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Buccal tissue changes associated with covid-19: a literature review

Alterações nos tecidos bucais associadas à covid-19: uma revisão de literatura

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Luana Paula Borges da Costa e Silva
Lattes: 4984830802979669
Graduada em odontologia pela Escola Bahiana de Medicina e Saúde Pública
IE: Escola Bahiana de Medicina e Saúde Pública
E-mail: luanapbcs@gmail.com

Eduardo Cezar Lima Silva de Miranda
Orcid: 0000-0003-0632-5394
Lattes: 6842518403251405
Especialista em cirurgia e traumatologia bucomaxilofacial
IE: Escola Bahiana de Medicina e Saúde Pública
E-mail: eduardoclsm@gmail.com

Maria Cecília Fonsêca Azoubel
Orcid 0000-0003-0325-6370
Doutora em ciências médicas - UFC - CE
Prof adjunta Escola Bahiana de Medicina e Saúde Pública
E-mail: mcazoubel@bahiana.edu.br

ABSTRACT

On December 31, 2019, cases of pneumonia of unknown etiology began to appear in the city of Wuhan, China, associated with a wholesale seafood market that traded live animal species. In January 2020, the World Health Organization (WHO) declared Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) a public health emergency of global concern. The majority of those infected with SARS-CoV-2 have developed mild symptoms, such as dry cough, digeusia, and fever. However, a small proportion of the affected individuals presented a severe clinical picture, which led to systemic complications and caused many patients to die. Besides systemic symptoms, changes in the oral tissues have been clinically observed, such as taste disorders, non-specific oral ulcerations, desquamative gingivitis, petechiae, and co-infections, among others. Recent studies indicate that the oral mucosa may be the target of the virus, from the observation of the distribution of angiotensin-converting enzyme 2 (ACE2) in its epithelial cells. From this premise, the oral cavity may play an active role in the pathogenesis of the novel coronavirus. This article, of descriptive nature, aims to report the cases of alterations in the buccal tissues associated with COVID-19, present in the literature, through searches performed on the Pubmed portal.

Keywords: COVID-19, Oral manifestations, SARS-CoV-2.

1 INTRODUCTION

On December 31, 2019 , 27 cases of pneumonia of unknown etiology were identified in Wuhan City, Hubei Province, China[1]. These patients mainly presented clinical symptoms of dry cough, dyspnea, fever, and bilateral pulmonary infiltrates on imaging examination . All cases were related to the Whuan Seafood Wholesale Market, which sells fish and a variety of live animal species including birds, bats, marmots and snakes[1].

On January 7, 2020, the etiologic agent was identified by the Chinese Center for Disease Control and Prevention (CCDC), and was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and subsequently the disease was named COVID-19 by the World Health Organization (WHO)[2]. On January 30, 2020, the WHO declared the Chinese outbreak of COVID-19 to be a public health emergency of global concern, posing a high risk to countries with vulnerable health systems [3].

After this statement, several studies on the new virus were initiated, among them a Chinese study by Cassaniti et al. (2020)[4] that showed a high expression of angiotensin-converting enzyme 2 (ACE2) receptors in the epithelial cells of the oral mucosa, suggesting that the oral cavity may play an active role in the pathogenesis of COVID-19[4] . The main source of transmission is the saliva droplets when an infected person coughs, sneezes or speaks; thereby the virus is released into the respiratory secretions**.** The viruses in these droplets can infect others if they make direct contact with the mucous membranes**.** Infection can also occur indirectly by touching a contaminated surface and then touching the eyes, nose, or mouth[5] , as SARS-CoV-2 remains viable in aerosol for 3 hours, plastic or stainless steel for up to 72 hours, copper for up to 4 hours, and cardboard for 24 hours[6] . Symptomatic patients are believed to be more contagious .[7]

Case reports have suggested[8] the occurrence of oral manifestations in patients with COVID-19. Such manifestations include pain, desquamative gingivitis, ulcers and blistering. All three cases reported, had ulcers or blisters in the oral cavity[8] . These were common elementary lesions seen in other viral processes, such as herpetic gingivostomatitis[9] .

