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COVID-19 Oral Manifestations: A Mini-Review Focused on Early Evidence

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ABSTRACT

Covid-19 has its etiology associated with infection by the New Coronavirus SARS-CoV-2, transmitted by inhalation of air carrying very small fine droplets and aerosol particles that contain the virus. Major signs and symptoms include fever, cough, and other symptoms associated with acute respiratory illness. However, there are reports of variation in clinical manifestations due to viral variants. Recent studies have documented various oral manifestations associated with COVID-19. In the medical literature, there can be evidence of numerous injuries such as: ulcer, papule, macule, plaque, hemorrhagic and necrotic lesions, with the tongue, labial mucosa and palate being the most affected oral regions. It is not yet clear whether oral lesions are directly caused by SARS-CoV-2, as coinfections or both. Understanding this problem may have relevant clinical implications and should be investigated in future studies.

Keywords: COVID-19; SARS-CoV-2; oral manifestations.

INTRODUCTION

SARS-CoV-2 is a highly transmissible and pathogenic coronavirus that emerged in late 2019 and caused an acute respiratory disease pandemic called COVID-19, remains to threaten people life and challenge public health. In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerge in humans and caused fatal respiratory disease. At the end of 2019, a novel coronavirus, SARS-CoV-2, appeared in Wuhan (China), and caused an outbreak of peculiar viral pneumonia [1, 2, 3].

Evidence suggests that SARS-CoV-2 transmission to humans can occur by three main ways. Such us droplet spray in short range, contact transmission and aerosol in long range. Droplet spray is generated when an infected person coughs, sneezes or even talks loudly and can be infective to others in close contact up to 6 feet (about 1.8 m). Some experts believe that this distance of 6 feet may not be safe enough a distance to prevent the spread of the virus [4, 5, 6].

Since the arrival of COVID-19, many drugs and drug mixtures have been studied. However, the search for a truly efficient treatment remains a challenge, along with experimental studies, irregular controlled trials and case series. There is limited evidence and data to support any therapy directly to fight the virus. There is consensus that almost all patients who have mild symptoms do not need any specific treatment for COVID-19. Although critically ill patients with dyspnea, hypoxia and other opportunistic infectious diseases or signs of organ failure are also candidates for specific medical care [7].

While drugs are being tested, vaccination is advancing in some places and remains very restricted in others. Vaccines are the primary public health measure needed and the simplest strategy to protect the population from COVID-19. Although it has proven effectiveness, it still has financial limitations and philosophical

resistance, as many individuals are reluctant to be immunized [8, 9, 10].

Mutations in the virus genome affect the diagnosis and treatment of infections, vaccine development and virus prevention. Since the S protein of SARS-CoV-2 is the central target of vaccines, mutations of this gene in regions that interact with the host cell's angiotensin-converting enzyme receptor 2 (ACE-2) may decrease the effectiveness of vaccines. Although SARS-CoV-2, unlike many other RNA viruses, have low sequence variability due to revision activity, genetic recombination is caused by exoribonuclease activity 3′-a-5′ nsp14 (Nsp14-ExoN) is a common event in virus replication. The generation of virus diversity and emerging variants must be constantly monitored in positive cases, vaccinated and unvaccinated [11, 12].

Considering the importance of the COVID-19 pandemic currently, even more because of the proven fact that several aspects of this disease are still unknown, along with signs and symptoms, this work is a narrative review focused on discussing the available information regarding the related oral manifestations to COVID-19.

SARS-CoV-2: Pathogenesis

The establishment of viral tropism depends on the susceptibility and permissiveness of a specific host cell. The patients often presented with respiratory-like illnesses that progressed to important pneumonia, observations mirroring the disease course of COVID-19, indicates that the lung is the primary tropism of SARS-CoV-2 [13, 14].

Activation of inflammatory signaling pathways and cytokine storm are relevant factors that lead to acute respiratory distress syndrome (ARDS) in COVID-19 patients. Overload secretion of pro-inflammatory cytokines and chemokines result in to the dysregulation of the innate immune system. The cytokine storm recruit inflammatory cells that infiltrate into the lung tissues and cause morphological and functional damage. Worth mentioning to the dysregulation of the immune system, dysfunction of the renin-angiotensin system (RAS) due to the downregulation of ACE2 is also associated with the mortality of COVID-19 patients. Both the mechanisms are directly or indirectly related with cytokine that promotes vascular hyperpermeability, vascular edema leading to hypercoagulation and hence multiorgan injury [15].

