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Oral Manifestations Associated with COVID-19: a Critical Review

Manifestações Orais Associadas ao COVID-19: uma Revisão Crítica

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Abstract

With a high global impact, the main target of recent health-related studies focuses on the current pandemic caused by COVID-19, a zoonotic infection mediated by the SARS-CoV-2 virus, which shows high transmission and mortality capacity. This paper aims to analyze, by means of a careful literature review , the current evidence on the manifestations of COVD-19 in the oral cavity, seeking to understand whether these are primarily from the virus, or secondary factors. This is a narrative literature review based on the research of articles carried out on the platforms: Pubmed, Google scholar, Scielo and Lilacs, in the period from June-August 2020, using the crossing of Decs / Mesh descriptors with the use of the Boolean operator AND. Only articles from 2020 were selected, in English or Portuguese and, after the search was refined, a total of 24 articles were selected. Among the manifestations expressed in the oral cavity, taste changes are present in most cases. In addition, vesiculobullous and ulcerative oral lesions have been observed in some case reports, however, due to the scarcity of information coupled with the recent emergence of this infection, further studies should be carried out in an attempt to prove or discard the association of COVID-19 with these oral manifestations.

Keywords: COVID-19. Mouth. Oral Manifestations.

Resumo

Com alto impacto global, o principal alvo de estudos recentes na área de saúde concentra-se na atual pandemia causada pelo COVID-19, uma infecção zoonótica mediada pelo vírus SARS-CoV-2, que apresenta alta taxa de transmissão e mortalidade. O presente trabalho objetiva analisar, por meio de uma revisão criteriosa da literatura, as evidências atuais sobre as manifestações da COVD-19 na cavidade oral, buscando entender se estas são principalmente de origem viral ou de fatores secundários. Trata-se de uma revisão narrativa da literatura a partir da pesquisa de artigos realizada nas plataformas: Pubmed, Google scholar, Scielo e Lilacs, no período de junho a agosto de 2020, utilizando o cruzamento dos descritores Decs / Mesh com os uso do operador booleano AND. Foram selecionados apenas artigos do ano de 2020, em inglês ou português e, após o refinamento da busca, foram selecionados 24 artigos. Dentre as manifestações expressas na cavidade oral, as alterações do paladar estão presentes na maioria dos casos. Além disso, lesões orais vesiculobolhosas e ulcerativas têm sido observadas em alguns relatos de casos, porém, devido à escassez de informações aliada ao recente surgimento dessa infecção, novos estudos devem ser realizados na tentativa de comprovar ou descartar a associação do COVID-19 com essas manifestações orais.

Palavras-chave*: COVID-19. Cavidade Oral. Manifestações Bucais.*

1 Introduction

The current pandemic caused by COVID-19 (Coronavirus Disease 2019), had its initial outbreak in December 2019 in the city of Wuhan, China. In March 2020, it was declared a pandemic by the World Health Organization, with a consequent state of a health emergency at the international level. The infectious agent identified as SARS-CoV-2 is responsible for severe acute respiratory syndrome, a new RNA virus belonging to the β-coronavirus family, which is the seventh virus capable of infecting humans[1-3].

COVID-19 is characterized by a viral infection with a high transmission capacity, proven through mortality rates ranging from 1% to more than 5%. It has an affinity for the receptors of the angiotensin-converting enzyme 2 (ACE2). These receptors are expressed in large quantities in the epithelial cells of the lung, intestine, kidneys, blood vessels, and oral mucosa[1,4,5]. The COVID-19 study has become the target of health-related research because of its high potential for contagion and lethality, especially concerning elderly patients over 65 years of age and those who have comorbidities, as they are associated with greater chances of death. The diseases that aggravate the condition of COVID-19 include lung, heart, and kidney disease, diabetes, and hypertension[4,5].

As COVID-19 is a new disease, its diagnosis and treatment have been challenging, considering the limited number of tests available to the populations of many countries. There is a need for more accurate and efficient diagnostic techniques with greater access to the population [1]. In this sense, studies suggest that saliva is a powerful sample source for the diagnosis of SARS-CoV-2, demonstrating that the oral cavity,

in addition to being a potential route of infection, can also be a great ally in the diagnosis of COVID-19[1,4,5].