Whenever a new disease appears in the world, it is necessary to pay attention to all types of manifestations that may be related to it. Considering that many pathologies present oral manifestations, it is important for the dental surgeon to recognize the possible clinical signs of COVID-19 in the oral cavity, associate them with the general clinical picture and differentiate them from other diseases with an immunological background. The present article aims at reporting the cases of oral tissue manifestations associated with COVID-19 found in the literature.

2 METHODOLOGY

The present study is a literature review of a descriptive nature, carried out by a broad search, consisting mainly of scientific articles, since the theme addressed is still very recent in the literature.

The electronic search was done through the Pubmed portal and the key words used were COVID-19, SARS-CoV 2 and oral manifestations. In the English language, the search was made with the following words: COVID-19, oral manifestations and SARS-CoV-2. Both present in the Health Science Descriptors (DeCS).

After the bibliographic survey, the criteria for inclusion selection covered the analysis of papers and their classification by topics addressed according to the proposal of the literature review: changes in the Oral Cavity Associated with COVID-19. The search covered international and recent publications, in the period between 2019 and 2021.

3 LITERATURE REVIEW

3.1 ANGIOTENSIN-CONVERTING ENZYME 2 (ECA2) RECEPTORS X COVID-19

The study by Xu et al. (2020)[10] brought findings suggesting that angiotensin-converting enzyme 2 (ACE2) plays an important role in cell entry , therefore cells expressing it may act as target cells and are susceptible to COVID-19 infection[10] . Another study, done by Xu et al. (2020)[11] reported the expression of ACE2 in the oral mucosa, mainly in the dorsal tongue and that this enzyme functions as a host receptor on which SARS-CoV-2 virus binds[11].

Brandão et al. (2020) [12] reported that the oral mucosa may be the target of the virus due to the distribution of ECA2 on the tongue and salivary glands, and may determine the route of infection by SARS-CoV-2. According to the authors, the interaction of this virus with ECA2 may disrupt the function of oral keratinocytes and the epithelial lining of the salivary gland ducts, resulting in painful oral ulcers. After infection of the oral keratinocytes/glandular tissues, there is increased permeability of the cell walls to pathogens and viral replication in the cells lining the oral mucosa, leading to ulcers and necrosis[12]. The interaction of SARS-CoV-2 with ECA2 receptors may also impair taste bud sensitivity, which could induce dysfunctional taste responses[13].

3.2 ETIOPATHOGENESIS OF ORAL MANIFESTATIONS

The etiopathogenesis of oral manifestations in patients diagnosed with COVID-19 is not yet elucidated, due to a small number of reported studies and multiple clinical aspects. Such aspects suggest co-infections, impaired immunity, and adverse reactions, rather than a genuine oral

mucosal infection caused mainly by SARS-CoV-2, as reported by Santos et al. (2020)[13] . N this study, the question arises: whether these manifestations could be a typically clinical pattern resulting from direct SARS-CoV-2 infection or a systemic consequence, given the possibility of co-infections, immune system depression, and adverse reactions to medical treatment[13] .

In the few cases reported in the literature, there is a great diversity of oral signs and symptoms, which compromises the conclusion about its etiology. The most frequently reported were: taste disturbances, non-specific oral ulcerations, desquamative gingivitis, petechiae, and co-infections such as candidiasis[13] . Dysgeusia, hypogeusia, and ageusia represented the subtypes of taste disorders. Opportunistic infectious lesions (fungal, viral, and bacterial) and autoimmune and inflammatory lesions (stomatitis, gingivitis) were considered oral cavity disorders, as were salivary gland disorders and other oral signs and symptoms in mucosal tissue . [13]

3.3 CLINICAL FEATURES OF PATIENTS WITH COVID-19

Brandão et al. (2020)[12] reported 8 cases of COVID-19 infection , with the appearance of oral necrotic ulcers and aphthous ulcerations that developed early in the course of the disease, and in regions expressing ACE2 receptors, after the development of dysgeusia. The oral manifestations appeared concomitant with loss of taste and odor . Oral lesions were more severe and generalized in patients with a more advanced age group. The lesions observed showed two well-defined and distinct patterns: one similar to aphthous, like ulcers in young patients with mild cases of COVID-19 and another with more widespread patterns, resembling necrotic ulcers of Herpes simplex virus (HSV-1), in the most severe cases and in immunosuppressed elderly .[12]

