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Oral lesions in patients infected with SARS-CoV-2: a case series

Lesões bucais em pacientes infectados por SARS-CoV-2: série de casos

Lesiones orales en pacientes infectados por SARS-CoV-2: serie de casos

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Abstract
As the COVID-19 pandemic spreads around the world, professionals must prepare for an increase in severely ill patients. Considering that professionals who perform oral care, especially the oral health team, is the most exposed to SARS-CoV-2, and that saliva can be the main vector in the transmission from person to person, it is essential that they are supported by the best evidence for their performance with risk reduction. In view of the literature, the clinical studies of COVID-19 do not often describe oral symptoms, and it is still uncertain whether these manifestations may be a typical clinical pattern resulting from direct SARS-CoV-2 infection or a systemic consequence, given the possibility of co-infections, impaired immune system and adverse drug reactions. As the prevalence of clinical manifestations is still unknown, the possible manifestations of COVID-19 in the oral cavity has been considered of wide and current interest. Therefore de aim of this study was to report a case series of oral lesions in patients infected with SARS-CoV-2.
Keywords: SARS-CoV-2; COVID-19; Dental care; Diagnosis, oral; Oral manifestations; Dental service hospital.

Resumo
À medida que a pandemia pelo COVID-19 se espalha pelo mundo, os profissionais devem se preparar para um aumento no número de pacientes gravemente enfermos. Considerando que os profissionais que realizam higiene bucal, principalmente a equipe de saúde bucal, são os mais expostos à SARS-CoV-2, e que a saliva pode ser o principal vetor na transmissão de pessoa a pessoa, é fundamental que tenham o apoio da melhor evidência de seu desempenho com redução de risco. De acordo com a literatura, os estudos clínicos de COVID-19 não costumam descrever sintomas orais e ainda não se sabe se essas manifestações podem ser um padrão clínico típico resultante de infecção direta por SARS-CoV-2 ou uma consequência sistêmica, devido a possibilidade de co-infecções, comprometimento do sistema imunológico e reações adversas a medicamentos. Como a prevalência das manifestações clínicas ainda é desconhecida, a possível manifestação da COVID-19 na cavidade oral tem sido considerada de amplo e atual interesse. Portanto, o objetivo deste estudo foi relatar uma série de casos de lesões orais em pacientes infectados com SARS-CoV-2.
Palavras-chave: SARS-CoV-2; COVID-19; Assistência odontológica; Diagnóstico bucal; Manifestações bucais; Unidade hospitalar de odontologia.

Resumen
La medida que la pandemia de COVID-19 propágase por el mundo, los profesionales deben prepararse para un aumento de enfermos gravemente comprometidos. Considerando los profesionales que realizan los cuidados bucales, en especial los equipos de sanidad bucal son los más expuestos al SARS-CoV-2, y que la saliva suele ser el principal vector en la transmisión de persona a persona, es fundamental que cuenten con el apoyo de la mejor evidencia de su desempeño en la reducción del riesgo. Teniendo en vista la bibliografía, los estudios clínicos de COVID-19, todavía no describen los síntomas orales y aún no se sabe si estas manifestaciones pueden ser un patrón clínico típico resultante de una infección directa del SARS-CoV-2 o una consecuencia sistémica, dado la posibilidad de coinfecciones, deterioro del sistema inmunológico y reacciones adversas a los medicamentos. Otros datos aún desconocidos, son, la prevalencia de las manifestaciones clínicas y las posibles manifestaciones de COVID-19 en la cavidad bucal, han considerado de amplio y de actual interés. Por lo tanto, el objeto de este estudio fue informar una serie de casos clínicos de lesiones bucales en pacientes infectados con SARS-CoV-2.
Palabras clave: SARS-CoV-2; COVID-19; Atención odontológica; Diagnóstico bucal; Manifestaciones bucales; Servicio odontológico hospitalário.

