

Review

An integrative review of oral manifestations in patients with COVID-19: signs directly related to SARS-CoV-2 infection or secondary findings?

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Abstract

We conducted an integrative review on oral manifestations in patients with COVID-19 based on the current available literature evidence. A bibliographic search was carried out on March 11, 2021, among published studies in the years 2019–2021 in the PubMed database and based on the search strategy (“COVID-19” AND “oral lesions” OR “oral mucositis” OR “oral manifestation”). After applying the inclusion and exclusion criteria, 29 articles were considered suitable for this review. A total of 110 cases of patients with COVID-19 who had oral manifestations were reported. The presence of ulcerated lesions was the most common finding, having a herpetiform and aphthous clinical pattern observed in most cases. Macules, petechiae, hemorrhagic blisters, pustular enanthem, mucositis, and halitosis were also among the most frequently described oral manifestations. The tongue was the most commonly affected site, followed by the palate and lip. Most of the reported cases were diagnosed only by the clinical aspect of the lesion associated with a positive SARS-CoV-2 test or the presence of other COVID-19 symptoms. Current scientific evidence still could not affirm that most of the oral lesions observed in patients with COVID-19 are related to the virus’s direct or indirect action on the oral mucosa. To confirm this association, prospective and longitudinal studies are further needed, together with a larger number of patients, complemented by histopathological examination of these lesions. Additionally, molecular techniques, such as immunohistochemistry and in situ hybridization, may be necessary to perform the differential diagnosis with other oral lesions.

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Introduction

COVID-19 is an infectious disease caused by the new coronavirus, SARS-CoV-2, showing clinical signs that range from

asymptomatic infections to severe respiratory syndromes. When symptomatic, the characteristic manifestations usually appear between the 2nd and the 14th days after exposure to the virus. They include fever, cough, shortness of breath, fatigue, myalgia,

headache, anosmia, taste disorders, sore throat, nasal congestion, nausea, vomiting, and diarrhea.¹

As the COVID-19 pandemic progresses, knowledge about the disease also evolves with the availability of new scientific evidence. Several reports of dermatological changes in patients with COVID-19 have been published, including symptoms such as erythematous rash, urticaria, vesicles, petechiae, and *livedo reticularis*.^{2–5} Changes in the oral mucosa have also been highlighted in some studies,^{6–26} although it is still impossible to be sure that the virus induces them.

The entry of the SARS-CoV-2 virus into the host cell, enabling infection, occurs through the angiotensin-converting enzyme 2 (ACE2), a transmembrane protein that functions as a virus receptor. This protein is expressed in high concentrations in the lungs, esophagus, ileum and colon, cholangiocytes, myocardial cells, renal tubular cells, and the bladder urothelial cells.²⁷ The presence of the virus is also found in oral cavity epithelium, with high expression in tongue and salivary gland duct epithelium.²⁸ Thus, these previous findings indicate that oral cavity may be a target for the SARS-CoV-2.^{6,27}

The distribution and expression of ACE2 in the oral cavity explain findings such as the presence of virus in the saliva of infected patients,²⁹ since contaminated salivary glands can act as a reservoir for eliminating the virus in saliva and also the high incidence of gustatory impairment since taste buds are mostly concentrated on the dorsal tongue surface.³⁰ A recent systematic review showed that almost half of patients with COVID-19 (i.e., 49.8%) had presented taste disorders.³¹

This integrative review was designed to analyze current evidence pertaining to oral manifestations in patients with COVID-19 and pointing to some gaps in knowledge that still need to be filled with new studies about the disease.

Material and methods

The question that moved the study carried out in this integrative review was: are there any other oral manifestations besides the taste disorders associated with COVID-19? The methodology for the integrative review followed the phases: (i) establishment of the research question; (ii) search of relevant studies; (iii) selection of studies based on pre-established inclusion criteria; (iv) data analysis and preparation; and (v) summary and communication of information.³²

The search was carried out on March 11, 2021, in the PubMed database. The search strategy employed included: (“COVID-19” AND “oral lesions” OR “oral mucositis” OR “oral manifestation”). Publications from 2019 to 2021 were retrieved, and no geographical restriction was imposed. The search was carried out based on the title, abstract, and keywords. The documents were then included or excluded according to the following criteria: (i) **inclusion**: publications that presented reports of oral manifestations, in addition to taste disorders, in suspected or confirmed cases of COVID-19. (ii) **exclusion**:

studies that exclusively discussed cases reported by other authors, publications that only addressed issues related to the treatment, diagnosis, or prognosis of COVID-19, and publications not available in English, Portuguese, or Spanish.

Based on the adopted search strategy, 266 studies were identified. Of these studies, 34 were excluded as they were found duplicated. The remaining 232 articles had their abstracts read by two reviewers. When an abstract indicated that the document may fit the inclusion criteria, it was retrieved in full to confirm its eligibility for inclusion. When an abstract was read and it was unclear whether the study should be included, the respective full article was also obtained and read in full. After applying the exclusion criteria, 23 publications were selected. To expand the scope of analysis of this review, the bibliographical references of the selected articles were searched to identify any other studies that may fit the inclusion criteria, which resulted in the inclusion of six other articles, bringing the final total to 29 studies.