The apparent relationship between SARS-CoV-2 and the oral cavity is also evident when it comes to signs and symptoms of the disease, considering that patients with the virus may present with mouth manifestations [4]. Understanding whether these signs in the oral environment are due to the viral pathogen or secondary factors will contribute to a greater understanding of the virus, facilitate the determination of early diagnosis, contribute to more effective treatment methods t, and consequently result in a more favorable prognosis[1].

Given the need to understand SARS-CoV-2 infection and its relationship to the oral cavity, the present study aimed to present and discuss the main oral manifestations found in positive patients, aiming to understand whether these signs and symptoms are derived from the virus or secondary conditions, such as systemic changes.

2 Development

2.1 Methodology

The methodological strategy defined for the present study was a descriptive study through a narrative literature review, based on the search for articles on the platforms PubMed, Google Scholar, Scielo, and Lilacs, from June to August 2020, using the crossing through the Boolean AND operator of the Decs / Mesh descriptors in English: "coronavirus AND oral manifestations" and in Portuguese: "coronavirus" AND "*manifestações orais*." The selection was adopted as a basis article whose title addressed the most pertinent virus characteristics as well as the apparent manifestation in the oral cavity.

First, the abstracts that were available in the established databases were collected. Twenty-six articles were found in PubMed, 3,960 in Google Scholar, one in Scielo, and two in Lilacs. After the initial reading, the journals that showed information about the virus and its apparent oral manifestations were selected to understand whether they derive from the virus itself or secondary conditions. The inclusion criteria established were articles relevant to the theme published in 2020, written in English or Portuguese. Journals that did not present their respective summaries on the platforms were automatically excluded.

After the previous analysis, 10 articles from PubMed, 14 from Google Scholar, and none from Scielo and Lilacs were included. Finally, 24 articles were included for the present narrative literature review, which are summarized in Table 1.

Table 1 - Crossings of the Decs/Mesh descriptors and number of studies found in the respective databases

Database	Crossing	Sample Identified	Excluded	Final Sample
Google Scholar	coronavirus AND oral manifestations	3,960	3,946	14
Pubmed	coronavirus AND oral manifestations	26	16	10
SciELO	coronavirus AND oral manifestations	1	1	0
Lilacs	coronavirus AND oral manifestations	2	2	0
Total		3,989	3,965	24

Source: Research data.

2.2 Dental surgery performance in pandemic time

Given the current public health calamity situation, health professionals within their respective areas are working to combat the new coronavirus. However, despite efforts, there is a constant increase in the spread of this pathogen. It is known that this infection has a zoonotic character, and it is believed that its origin was in pangolins and bats, which are widely consumed in oriental cuisine[3,6].

Therefore, through molecular observations, comparisons were made of SARS-CoV-2 genome in varied species. It was possible to observe the virus mutations, which could adapt to different hosts, from bats to pangolins and later to humans. This characteristic zoonotic relationship was also observed in the coronavirus that causes the Middle East Respiratory Syndrome (MERS-2012) and Severe Acute Respiratory Syndrome (SARS-2002), which had camels and civets as intermediate hosts, respectively[7,8].

When infected, the individual starts to present the virus abundantly in nasopharyngeal secretions and saliva, strengthening the idea that the predominant means of contagion is through contaminated droplets[3]. Dental surgeons (DSs) are constantly exposed to aerosols from the oral environment, and for this reason, they are among the most exposed professionals to contracting viral infections[3,6].

Because of this situation, specific suggestions for dental practice have been established, including screening and patient management, along with infection control strategies, which include primary assessment, guidance through virtual contact, observing the need for dental treatment, and assessment of the patient's vital signs, with special attention to body temperature. During the service, the use of personal protective equipment, through N95 masks, hats, glasses, face shields, disposable waterproof aprons, and gloves, is essential, and the use of hand instruments or rotating pens should be chosen without water spray, to not generate and propagate aerosols. For the same reason, the triple syringe and spitting bowl should not be used, replaced by washing with disposable and saline syringe, and frequent oral cavity aspiration. The use of absolute isolation is also indicated, aiming at greater aerosol control[6,9].