1. Introduction

Coronaviruses belong to the family of Coronaviridae, of the order Nidovirales, comprising large, single and genome-stranded RNA (Chan et al., 2020; Peng et al., 2020). Coronavirus disease 2019 (COVID-19) is the third coronavirus infection in two decades, originally described in Asia, after severe acute respiratory syndrome (SARS) (Peng et al., 2020; Sabino-Silva & Jardim, Siqueira, 2020).

COVID-19 can cause severe respiratory diseases in humans and has been a potential threat to human health, largely because of its high transmissibility attracting worldwide attention after the severe acute respiratory syndrome (SARS) pandemic in 2003 (Tysiąc-Miśta & Dziedzic, 2020), followed by the Middle East respiratory syndrome (MERS) in 2012 (Bao et al., 2020; Tysiąc-Miśta & Dziedzic, 2020).

As the COVID-19 pandemic spreads around the world, professionals must prepare for an increase in severely ill patients (Chan et al., 2020; Peng et al., 2020; Sabino-Silva, Jardim & Siqueira, 2020; Tysiąc-Miśta & Dziedzic, 2020).

Dental care, whether by the hospital's own means or by outsourced services, must be provided to every critical patient who presents some need in their oral structures or attached areas (WHO, 2020). Therefore, considering that professionals who perform oral care, especially the oral health team, is the most exposed to SARS-Cov-2, and that saliva can be the main vector in the transmission from person to person, it is essential that they are supported by the best evidence for their performance with risk reduction (Bao et al., 2020; Tysiąc-Miśta & Dziedzic, 2020).

There is growing evidence that the angiotensin-converting enzyme 2 (ACE-2) is the main host cell receptor for SARS-CoV-2 severe acute respiratory syndrome (Brandão et al., 2021). After SARS-CoV-2 enters through the airways, the virus adheres to the mucosa of the upper respiratory epithelium from the recognition and binding of the viral surface protein, called protein S, to the ACE-2 receptor, allowing the virus to enter the target cell (Jin et al., 2020; Prajapat et al., 2020; Zhou et al., 2020). And the respiratory cell tropism causes respiratory symptoms.

These receptors are highly expressed in various types of cells, which can determine lesions in different organs, such as the lingual mucosa and the salivary glands (Xu, Li et al. 2020; Xu, Zhong et al 2020; Wang & Xu, 2020). The interaction of SARS-CoV-2 with ACE-2 receptors on tongue and salivary gland epithelial cells may alter the sensitivity of the taste buds, which may explain the development of dysgeusia in patients with COVID-19 (Mariz et al., 2020).

It is important to understand that SARS-CoV-2 can also infect and replicate in keratinocytes, oral fibroblasts and cells lining the epithelium of the salivary gland ducts resulting in painful oral ulcers (Mariz et al., 2020; Sungnak, Huang & Bécavin, 2020; Xu, Li et al., 2020; Xu, Zhong et al., 2020; Zou et al., 2020).

Oral signs and symptoms related to COVID-19 are taste disorders, nonspecific oral ulcerations, scaly gingivitis, petechiae and co-infections, such as candidiasis (Amorim dos Santos et al. 2020; Cebeci Kahraman & Çaşkurlu, 2020; Martín Carreras- Presas et al. 2020). However, it is still uncertain whether these manifestations may be a typical clinical pattern resulting from direct SARS-CoV-2 infection or a systemic consequence, given the possibility of co-infections, impaired immune system and adverse drug reactions (Amorim dos Santos et al., 2020; Dziedzic & Wojtyczka 2020).

In view of the literature, the clinical studies of COVID-19 do not often describe oral symptoms. Despite the lack of reported studies, dysgeusia has been the most described oral manifestation, with an overall prevalence of 45%. The positive association with mild and moderate degrees of severity, and also with females, being reported with moderate certainty of evidence (Amorim dos Santos et al., 2020).