Coagulation is a natural defense mechanism that seals off damaged blood vessels and prevents local pathogens from spreading further into the systemic circulation. However, dysregulated clotting (thrombosis) can cause pathologically harmful effects by obstructing blood flow, which can lead to clotting disorders with dangerous clinical consequences. The intense platelet aggregation and upregulation of coagulation-inducing factors such as the Von Willebrand factor (vWF), factor VIII, and plasminogen activator inhibitor-1 (PAI-1) are suggested to be causative factors of coagulopathy caused by SARS-CoV-2 infection. It is relevant to mention the induction of PAI-1 by SARS-CoV-2 infection seems to be a significant event in the pathogenesis of COVID-19 because PAI-1 can inhibit urokinase-type plasminogen activator (uPA) and tissue plasminogen activator (tPA). Thus, both uPA and tPA are essential for plasmin activation, plasmin-mediated fibrinolysis is suppressed by PAI-1 influence during SARS-CoV-2 infection [12, 16].

The T cell-mediated immune response is a relevant aspect, which can be contributed to predict survival outcomes, and at some stages of disease progression, T cell suppression is not uncommon in respiratory viral infections, including SARS and MERS. Additionally, scientific evidence shows that T cell suppression is a feature linked to all stages of COVID-19 and also asymptomatic cases, suggesting the direct involvement of a SARS-CoV-2 as its etiology [17].

Clinical manifestations

Clinical symptoms are shown to occur most ordinarily between days four and five from exposure; however, studies have shown that the period will last up to fourteen days. The foremost common symptoms reportable to date embody fever, cough, fatigue and shortness of breath, that are the same as different infectious for several agent infections, as well as, the seasonal respiratory disorder [18].

ACE2 the input receptor for the SARS-CoV-2 causative coronavirus, is expressed in various extrapulmonary tissues, direct damage to viral tissue is a plausible injury mechanism. COVID-19 is best known for causing important respiratory pathology, and may also result in several extrapulmonary manifestations that are also clinically relevant. These conditions add thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, hepatocellular disturb, gastrointestinal symptoms, acute kidney injury, hyperglycemia and ketosis, neurological complications, eye symptoms, and dermatological disorders [19].

As the number of COVID-19 cases grows worldwide, more and more neurological manifestations are emerging involving the central and peripheral nervous system, as well as skeletal muscles. In this context, manifestations such as headache and dizziness; cerebrovascular events, meningoencephalitis, encephalopathy and myopathy. One concern for neurologists is how COVID-19 affects patients with an underlying neurological disease. Infections are known to unmask or aggravate the autoimmune neuromuscular diseases such as myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, acquired multifocal demyelinating sensory and motor neuropathy, and some degenerative disorders such as amyotrophic lateral sclerosis and spinal muscular atrophy. Patients with mitochondrial and metabolic myopathies are at increased risk of developing rhabdomyolysis with fever and infection, but the magnitude of these risks still needs to be further studied scientifically [20].

Smell and taste are important sensory functions for the maintenance of health and quality of life. ACE2 is expressed in the nasal mucosa, where it participates in the respiratory inflammatory process and regulates the levels of inflammatory peptides such as bradykinin [21]. However, in patients with COVID-19 such an important inflammatory component does not seem to be present and the change in smell is usually not accompanied by rhinitis symptoms. A possible justification could be that the virus damages the olfactory pathways. Histopathological analysis of anosmic mice revealed minimal destruction of the olfactory epithelium which was however abnormal due to the predominance of immature neurons, an indication of an accelerated cell turnover [22]. The reduction in neuronal lifespan in the epithelium is most likely to be the consequence of a decrease in the trophic support provided [23].

Chemosensory disorders

Chemosensory disorders are diseases or problems associated with the sense of smell and/or taste. Taste disorders can be quantitative or qualitative disorders, of which hypogeusia is a decrease sense of taste, ageusia is the absence of a sense of taste, and dysgeusia is a qualitative distortion of taste perception [24].