In general, the pandemic required the DS adaptation, especially while working in a dental office environment, so that the professional employs measures to reduce the risks of contagion and control the disease transmission chain [10]. Meanwhile, the SARS-CoV-2 pandemic scenario made the importance of the dental field notorious, especially concerning the care of hospitalized patients[9,11], given that care and treatment include the maintenance of daily oral hygiene and therapies that alleviate or prevent sequelae from antineoplastic treatments, which cannot be discontinued[10,11]. Many of these hospitalized patients fall into the risk group, which makes dental care even more challenging and emphasizes the importance of biosafety practices by DSs to avoid viral contagion[11].

The oral cavity is a gateway for several microorganisms with the potential to generate a generalized infection. Thus, care related to the oral environment is essential in hospitalized patients, especially when they are in more severe conditions; hospitalized in intensive care units. Dental care in these patients mainly aims at maintaining oral hygiene through variable brushing protocols, which may include associations with the use of 0.12% chlorhexidine four times a day, together with chlorhexidine gel, three times a day, and mitigating the chances of spreading microorganisms, which prevents systemic infections [9]. In addition, it is not uncommon for intubated patients to experience traumatic injuries in the oropharyngeal region due to mechanical trauma to the orotracheal tube, which requires the DS performance, since such injuries, in addition to presenting painful symptoms, serve as a gateway for microorganisms[9].

Infection with SARS-CoV-2 can lead to pneumonia, and mechanical ventilation is often necessary. Meanwhile, pneumonia associated with mechanical ventilation, which represents a condition in which pneumonia manifests itself after the orotracheal tube installation, also represents a risk factor that delays the recovery of these patients. Due to the ability to prevent or ameliorate these possible complications, through the care of the oral cavity through proper hygiene, maintaining the balance of commensal and opportunistic bacterial flora, dental care is essential and exemplifies the importance of DSs in the care of positive patients [9].

In the field of care for hospitalized patients, dentistry integrates interdisciplinary teams composed of doctors, speech therapists, nutritionists, psychologists, physiotherapists, and nurses, who work together to prevent oral infections and reduce the likelihood of more serious cases, which directly interfere with the quality of life and reduce morbidity and mortality rates[9]. With the insertion of dentistry in the care of hospitalized patients, some oral changes began to be observed in patients that tested positive for COVID-19[1,9,11]. However, as it is a new disease, it is necessary to clarify whether these changes are caused by the virus or by secondary factors, such as the patient's systemic condition and/or the use of medications[1].

2.3 Manifestations observed in oral cavity

Patients diagnosed with COVID-19 may have mild signs and symptoms similar to the flu syndrome, to more serious conditions such as fulminant pneumonia and potentially lethal breathing difficulties[2]. COVID-19 has a considerable variety of clinical manifestations, and due to the high rate of occurrence, the diagnosis is commonly made through clinical findings associated with laboratory tests[2,12]. To determine the final diagnosis of the disease, specific tests, CT scans, and clinical and epidemiological investigations are performed. When available, tests turn out to be a very useful tool if performed and interpreted correctly. Currently, two test options are available: reverse transcription followed by polymerase chain reaction (RT-PCR) and serology[12,13].

Considering the gold standard, RT-PCR can detect the virus RNA. For this reason, it is advisable to perform it even in the first week of symptoms, since in this period, there is a greater amount of the pathogen in the body. Although considered a gold standard, the technique is still prone to errors, and to reduce the chances of misunderstanding, it is a clinical criterion to repeat the exam or use the second diagnostic option, the serological test. This involves the detection of immunoglobulins of the IgA, IgM, and IgG classes against the COVID-19 infection, using the enzyme-linked immunosorbent assay (ELISA) technique. Unlike RT-PCR, the serological test is recommended to be performed from the second week of suspected contagion, considering that antibodies of the IgG class tend to appear later in the body[13].