In a detailing of case reports described by Brandão et al. (2020)[12] , four of them were young patients, aged between 28 and 35 years, without relevant past medical history and with a positive diagnosis for COVID-19, the oral manifestations present were: oral ulcer on the tonsillar pillar, where the lesion was superficial and with a circular pattern, covered by a fibrinopurulent membrane and surrounded by an erythematous halo . Painful ulcers were also observed on the ventral region of the tongue, with a whitish pseudomembrane surrounded by an erythematous halo. In addition, aphthous ulcers were found on the upper, lower labial mucosa, on the lateral border of the tongue, and multiple ulcers on the apex and lateral borders of the tongue . In both reported cases, the patients had ageusia or anosmia, had no history of oral ulcers and had regression of lesions after recovery from COVID-19 infection .[12]

Still related to the cases reported by Brandão et al. (2020)[12] , the other clinical pictures described were elderly patients, aged between 71 and 82 years, with relevant systemic conditions

and some similar, such as: chronic obstructive pulmonary disease (COPD), hypertension, and diabetes. In all cases, a saliva sample was collected to perform the polymerase chain reaction (PCR) test for herpes simplex virus (HSV-1). Only one of the patients tested negative to saliva PCR for HSV-1. The clinical sign present in the oral cavity was: shallow aphthous ulcers of varying sizes and irregular margins, covered with a mucopurulent membrane, suggesting superficial necrosis on the mucosa of the upper and lower lip, as well as the anterior dorsal tongue.

Other clinical signs presented were: small hemorrhagic ulcerations affecting the upper and lower lip, and also focal areas of shallow necrosis on the anterior dorsal region of the tongue and an ulcer on the right lateral border of the tongue, as well as a discrete area on the anterior hard palate affected by petechiae and a shallow necrotic area. A painful necrotic ulceration was also observed on mucosa of the right lower lip. All patients who tested positive for HSV-1, started treatment with intravenous acyclovir 250 mg /m^2 , 3 times a day, for 7 days, but showed no clinical improvement. Therefore, as an adjunctive measure to control the pain associated with the oral ulcers, photobiomodulation therapy (PBMT) was initiated for ten consecutive days. Patients reported relief of symptoms and regression of oral lesions around 10 days after phototherapy .[12]

Another work by Santos et al. (2020)[14] addressed the case of a male, 67 years old , transplanted and for this reason was using immunosuppressants regularly, with medical history of coronary heart disease, systemic hypertension, polycystic kidney disease . After 24 days of hospitalization for COVID-19, a persistent white plaque was observed on the dorsum of the tongue. This lesion was previously treated by physicians with intravenous fluconazole and oral nystatin, but no regression was observed. In addition to the white plaque, the dental surgeon also observed multiple yellowish ulcer spots on the dorsum of the tongue reminiscent of the end stage of recurrent herpetic lesions. A tongue scraping culture was performed, which was compatible with *Saccharomyces cerevisiae*[14]. Skin lesions were not observed during the patient's physical examination. At this point, the patient maintained the antifungal drugs, rinsed with chlorhexidine digluconate (0.12%), without alcohol, and made daily applications of 1% hydrogen peroxide. After two weeks, there was complete remission of the white lesions on the dorsum of the tongue[14]. In a new intraoral examination, it was observed that the patient had an asymptomatic geographic tongue classified as severe according to the recently published severity index[15].

The authors Sinadinos and Shelswell (2020)[16] described, reports of three patients with oral manifestations. One of these patients had confirmed COVID-19 infection and two patients were awaiting serologic testing for confirmation. Both patients reported pain on the palate or tongue. In the first case, the patient had lesions similar to recurrent herpetic stomatitis. The second case,

revealed unilateral palatal ulceration with no history of previous herpetic infection. In the last case, the patient started to develop dermatological symptoms, blisters on the labial mucosa and desquamative gingivitis. All cases were treated with topical antiseptics and had regression of the lesions .[16]