Results and discussion

Increasing evidences of skin manifestations related to COVID-19 and high expression of ACE2 in oral epithelium, raised the question whether the SARS-CoV-2 could cause other oral manifestations besides taste impairment. Table 1 allows verifying the articles identified in this review according to the author, age and sex of the patient, test for diagnostic confirmation of SARS-CoV-2 infection, observed oral manifestations, anatomical location, latency, management of oral lesions, and presence of associated cutaneous manifestations.

Oral manifestations were reported in 110 patients of this review. Lesions were found to be more prevalent in women ($n = 68/61.8\%$).^{6–26} Three cases did not mention patient's sex.³³ Patient age was specified in 26 articles (mean age of 42.5 years). SARS-CoV-2 infection was confirmed in 94.5% cases by polymerase chain reaction (PCR) ($n = 104$),^{6–13,15,17–26,33–38} in three (2.7%) cases by antibody measurement (IgG),^{16,39,40} and not investigated in the remaining three (2.7%) cases because of the patient's mild symptoms.^{11,14} In the three cases in which the infection's diagnostic confirmation was not performed, one of the patients had systemic symptoms of COVID-19 (e.g., fever, asthenia, hyposmia, and dysgeusia), and the second was asymptomatic, but the wife had a confirmed infection.¹¹ The third had only systemic symptoms (e.g., fever and cervical lymphadenopathy), which the necrotizing ulcerative gingivitis presented by the patient could justify those symptoms.¹⁴ In the three cases in which the diagnosis was confirmed by antibody measurement (positive IgG), one of the patients had the IgM test performed during the symptoms and the IgG test two weeks before the oral lesions appeared⁴⁰; the other performed only three weeks before the oral lesions appeared¹⁶; and the last one did not mention when the test was performed.³⁹ However, since these antibodies are produced later during the

Table 1 Screened list of articles, year of publication, age, sex, test for diagnostic confirmation of SARS-CoV-2 infection, observed oral manifestations, anatomical location, latency and management of oral lesions, and presence of associated skin manifestations

Author	Age/sex	Diagnostic test	Oral manifestations/ anatomical location	Latency	Management of oral manifestations	Skin lesions
Amorim dos Santos et al. ³⁴	67 M	Positive RT-PCR	Ulcers resembling HSV (tongue dorsum), candidiasis (tongue dorsum), and geographic tongue	34 days after the onset of symptoms	Fluconazole, nystatin, chlorhexidine, and hydrogen peroxide	INA
Ansari et al. ⁷	56 F	Positive RT-PCR	Ulcers resembling HSV (hard palate)	15 days after the onset of symptoms	Diphenhydramine, dexamethasone, tetracycline, and lidocaine	INA
	75 M	Positive RT-PCR	Ulcers resembling HSV (anterior of the tongue)	7 days after hospitalization	Diphenhydramine, dexamethasone, tetracycline, and lidocaine	INA
Glavina et al. ⁸	40 F	Positive RT-PCR	Ageusia, ulcers resembling HSV (palate), hairy tongue, and nonspecific white lesions (ventral side of the tongue)	7 days after the confirmation of SARS-CoV-2 infection	Acyclovir, antiseptic, nystatin, panthenol, and local anesthetic	INA
Jimenez-cauhe et al. ⁹	^a F	Positive RT-PCR	Macules and petechiae (palate)	^a	INA	Yes
	^a F	Positive RT-PCR	Macules and petechiae (palate)	^a	INA	Yes
	^a F	Positive RT-PCR	Macules and petechiae (palate)	^a	INA	Yes
Chaux-Bodard et al. ³⁵	45 F	Positive RT-PCR	Irregular ulcer (dorsal side of the tongue)	8 days before the COVID-19 test	Follow-up	Yes
Jimenez-Cauhe et al. ¹⁰	^b	Positive RT-PCR	Macular enanthema (palate)	12 days after the onset of symptoms	INA	Yes
	^b	Positive RT-PCR	Petechiae enanthema (palate)	2 days before the onset of symptoms	INA	Yes
	^b	Positive RT-PCR	Macular with petechiae enanthema (palate)	19 days after the onset of symptoms	INA	Yes
	^b	Positive RT-PCR	Macular with petechiae enanthema (palate)	24 days after the onset of symptoms	INA	Yes
	^b	Positive RT-PCR	Petechial enanthema (palate)	2 days after the onset of symptoms	INA	Yes
Martín Carreras-Presas et al. ¹¹	56 M	Suspected	Dysgeusia and ulcers resembling HSV (hard palate)	Simultaneous	Valaciclovir, chlorhexidine, and hyaluronic acid	INA
	58 M	Suspected	Ulcers resembling HSV (hard palate)	INA	Topical antiseptic	INA
	65 F	Positive RT-PCR	Blisters (labial mucosa) and desquamative gingivitis (erythema multiforme-like)	23 days after the onset of symptoms	Prednisolone, chlorhexidine, and hyaluronic acid	Yes