The manifestations triggered by COVID-19 in the oral cavity have not been fully elucidated[12]. However, the literature reports clinical cases with manifestations in the upper digestive tract[2,12], which makes the analysis of these manifestations relevant, as they can contribute to the understanding of the relationship between the virus and the oral cavity.

The symptoms caused by the virus may vary according to disease severity. Of all affected patients, about 20% of them are hospitalized; that is, the vast majority are asymptomatic or show mild symptoms, remaining in isolation, and being monitored in their respective homes. In this context, the collection of information on the oral manifestations of COVID-19 becomes scarce and limited, especially when it comes to patients who do not need hospital care[14].

Olfactory and gustatory changes have been observed in patients diagnosed with the disease [14]. Sudden anosmia and ageusia are described as important symptoms of the infection, with clinical characteristics that must be considered during the patient evaluation[15]. However, positive patients can manifest only minimal changes in smell and taste, characterizing hyposmia and hypogeusia, respectively[1,15].

In addition to the olfactory and gustatory changes, dermatological implications such as vasculitis, skin rash, urticaria, and varicella-type lesions were observed in

patients affected by the virus[16,17]. Some of these patients also demonstrated associated vesiculobullous lesions and ulcers in the oral cavity[18].

The understanding between oral manifestations and SARS-CoV-2 is necessary, and given the current scenario, this understanding has been structured based on the analysis of clinical cases. In the current scientific literature, Martin et al.[18] evaluated a 65-year-old woman with obesity and systemic arterial hypertension controlled by diuretics and ACE inhibitors. This patient had bilateral pneumonia due to infection by COVID-19, in addition to associated skin rashes and complaints of pain on the tongue since the beginning of hospitalization, with no history of intraoral examination. After a week, blisters on the inner lip mucosa were observed, in addition to scaly gingivitis. Hyaluronic acid and mouthwash with chlorhexidine were prescribed, and the general practitioner prescribed prednisolone 30 mg/d. The lesions improved in three days, and a biopsy, performed only on the skin by a dermatologist, revealed nonspecific morphological findings with some criteria suggestive of viral rash or urticarial dermatitis with mild blood leakage. The patient in question had common elementary lesions seen in different viral infections, such as hand, foot, and mouth disease and herpetic gingivostomatitis.

Similar clinical manifestations were observed in two other patients. The first was a 45-year-old woman, with the presence of an ulcer on the back of the tongue. During anamnesis and intraoral physical examination, it was possible to notice the presence of inflammation in the papillae of the tongue during the 24-hour period, followed by 24 h of the erythematous macula, with progression to irregular and symptomatic ulcers. After 10 d, the ulcer completely healed. On the third day after the appearance of the lesion in the oral cavity, a flat erythematous lesion was observed on the big toe, symptomatic during the first 48 h, becoming asymptomatic after this period[12]. The case in question is compatible with intraoral herpetic lesions, which are commonly found in immunosuppressed patients.

The second patient, a 42-year-old man, presented a positive diagnosis for COVID-19 and a medical history of hypertension. Upon admission to the hospital, he exhibited fever, cough, shortness of breath, and skin lesions similar to petechiae and vesiculobullous lesions, which were treated with dexamethasone and dipyrone for one week. The patient also had complaints of painful lesions in the oral cavity. On physical examination, oral mucosa ulceration was observed, in addition to red spots on the hard palate, tongue, and lips, which regressed within 3 wks. Biopsy of the ulcerated lesion revealed areas of hemorrhage and small thrombotic vessels, microscopic aspects that, when added to the patient clinical aspect, were suggestive of an association with COVID-19[19].

The strategies to combat SARS-CoV-2 vary according to the financial and governmental conditions of each country. Thus, it is observed that in some cases, the prediagnosis is performed based on the signs and symptoms observed in the patient, until there is the opportunity for confirmation through the available tests. In this context, understanding oral manifestations can make a relevant contribution to the early diagnosis of the disease[12,19].

SARS-CoV-2 has been associated with variable inflammatory reactions, which can cause vascular inflammation. Erythematous eruptions have been described as a possible sign of COVID-19; however, verification through observational studies is necessary[12].