As the prevalence of clinical manifestations is still unknown, the range of manifestations of COVID-19 in the oral cavity has been considered of wide and current interest. Therefore, understanding the pathogenesis of COVID-19 infection is vital for the control of possible oral lesions and infections that may appear in dental offices associated with patients with COVID-19.

2. Methodology

The present descriptive study consists in a case report series developed from the collaboration between hospital dentistry teams from different institutions located in different regions of Brazil. The study was submitted and approved by the research ethics committee, under CAAE protocol 45065721.6.0000.8447. The participants in this study agreed to the Free and Informed Consent Term, respecting the Declaration of Helsinki ethical principles (Pereira et al., 2018).

3. Case Reports

Case 1: Male patient, 24 years old, came to the dental office complaining of pain, burning and multiple oral lesions, reported fever (39.2ºC) for 3 days. Vital signs were normoreactive. The patient does not have comorbidities or use any

medication or drugs. Inflammatory lymphadenopathy was observed in the submandibular, pre and post auricular regions. It was observed in the clinical exam: labial commissure with areas of vesicle and ulcerations, erosion on the dorsum and lateral side of the tongue showing extensive depapilated areas (Figures 1A and 1B). Free and inserted marginal gum showed edema and generalized flushing (Figure 1C). Multiple ulcers in the mucous jugal region, in the soft palate and uvula were observed (Figure 1D and 1E). The oropharynx and tonsils were erythematous and hyperplastic (Figure 1F). The clinical condition is compatible with recurrent intraoral herpetic infection. Complementary tests (hemogram) show a significant decrease in lymphocytes and platelets. RT-PCR for Sars-CoV-2 was non-reactive. The herpes simplex protocol was followed for treatment (acyclovir 200mg every 6 hours for 5 days, ascorbic acid 1g per day and for mucosal hygiene 0.12% chlorhexidine was indicated every 12 hours for 7 days). The lesions disappeared completely in 14 days. In view of the COVID-19 pandemic and several reports related to similar oral changes in patients infected with SARS-CoV2 and the possibility of an immunological window for RT-PCR, serology for COVID-19 (IgM / IgG) - CLIA was requested. The result showed, reactive IgG and non-reactive IgM.

Figure 1. Vesicles and ulcerations areas in labial commissure and lateral side of the tongue (A); erosion on the dorsum of the tongue with extensive depapilated areas (B); edema and generalized flushing in free and inserted marginal gum (arrows, C); multiple ulcers in the soft palate (arrows, D), in the mucous jugal region and uvula (arrows, E); oropharynx and tonsils were erythematous and hyperplastic (arrows, F).

Source: Own authorship.

Case 2: Female patient, 66 years old, transferred from an urgent and emergency hospital in the state of Paraíba to a referral hospital towards neurological surgery for treatment of dehiscence of a frontal surgical wound with bone exposure, with drainage of pyogenic secretion. However, the antigenic test for COVID-19 results positive, furthermore, chest tomography was performed 3 days after diagnosis, revealing multiple ground-glass opacities and sparse consolidation foci, which approximate 50% of pulmonary involvement. The patient was referred from the COVID-19 ward to COVID-19 ICU, needing to be intubated on mechanical ventilation throughout hospitalization, with posterior tracheostomization to continue with mechanical ventilation. During hospitalization at the COVID-19 ICU (30 days after diagnosis), the Dentistry team was called in to assess

oral lesions presented by the patient. In the analysis of vital signs, it was observed that the patient was tachypneic and hemodynamically compensated at the expense of noradrenaline. In the complementary exams iron deficiency anemia was observed, moreover falling leukocytes, high values of urea and creatinine, normal glycemia and INR 2 were detected. The patient used Clexane as an anticoagulant, polymyxin B (13 days), amikinine (4 days), anidulafungin (13 days), methadone and norepinephrine. In the dental evaluation, it was observed that the patient had trismus. No inflammatory lymphadenopathy or skin changes were observed. On clinical examination, multiple ulcerated lesions were seen on the dorsum of the tongue, upper and lower labial mucosa and labial commissure with areas of ulcerations and crusts (Figure 2). Free and inserted marginal gum with normal appearance. For treatment, a lip hydration protocol was followed with the placement of gauze pads with AGE oil to remove the crusts and the application of a topical corticoid (Clobetasol at 0.05%) in the lesions 3 times a day for 5 days. For mucosal hygiene, 0.12% chlorhexidine was indicated every 12 hours for 7 days. The lesions disappeared completely in 10 days.