Olfactory and taste dysfunctions are common in patients with COVID-19 and may constitute the first symptoms in the clinical of the infection. The greater dissemination of this to the population can favor early diagnosis, as well as increase surveillance for viral transmission. A review and meta-analysis published in July 2021 showed that in ten studies 52.73% prevalence of olfactory dysfunction. Nine studies were analyzed for taste dysfunction with the prevalence of 43.93% [25].

Studies have verified anosmia and ageusia simultaneously. These findings suggest that ageusia in these patients is most

likely secondary to a reduction perception of taste as a consequence of anosmia. Nonetheless, sensorineural impairment due to direct viral injury cannot be excluded, requiring further investigation with this objective [26, 27, 28].

The interaction of SARS-CoV-2 with gustatory components and ACE2 receptors supports a direct effect in COVID-19–related taste disorders. First, the peripheral nervous system is affected by the new coronavirus, and as gustatory buds are innervated by cranial nerves, related functions may be impaired, resulting in taste disorders [29]. SARS-CoV-2 may bind essential salivary mucin components, such as sialic acid, consequently accelerating taste particle degradation and disturbing gustatory sensation. In addition, the tongue presents a high expression of ACE2 and its interaction with SARS-CoV-2 may affect normal gustatory functions through dopamine and serotonin synthesis pathway coregulation. Furthermore, ACE inhibitors and ACE2 blockers are associated with impairment of taste sensation [30].

Oral lesions in COVID-19

Enanthema can be associated with viral diseases, including dengue, Ebola virus disease, herpangina, human herpes virus infections, measles, and roseola. In COVID-19 they are also present in several cases. Infectious diseases of viral etiology constitute approximately 88% of the causes of enanthema. Several types of enanthema such as aphthous ulcers, Koplik's spots, Nagayama's spot, petechiae, papulovesicular or maculopapular lesions, white or red spots, gingival and labial swelling have been widely described in these infections. Mucosal involvement is wide, both keratinized, such as on the hard palate, gums and tongue dorsum, and non-keratinized ones, such as lips and mouth, may be involved [31].

Ulcers are frequently found in COVID-19 patients. It has even been suggested that oral ulcers may be an early sign of infection [32, 33]. The first case of an oral lesion in a patient diagnosed with COVID-19 was mentioned with a characterization of an ulceration on the dorsal side of the tongue that developed after an erythematous macular lesion, which can be attributed to vasculitis [33].

A study of 666 patients conducted in Spain reported oral lesions in more than 25% of patients. This included inflammation of the lingual papillae, glossitis with lateral indentations, aphthous stomatitis, mucositis and glossitis with irregular depapilation [34].

ACE2 expression in salivary gland epithelial cells is even greater than in lung cells, indicating that salivary glands may be a potential target for COVID-19. The glands and their ducts can be damaged and, therefore, a healing process of fibroblasts can occur with the initiation of fibrous connective tissue. This mechanism may underlie the initial manifestations of COVID-19, such as acute sialadenitis accompanied by pain and edema in the parotid and submandibular glands. This process can be followed by chronic sialadenitis due to reduced saliva secretion leading for infections and calculi in the salivary ducts [35, 36].

It has been deliberate whether oral lesions can be caused by the virus or are secondary mechanism. There is still no most evidence to support pronounced oral damage by SARS-COV-2 [37]. An acute infection by COVID-19, together with associated therapeutic measures, can contribute to triggering changes in the oral mucosa, which can cause various opportunistic fungal infections, recurrent oral herpes simplex virus infection, ulcerations or non-specific, dysgeusia, drug eruptions, xerostomia related to decreased salivary flow, ulcers and gingivitis. Added to this is the evidence that damage to the oral mucosa is more frequently reported during the hospital stay, corroborating the hypothesis of coinfections, impaired immunity or adverse reactions to the drugs used [38].

CONCLUSION

Considering the magnitude of the COVID-19 pandemic and the fact that it is still a global challenge, research involving the various knowledge gaps about a new disease can positively impact in conduct of the pandemic. In this context, studies focused on oral manifestations should be encouraged for a better understanding of the etiology of these lesions, as the data presented are not able to determine or not a causal relationship between COVID-19 and oral lesions associated with the disease.

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