Martin et al.[18] reported a clinical case of a 56-year-old man, systemically healthy, with suspicion of COVID-19, who exhibited signs and symptoms characteristic of the disease and painful symptoms on the palate and throat. Through teleconsultation, photographs of the symptomatic areas were sent by the patient, and the professionals observed the presence of similar lesions with recurrent herpetic stomatitis. However, this was the first time that the patient had manifested these injuries. The health professionals responsible for the case opted for the prescription of acyclovir (500 mg every 8 h for 10 d) and topical use of antiseptics (chlorhexidine and hyaluronic acid). After 10 d, the oral lesions had completely disappeared. The same authors reported another clinical case of a 58-year-old man who was systemically compromised, with a diagnosis of underlying diabetes and hypertension. After his wife was diagnosed with COVID-19, the couple were isolated . Subsequently, through teleconsultation, the patient reported the presence of a painful lesion on the palate. A photograph was sent to professionals in the field, with multiple small unilateral palatal ulcerations of small diameter, with no history of previous herpetic infection. The intervention measure adopted was the use of a topical mouthwash; however, the rinse used was not informed. After one week, the lesions regressed [18]. It is noted, therefore, the similarity between the clinical cases regarding the location of the lesions, both on the palate, as well as the clinical sign of associated painful symptoms in the two cases evaluated. However, it is necessary to make a differential diagnosis of infection by the herpes simplex virus (HSV-1), which has similar clinical characteristics to the lesions mentioned above and is sometimes also diagnosed by PCR in patients positive for COVID-19[20].

Brandão et al.[20] carried out the largest study of a series of cases related to oral lesions to COVID-19. A total of eight patients were diagnosed with SARS-CoV-2, three of whom had ulcerative oral lesions of varying sizes, margins, and characteristics, located on the upper/lower lip and in different regions of the tongue. Treatment with 250 mg/m^2 intravenous acyclovir was instituted three times a day for 10 d. However, the approach did not present a satisfactory result and the option was then to use daily laser photobiomodulation (PBMT) for 10 consecutive days (Twin Flex, MMOptics, São Carlos, Brazil), which demonstrated effectiveness in an average of 9 d of application. The other cases showed similar lesions in the

oral cavity, with the involvement of the tonsillar pillar and presentation of petechiae on the hard palate. The therapeutic interventions for the five cases varied , which included the use of laser photobiomodulation and even a patient's refusal to undergo treatment[20].

The fact that the presence of oral lesions in these patients diagnosed with COVID-19 does not guarantee the association between lesions in the oral cavity and the virus in question, it raises the question whether the lesions are caused by a viral infection or whether the patients had low immunity due to COVID-19, and for this reason, they presented secondary oral lesions.

SARS-CoV-2 has an affinity for ACE2 receptors present in cells of the oral cavity and, especially, in the tongue epithelium. Therefore, these cells can host SARS-CoV-2 with the possibility of promoting reactions in these related tissues. Given the above, studies suggest that this characteristic may be related to the taste changes present in these patients. Mariz et al.[21] through animal studies and clinical observations, proposed that the dysgeusia reported during SARS-CoV-2 infection can be derived from the accumulation of ACE2 in the taste buds, which would cause eventual changes[4,5,21,22].

The relationships observed between the virus and the ACE2 receptors present in the oral cavity show possible explanations for the apparent oral manifestations found in patients diagnosed with COVID-19. However, more studies are needed to prove or discard this theory as well as a greater understanding of the manifestations found in these patients[5,22]. The main manifestations in the oral cavity of COVID-19 are summarized in Table 2.