Riad et al. (2020)[17] published an article in the year 2020, in which they gathered eight cases present in the literature that reported the oral manifestations adjacent to SARS-CoV-2 infection. Riad et al. (2020)[17] published an article in the year 2020, in which they gathered eight cases present in the literature that reported the oral manifestations adjacent to SARS-CoV-2 infection. The signs described were: erythematous lesions, erosions on lips and oral mucosa, irregular asymptomatic ulcer on the dorsal region of the tongue or painful recurrent herpetic stomatitis on palate, accompanied by sore throat and several small painful ulcers on palate unilaterally. Blisters on the inner labial mucosa with desquamative gingivitis, tongue pain, and several small painful ulcers with irregular margins on the hard palate and tongue were also noted. Other clinical signs reported were severe halitosis with erythema and generalized gingival edema, and necrotic interdental papillae with unprovoked gingival bleeding[17]. The authors concluded, based on these eight reported cases, that the masticatory mucosa was affected in 75% of cases (2 on the dorsum of the tongue, 3 on the hard palate, 1 on the gingival mucosa), while 25% of manifestations were on the lining mucosa (1 on the labial mucosa, 1 on the buccal mucosa)[17].

In addition to these reported manifestations, Patel and Woolley (2020)[18] observed a spontaneous increase in the prevalence of necrotizing periodontal disease (NPD) in proportion to the number of confirmed cases of COVID-19. According to the authors the etiology of NPD lesions may be associated with bacterial co-infections, occurring orally in patients with COVID-19. [18]This study reported the case of a patient seen at King's University Hospital with necrotizing periodontal disease (NPD) and suspected COVID-19. The patient was a 35-year-old female, with no medical history of comorbidities and was seen in the dental emergency department reporting fever, halitosis, severe gingival pain, and bleeding. The fever occurred 3 days prior to any oral symptoms. She presented with bilateral submandibular lymphadenopathy, and intraoral examination confirmed severe halitosis, erythema and generalized gingival edema, and necrotic interdental papillae in both maxillary and mandibular labial sextants. He also presented spontaneous bleeding in the gingival sulcus. Based on these clinical findings, the diagnosis was necrotizing gingivitis. Although COVID-19 was suspected, it was not possible to perform the test at the time of the clinical manifestations. The patient was treated with antibiotic therapy: 400 mg metronidazole three times a day for 5 days, 0.12% chlorhexidine mouthwash twice a day for 10

days. After 5 days, the patient returned and complete resolution of the clinical condition was noted.[18]

Marouf et. al. (2021) [19] reported the association of periodontal disease with the severity of coronavirus infection, through a case-control study at Hamad Medical Corporation (HMC) Hospital in the state of Qatar. In this study, two groups were created. The case group, consisting of patients with complications of COVID-19: deaths, assisted ventilation, and ICU admissions, and the control group, consisting of patients who were discharged without major complications. Periodontitis was defined when bone loss was detected in two or more non-adjacent teeth, and interdental bone loss was measured in the posterior sextants using the cemento-enamel junction (CEJ) and total root length as reference. Periodontal condition was evaluated by posterior interproximal radiographs and panoramic radiographs.

Thus, patients were classified into two groups: early periodontitis (stage 0-1), in which bone loss was less than the coronal third of the root length on interproximal radiographs; and the periodontitis group (stage 2-4), with bone loss greater than the coronal third of the root length on interproximal radiographs. A total of 568 patients with a diagnosis for COVID-19 were included for the analysis. Among these, 40 had complications (cases) and 528 were discharged without any complications (controls). Of this total, 258 had periodontitis and 33 of these had complications. Of the remaining 310 patients without a diagnosis of periodontitis, only 7 had a worsening of the infection. Blood levels of Glycosylated Hemoglobin (HbA1c), Wihte Blood Cells (WBC) and C-Reactive Protein (CRP) were significantly higher in patients with COVID-19 and periodontal disease, than in those without periodontal disease. Thus, this study concluded that successful treatment of periodontitis results in an improvement in serum markers of systemic inflammation, as well as systemic metabolic control. It further identified that the risk of COVID-19 complications was significantly higher among patients with moderate to severe periodontitis compared to those with milder periodontitis or no periodontitis[19].

4 DISCUSSION

COVID-19 is a recently described pathology, i.e., unprecedented, and it has brought numerous impacts on general health. Many of its manifestations still lack further scientific knowledge, about its pathophysiology, clinical course and magnitude. [13,17]

Regarding systemic health, manifestations are reported to include pulmonary impairment[20], cardiovascular disorders[21], renal and hepatic dysfunction[21], and various sequelae with varying frequencies, such as neurological disorders[20,22,23] and chronic fatigue[24].