Figure 2. Multiple ulcerated lesions on upper and lower labial mucosa and labial commissure with areas of ulcerations and crusts.

Source: Own authorship.

Case 3: Female patient, 87 years old, diagnosed with COVID-19 (positive IGM and IGG in the rapid test and non-detectable RT-PCR) and urinary sepsis was transferred from a smaller hospital to the ICU of a COVID-19 hospital reference. On chest tomography, multiple ground-glass opacities with bilateral multifocal distribution were observed, with an approximate extension of less than 50% of pulmonary involvement. During admission to the COVID-19 ICU, the patient required orotracheal intubation for 10 days, and the Dentistry team was called in to assess oral lesions presented by the patient. In vital signs analysis, it was observed that the patient had saturation varying between 91 and 96%, breathing spontaneously with O2 supplementation. Complementary tests revealed normal leukocytes, preserved renal function, falling inflammatory markers and hypokalemia. The patient used dexamethasone, liquemine and AAS. In the dental evaluation, skin and oral mucosa lesions were observed, as well as submandibular, pre and post auricular inflammatory lymphadenopathy. In the clinical examination, it was observed: total edentulous patient with ulcerated areas on the lower lip, labial commissure and on the dorsum of the tongue (close to the apex) (Figure 3). No lesions were observed in the region of the jugal mucosa, gingival pad and palate (soft and hard). In the oropharynx region, the tonsils were erythematous. The clinical condition was compatible with stomatitis, with differential diagnosis of perioral pressure ulcer. For treatment, a protocol was followed with the use of a topical corticoid (clobetasol gel 0.05%) to be applied 3 times a day for 5 days and lip hydration with AGE oil 2 times a day. For mucosal hygiene, 0.12% chlorhexidine was indicated every 12 hours for 7 days. The lesions disappeared completely in 14 days.

Figure 3. Total edentulous patient with ulcerated areas on the lower lip and labial commissure.

Source: Own authorship.

Case 4: A 34-year-old female patient attended a dental appointment at the Primus Odontologia Institute in Curitiba, complaining of extreme burning on her hard palate, making it impossible for her to eat properly and drink liquids at a hot temperature, with citrus content or acidic pH. Salty foods also reported discomfort, which led to an important change in diet due to the presence of lesions and increased burning as described. On physical examination, he had no abnormal lymph nodes. Vital signs were normal, with no comorbidity; and in the anamnesis, the patient reported not using any medication. On oral examination, ulcerated, erythematous and vesicle regions were observed in the region of inserted gingiva and hard palate. In the middle and posterior third of the hard palate was compatible with recurrent intraoral herpetic infection (Figure 4A), these injuries were probably the cause of the constant oral burning presented in feeding. Complementary tests (hemogram) with mild lymphopenia. RT-PCR for Sars-CoV-2 was reagent and serology for COVID-19 (IgM / IgG) - CLIA were only reagents for IgG. The proposed treatment was low laser intensity application (660 nm range). It was applied by scanning with a dose of 3J, every 48 hours, for 1 week in all injured area, and mouthwashes of 0.12% chlorhexidine 2X a day. After 7 days, in the fourth session, the patient no longer reports burning, returns to eating normally and there is a visible improvement in the region irradiated with the laser, showing an evident reduction in the erythematous area and total remission of the vesicle lesions. After 14 days, the lesions disappeared completely (Figure 4B).