Table 2 - Findings in the literature of oral manifestations in patients diagnosed or suspected of having COVID-19

Author(yr)	Martin et al.[18]	Bodard et al.[12]	Soares et al.[19]	Brandão et al.[20]
Patient's gender	1 woman and 2 men	Woman	man	5 men 3 women
Patient's age	56−65	45	42	28−81
Main signs and general symptoms	Bilateral pneumonia and skin rashes. Asthenia, fever, hyposmia, dysgeusia, and enlarged lymph nodes in the neck	Mild asthenia	Fever, cough, pain, and shortness of breath	Fever, dyspnea, cough, malaise
Injury evolution time	7 d	24 h	Not informed	± 6 d
Clinical characteristics of oral lesions	Blisters on the inner mucosa of the lip, scaly gingivitis. Small diameter unilateral palatal ulcerations. Painful symptoms in tongue, palate, and throat	Inflammation of the tongue papillae with progress to an erythematous macula and later an irregular and asymptomatic ulcer	Ulceration in the oral mucosa and red spots distributed on the hard palate, tongue, and lips	Aphthous, necrotic and hemorrhagic ulcerations. Petechiae on the palate
Differential diagnosis	Elementary lesions are seen in viral infections, such as hand, foot, and mouth disease and herpetic gingivostomatitis	Not informed	Not informed	Herpetic infection
Treatment employed	Hyaluronic acid, mouthwash with chlorhexidine and prednisolone 30 mg/d	Not informed	Dexamethasone and dipyrone for one week	Intravenous acyclovir 250 mg 3x daily/10 d, daily photobiomodulation/10 d mouth rinse with 0.12% non-alcoholic chlorhexidine
Healing time	3 d	10 d	3 wks	± 7 d

Source: Research data.

2.4 COVID-19 and Kawasaki syndrome with oral manifestations

As it is a new disease, information about COVID-19 is still scarce. Despite this, a possible synergistic correlation between SARS-CoV-2 and other systemic diseases present in the oral cavity is observed[23].

Reported for the first time in Japan, Kawasaki syndrome (KS), still of unknown etiology, is characterized as an acute vasculitis, usually limited to medium-caliber vessels. This syndrome affects mostly babies and young patients. During the acute phase, affected patients may demonstrate hemodynamic instability, a condition known as Kawasaki disease shock syndrome. It is a rare disorder and is, therefore, difficult to diagnose. Thus, the dental field contributes significantly, considering that it has manifestations in the stomatognathic

region. The most common signs and symptoms of KS include high fever, redness in the palms and soles, conjunctivitis, oropharyngeal stomatitis, lymphadenopathy, and possible cardiac involvement[23].

Being considered one of the epicenters of COVID-19, the Bergamo region in Italy was one of the first places to report the disease in Europe. Given the scenario of constant contamination by SARS-CoV-2 in this region, there was also an increasing occurrence of KS cases, with a 30-fold increase in its incidence. In addition, patients diagnosed with this syndrome after the onset of the pandemic showed more advanced age, signs of an immune response to SARS-CoV-2, higher rates of cardiac involvement, and atrophy activation syndrome (MAS). These findings suggest that SARS-CoV-2 may promote the severe form of Kawasaki's disease[23,24].

Verdoni et al.[23] in an observational cohort study conducted in the province of Bergamo, compared the symptomatic presentations of Kawasaki disease before and after the pandemic. The results showed that patients diagnosed after the onset of the pandemic manifested the most severe form of KS, with greater cardiac involvement and MAS characteristics. Because of this apparent association among diseases, the study points to the possibility of an outbreak of KS in countries affected by COVID-19[23,24], possibly because viral infection by SARS-CoV-2 has already shown that it can interfere with the host circulatory system as well as KS, which is proven to be a vascular disease. Thus, in the presence of COVID-19, there is a tendency to enhance the hemodynamic instability associated with KS.

3 Conclusion

In analyzing the information presented, it can be considered that among the manifestations expressed in the oral environment, taste changes are present in most cases. Regarding vesiculobullous lesions, there is a need for further observational studies to confirm or discard the direct relationship of these lesions with SARS-CoV-2. In the same way, the apparent synergism relationship between COVID-19 and KS should be better evaluated.

The scarcity of information about this new disease and its possible manifestations in the oral cavity presented itself as a limitation to the present study, with few reports, among them some based on teleconsultation, exemplifying the difficulty of an adequate evaluation during this pandemic period. However, all information related to SARS-CoV-2 contributes to possible improvements in treatment and the consequent prognosis and quality of life of the affected patient.

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