 1 developed an erythema multiforme-like lesion, shows 33%chances of getting it [15]. Jimenez-Cauhe in 2020 treated erythema multiforme-likesymptoms in a severe case of COVID with systemic corticosteroids after hospital release 23.

Angina Bullosa-like Lesions:

It is commonly manifested in patients suffering from COVID-19 disease and presents with tender subepithelial, blood blisters on the oral mucosa [24]. In a case seriesreported by Cruz Tapia in 2020 on 4 COVID-

19 patients, 2 patients developed angina bullosa hemorrhagic-like lesions, which shows a 50% chance of occurrence in COVID-19 patients [25]. Another cross-sectional study was done by Favia in 2021 on 123 COVID-19 patients in Italy, out of whom11 patients had developed Angina bullosa, which shows 9% chances of getting it [1].

All reported cases of Angina bullosa haemorrhagica (ABH) have received conservative treatment, both during normal and covid periods. Most doctors believe that there is no need for a particular ABH treatment. Benzydamine hydrochloride mouthwash, anti-inflammatory medicines,and corticosteroids have been used in circumstances when patients experienced pain or discomfort [24].

Oral mycoses:

There have been numerous reports of secondary infections following COVID-19 disease, and this is a subject that needs serious consideration [26]. The risk factor for developing a fungal infection in COVID-19 patients is the underlying viral infection, useof steroids and other drugs in the course of treatment, ventilator-associated fungalinfections, xerostomia disorders, and/or existent diabetic mellitus. These manifest either along with COVID-19 disease or during the first few days after recovery. When treating patients who have underlying comorbidities like diabetes, attending clinicians must always be on the lookout for the presence of these mycoses [27]. Oral candidiasis, aspergillosis and mucormycosis (also called “black fungus”) are some common fungal infections found in these patients. A thorough oral check-up should bedone in these patients for early detection and treatment of oral mycoses can significantly reduce morbidity and enhance patients’ health condition [26,27].

In addition to aggressive surgical procedures, antifungals such as amphotericin B, posaconazole, or isavuconazole are frequently used in the treatment of mucormycosis. Early identification and treatment are essential for patients with mucormycosis linked with COVID-19.Antifungal medications such voriconazole, posaconazole, and isavuconazole are used to treat COVID-19-associated pulmonary aspergillosis [26].

Angular cheilitis:

Also called angular stomatitis, presents with red, swollen patches on one or both corners of mouth. These lesions in COVID-19 individual scan be related to a variety of local irritants, including hypersalivation [28]. Nystatin, neomycin, and triamcinoloneacetonide 0.05% were mostly used in thetreatment of angular cheilitis [15].

CONCLUSION

There is a lot of ground to cover when discussing oral manifestation in COVID-19 individuals. As previously stated in this analysis, Human oral tissues have an abundance of ACE2 receptors, which allows SARS-CoV-2 to infect host cells. Thus, SARS-CoV-2 is most likely to flourish in oral environments. When the virus comes infects the human body, it leads to disruption of oral microecology balance. This in turn allows the entry of foreign bodies easily intothe lungs through the mouth, which results in lung infection and increase the complicationof the disease.

There is still inadequate information about the etiology of the oral lesions in COVID-19patients. Oral lesions in these patients heal assoon as the patient recovers from the disease,which proves that oral lesions are directly or indirectly linked with COVID-19 infection. These

worsen the woes of the patient bymaking it difficult in mastication, deglutitionand altering the taste response. The drugs used for treatment of the oral lesions benefits by giving a symptomatic relief and fastening healing resulting in better patient comfort.

In order to aid medical and dental professionals in identifying and avoiding the onset of the disease's transmission, this thorough analysis provides a workable categorization and a summary of the orofacial features of COVID-19. It has been shown that spit droplets from breathing, sneezing, and talking are how SARS-CoV-2 spreads. The quantity of SARS-CoV-2 in the oral cavity may be associated to severity and viral excretion. Cleaning of oral cavity and gargling can reduce the number of oral viruses. Therefore, Oral healthcare has the potential to reduce the spread of illnesses bylowering the viral load in the mouth. Wearing a surgical mask or a N95 mask, as well as gargling with salt water and cleaning one's teeth thoroughly, may help patients from contracting SARS-CoV-2. When caring for patients with periodontal illnesses, medical professionals should take additional measures, such as wearing masks, disinfecting the air in the facility to stop the spread of saliva droplets, and reducing the formation of aerosols during oral surgery.

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