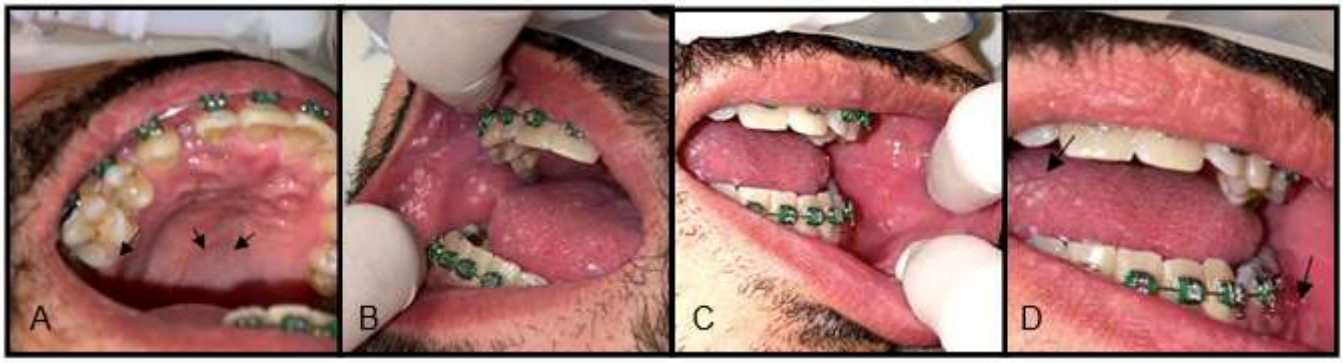
Figure 4. Lesions in the middle and posterior third of the hard palate was compatible with recurrent intraoral herpetic infection (A) and the total remission after the treatment (B).

Source: Own authorship.

Case 5: A 43-year-old male patient was admitted to the Santa Casa de Mercy in Porto Alegre complaining of headache, myalgia, fever above 38 °C, persistent diarrhea for 6 days and respiratory symptoms, with dyspnea in the 24 hours prior to admission. The RT-PCR for Sars-CoV-2 was a double test reagent, two days apart. Treatment was started with enoxaparin 40mg injectable solution every 24h, 6mg dexamethasone every 24h and analgesics. Vital signs were within normal

standards. Complementary tests (blood count) show a significant decrease in lymphocytes and platelets from the first to the third day of hospitalization. The patient did not present comorbidities or use any medication or drugs. Submandibular lymphadenopathy was observed, whose lymph nodes were mobile and painful. In the oral clinical examination, papules with an erythematous and umbilicated center showing the inflammation of the ductal epithelium of the smaller palatine glands was observed (Figure 5A). In the jugal mucosa, alveolar mucosa and dorsum of the tongue, a clinical condition compatible with pseudomembranous candidiasis was evident (Figures 5B, 5C and 5D). For the treatment of candidiasis, a 50 mg / day fluoconazole protocol was followed for 7 days and for oral mucosa hygiene, the protocol with 0.12% chlorhexidine every 12 hours was indicated. In 16 days, the patient presented remission of the oral lesions.

Figure 5. Papules with an erythematous and umbilicated center showing the inflammation of the ductal epithelium of the smaller palatine glands (arrows, A); a clinical condition compatible with pseudomembranous candidiasis was evident in the jugal mucosa (B and C), alveolar mucosa and dorsum of the tongue (arrows, D).



Source: Own authorship.

4. Discussion

Different clinical manifestations are being observed during SARS-CoV-2 infection, including oral manifestations directly associated with the virus, secondary lesions associated with systemic repercussions related to the virus, or secondary lesions to the treatment of patients with SARS-CoV-2 (Brandão et al., 2021; Mariz et al., 2020). In this series of cases, lesions similar to other pathological changes were observed in terms of the form, type and locations of lesions.