Regarding the oral cavity, COVID-19 is also associated with clinical manifestations, which represent an alteration of homeostasis conditions, such as necrotic and aphthous ulcers[12], white plaque[14], vesicles[16], erosions on lip and oral mucosa[17], and erythematous lesions[17].

Recent studies have reported that there is an expression of ACE2 in the oral mucosa[11] and that it plays an important role in the entry of the virus into the cell; therefore, cells expressing these receptors become hosts of SARS-CoV-2[10]. Thus, it is suggested that the oral cavity may be involved in the pathogenesis of COVID-19[4]. According to Brandão et al. (2020)[12], this receptor-virus interaction may cause a pause in the functionability of oral keratinocytes and salivary glands, and may result in ulcers and necrosis[12].

The eight cases reported by Brandão et al. (2020)[12] involving patients affected by COVID-19, presented oral necrotic ulcers, aphthous ulcerations, and these manifestations appeared concomitantly with dysgeusia. Santos et al. (2020)[13] pointed out in their article that the interaction of SARS-CoV-2 with ECA2 receptors may interfere with taste bud sensitivity, which would explain this loss of taste[13].

Some authors noted the presence of ulcers, vesicles on the mucosa, and scaly gingivitis. Carreras-Presas et al. (2020) [8] described manifestations that included pain, desquamative gingivitis, ulcers and vesicles. [8]Sinadinos and Shelswell (2020) [16] also described vesicles on the labial mucosa, desquamative gingivitis and herpes-like lesions[16]. Riad et al. (2020)[17], Santos et al. (2020)[13] and Sinadinos and Shelswell (2020)[16] evidenced the presence of lesions similar to recurrent herpetic stomatitis.

In addition to these intraoral clinical manifestations, other authors have observed relationships between COVID-19 and periodontal disease. Patel and Woolley (2020) [18] reported a case of suspected COVID-19 in which the clinical diagnosis was necrotizing gingivitis. Similarly, Marouf et. al. (2021) ,[19] through a case-control study, suggested a relationship of periodontal disease with the severity of SARS-CoV-2 infection.

In addition to the alterations in the oral cavity, other systems of the organism have also suffered the influence of the new coronavirus, in highlight, the central nervous system (CNS). Both present similar etiopathogenesis, associated to the affinity of membrane receptors of the angiotensin-converting enzyme 2, which is also expressed in the nervous tissue, becoming, therefore, a possible itinerary of brain invasion of the virus[22] . From this evidence, some CNS alterations have been described, such as: cases of viral encephalitis, meningitis, acute hemorrhagic necrotizing encephalopathy .[23]

It is virtually unanimous in the available scientific literature that COVID-19 is associated with changes in the oral cavity. However, these manifestations do not present a uniform pattern of color, shape, site or host. Added to this is the fact that the evidence available to date comes from case reports, which is perfectly justifiable since this is a recently described pathology of which there is no history of knowledge. Clearly, this limits the finding of conclusive evidence in this respect, but on the other hand, it motivates the continuity in the search for this knowledge, with the major objective of helping in the diagnosis and management of patients affected by COVID-19.

5 FINAL CONSIDERATIONS

The oral manifestations of COVID-19 reported in the present studies include: ulcers; aphthous lesions; petechiae; white plaque; recurrent herpetic stomatitis-like lesions; desquamative gingivitis; erythematous lesions; erosions on the lip and oral mucosa; and gingival edema.

Due to the actuality of the theme, there are still few studies in the literature that report the alterations in the oral cavity and that elucidate, with scientific support, the direct or indirect participation of SARS-CoV-2 in the appearance of these lesions;

More studies are needed to establish diagnostic and etiological relationships regarding these manifestations;

The studies present in this review broaden the picture of COVID-19 beyond respiratory complications, showing the importance of understanding the complexity of the virus in both the medical and dental fields.

REFERENCES

Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan,China: The mystery and the miracle. *J Med Virol*. 2020; 92:401-02. doi: 10.1002/jmv.25678

World Health Organization. (11 February 2020). WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Retrieved from https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020

World Health Organization. (1 February 2020). Novel Coronavirus (2019-nCoV) Situation Report – 12. Retrieved from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200201-sitrep-12-ncov.pdf?sfvrsn=273c5d35_2

Cassaniti I, Novazzi F, Giardina F, Salinaro F, Sachs M, Perline S, et al. Performance of VivaDiag COVID-19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department. *J Med Virol*. 2020;92:1724–27.doi:10.1002/jmv.25800

Joseph T. Internacional pulmonologist´s consensus on covid-19. 2ª edição. [internet]. 22/04/2020. [citado em 06/06/2020]; 2:1-11. Disponível em: https://www.saudedafamilia.org/coronavirus/artigos/international_pulmonologists_consensus.pdf

Doremalen NV, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564-7. doi:10.1056/NEJMc2004973

Casanova LM, Jeon S, Rutala WA, Weber DJ, Sobsey MD. Effects of air temperature and relative humidity on coronavirus survival on surfaces. *Appl Environ Microbiol*. 2010;76(9):2712-7. doi:10.1128/AEM.02291-09

Carreras-Presas CM, Sánchez JA, López-Sánchez AF, Jané-Salas E, Pérez MLS. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. *Oral Dis*. 2020; 10: 1-10. doi: 10.1111/ODI.13382

Scully C, Samaranayake LP. Emerging and changing viral diseases in the new millennium. *Oral Dis*. 2016; 22(3):171-9. doi:10.1111/odi.12356

Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci*. 2020; 63(3):457-60. doi: 10.1007/s11427-020-1637-5.

Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12(8):1-5. doi: 10.1038/s41368-020-0074-x.

Brandão TB, Gueiros LA, Melo TS, Prado-Ribeiro AC, Nesrallah ACFA, Prado GVB, et al. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;00(00)1-7. doi: 10.1016/j.oooo.2020.07.014.

Santos JA, Normando AGC, Silva RLC, Acevedo AC, De Luca Canto G, Sugaya N, et al. Oral Manifestations in Patients with COVID-19: A Living Systematic Review. *J Dent Res*. 2020;00(0):1-14. doi: 10.1177/0022034520957289.

Santos JA, Normando AGC, Silva RLC, Paula RM, Cembranel AC, Silva ARS, et al. Oral mucosal lesions in a COVID-19 patient: New signs or secondary manifestations? *Int J Infect Dis*. 2020;97:326-28. doi: 10.1016/j.ijid.2020.06.012.

Picciani BLS, Santos LR, Teixeira-Souza T, Dick TNA, Carneiro S, Pinto JMN, et al. Geographic tongue severity index: A new and clinical scoring system. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;129(4):330-338. doi: 10.1016/j.oooo.2019.12.007.

Sinadinos A, Shelswell J. Oral ulceration and blistering in patients with COVID-19. *Evid Based Dent*. 2020;21(2):49. doi: 10.1038/s41432-020-0100-z.

Riad A, Klugar M, Krsek M. COVID-19-Related Oral Manifestations: Early Disease Features? *Oral Dis*. 2020;00:1-3. doi: 10.1111/odi.13516.

Patel J, Woolley J. Necrotizing periodontal disease: Oral manifestation of COVID-19. *Oral Dis*. 2020;00:1-2. doi: 10.1111/odi.13462.

Marouf N, Cai W, Said KN, Daas H, Diab H, Chinta VR, et al. Association between periodontitis and severity of COVID-19 infection: A case-control study. *J Clin Periodontol*. 2021;48(4):483-491. doi: 10.1111/jcpe.13435

Wang F, Kream RM, Stefano GB. Long-Term Respiratory and Neurological Sequelae of COVID-19. *Med Sci Monit*. 2020;26:e928996. doi: 10.12659/MSM.928996.

Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview. *Clin Imaging*. 2020;66:35-41. doi: 10.1016/j.clinimag.2020.05.013.

Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*. 2020;11(7):995-998. doi: 10.1021/acschemneuro.0c00122.

Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55-58. doi: 10.1016/j.ijid.2020.03.062.

Wostyn P. COVID-19 and chronic fatigue syndrome: Is the worst yet to come? *Med Hypotheses*. 2021;146:110469. doi: 10.1016/j.mehy.2020.110469.