The differential diagnosis of probable injuries due to SARS-CoV-2 and late stage of recurrent oral herpes lesions has been a recent challenge, as well as, due to intubation, the report of secondary injuries such as perioral pressure ulcers (Amorim dos Santos et al., 2020; Sleiwah et al., 2020; Zingarelli et al., 2020). The alterations in salivary glands have also been observed microscopically, with intense lymphocytic infiltration (Soares et al., 2020).

To better understand this mucosal tropism of the virus, some mechanisms related to its replication have been studied. SARS CoV-2 uses angiotensin-converting enzyme 2 (ACE-2) to enter cells, so the presence, quantity and location of ACE-2 receptors can determine sites of greater viral replication (Salamanna et al., 2020). Therefore, the existence of ACE-2 receptors on the tongue, salivary glands and oral mucosa may explain regions for greater contamination and presence of SARS CoV-2. These receptors on the tongue, salivary glands and oral mucosa may be related to the development of dysgeusia, ulcerations, inflammation and erosion of the oral mucosa (Mariz et al., 2020; Tong et al., 2020; La Rosa et al., 2021). In most of the reported cases, lesions in different areas of the oral mucosa were observed, as well as reports of loss of taste and smell, which suggests a strong relationship between the loss of function of these cells caused by the virus.

According to Brandão et al., (2021) the interaction between SARS CoV-2 and ACE-2 can interrupt the function of oral keratinocytes and the epithelial lining of the salivary gland ducts, resulting in painful oral ulcers, which reinforces the evidence in the clinical case 5 and most of the cases that presented ulcerations.

The pathogenesis of oral lesions is still being investigated, but hypotheses are being formulated. For example, the presence of viral particles in cutaneous blood vessels could induce lymphocytic vasculitis by production of cytokines, such as interleukin-1 (IL-1), gamma interferon (IFN-y) and tumor necrosis factor alpha (TNF-α), by CD4 helper T lymphocytes and the migration of eosinophils, CD8 cytotoxic T cells, B cells and natural killer cells (NK) (Lee, Kossard & McGrath, 2008; Gianotti, 2020). Another possible hypothesis would be the correlation of SARS CoV-2 and the formation of micro thrombosis by increasing inflammatory reactivity in the vascular wall, reducing microvascular blood flow causing lack of oxygenation which could justify oral lesions such as ulcers, thrush, and macules (Brandão et al., 2021; Manalo et al., 2020; Cebeci Kahraman & Çaşkurlu, 2020; Ciccarese et al., 2020), showing the different possibilities of lesions in the oral cavity in all clinical cases presented.

Recent publications associate oral lesions with complications such as thrombocytopenia or even anticoagulated patients in a hospital environment (Cruz Tapia et al., 2020; Soares et al., 2020; Riad et al., 2020; Amorim dos Santos et al., 2020; Corchuelo & Ulloa, 2020). It is worth noting that in clinical case 1 the patient had significant thrombocytopenia and several ulcerative lesions in the oral cavity. In clinical cases 2,3 and 5, patients used antiaggregants or anticoagulants, which reinforces aspects related to possible ulcerations.

According to Cruz Tápia et al. (2020), clinical manifestations and histological findings suggest the possibility of the oral cavity presenting hematological vascular damage associated with SARS CoV-2.

According to Forbes et al. (2019), risks of reactivation of Herpes Simplex Virus type 1 (HSV-1) may increase when the patient is subjected to high levels of fatigue and stress, which may, perhaps, have occurred due to the presence of herpetiform lesions in patients referring to clinical cases 1, 4 and 5, where lymphopenia was also observed in the hemogram.

5. Final Considerations

The interaction of ACE-2 receptors with SARS-CoV-2 and the reduction of lymphocytes can be etiogenic mechanisms for the appearance of several oral manifestations, present in most clinical cases. The knowledge of the various pathologies manifested in the oral cavity of the patient infected by SARS-CoV-2 can be a prodromal sign that precedes the evolution of the disease to more severe clinical conditions. Thus, further studies are required to establish a robust relationship between different oral manifestations during SARS CoV-2 infection.

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