Table 1 Continued

Author	Age/sex	Diagnostic test	Oral manifestations/ anatomical location	Latency	Management of oral manifestations	Skin lesions
Soares et al. ³⁶	42 M	Positive RT-PCR	Ulcers (buccal mucosa) and reddish macules (hard palate, tongue, and lips)	INA	Follow-up	Yes
Tomo et al. ¹²	37 F	Positive RT-PCR	Dysgeusia, burning sensation (tongue and soft palate), dry mouth, diffuse erythema and depapillation (borders of tongue)	9 days after the onset of symptoms	Chlorhexidine	INA
Ciccarese et al. ¹³	19 F	Positive RT-PCR	Erosions, ulcerations, and blood crusts (labial mucosa), petechiae (palate and gingiva)	5 days after the onset of symptoms	INA	Yes
Patel and Woolley ¹⁴	35 F	Suspected	Halitosis, edema, and erythema (gingiva), necrosis (interdental papillae), and bleeding (gingival sulcus)	3 days after the onset of fever	Metronidazole and chlorhexidine	INA
Cebeci Kahramanand and Çaşkur ⁴⁰	51 M	IgG and IgM positive	Ageusia, erythema (oropharynx), petechiae (hard palate), and pustular enanthema (soft palate)	10 days after the onset of symptoms	INA	INA
Dominguez-Santas et al. ¹⁵	43 F	Positive RT-PCR	Ulcer (buccal mucosa)	4 days after the onset of symptoms	INA	INA
	33 M	Positive RT-PCR	Aphthous ulcer (superior mucogingival junction)	3 days after the onset of symptoms	INA	INA
	37 M	Positive RT-PCR	Aphthae (ventral side of the tongue)	5 days after the onset of symptoms	INA	INA
	19 M	Positive RT-PCR	Clustered aphthae ulcers (labial mucosa)	Simultaneous	INA	INA
Corchuelo and Ulloa ¹⁶	40 F	IgG positive	Petechiae (lip), candidiasis (dorsum of the tongue), melanin pigmentation (gingiva), aphthous ulcers (gingiva and tongue), dry mouth, and hypogeusia	INA	Nystatin and topical chlorhexidine	Yes
Brandão et al. ⁶	81 M	Positive RT-PCR	Dysgeusia, clustered ulcers (lip), ulcers (tongue and labial mucosa)	Dysgeusia present on the 1st day and ulcers after 10 days of symptom onset	Acyclovir and photobiomodulation	INA
	71 F	Positive RT-PCR	Dysgeusia, hemorrhagic ulcerations (lips), and focal ulcerative areas of necrosis (dorsum of the tongue)	During the hospitalization	Acyclovir and photobiomodulation	INA
	83 F	Positive RT-PCR	Ulcer (tongue), erythema/petechiae, and shallow necrotic area (hard palate)	During the hospitalization	Photobiomodulation	INA

Table 1 Continued

Author	Age/sex	Diagnostic test	Oral manifestations/ anatomical location	Latency	Management of oral manifestations	Skin lesions
	72 M	Positive RT-PCR	Hemorrhagic ulceration and necrotic ulceration (lip)	During the hospitalization	Acyclovir and photobiomodulation	INA
	32 F	Positive RT-PCR	Dysgeusia and shallow ulcers (lateral border of the tongue)	10 days after the onset of symptoms	Follow-up	INA
	35 M	Positive RT-PCR	Ageusia and major aphthous-like ulcer (tonsillar pillar)	6 days after the onset of symptoms	Follow-up	INA
	29 M	Positive RT-PCR	Ageusia and ulcer (ventral portion of the tongue)	Ageusia after 6 days, and ulcer after 8 days of symptom onset	Follow-up	INA
	28 M	Positive RT-PCR	Ageusia, aphthous-like ulcers (labial mucosa and lateral border of the tongue)	Ageusia after 6 days, and ulcer 8 days after the onset of symptoms	Chlorhexidine	INA
Kitakawa et al. ¹⁷	20 F	Positive RT-PCR	Crusted lesions resembling HSV (lip)	INA	Neomycin and bacitracin	INA
Aghazadeh et al. ¹⁸	9 F	Positive RT-PCR	Vesicles and erosions (lips, tongue, and buccal mucosa)	Simultaneous	Follow-up	Yes
Cruz Tapia et al. ¹⁹	41 F	Positive RT-PCR	Angina bullosa hemorrhagic-like lesion (hard palate)	During quarantine time	Follow-up	INA
	51 F	Positive RT-PCR	Vascular-like purple macule (hard palate), papule-plaque (hard palate)	Simultaneous	INA	INA
	55 F	Positive RT-PCR	Purple bulla (tongue)	During quarantine time	Follow-up	INA
	41 M	RT-PCR positive	Dysgeusia, burning mouth, and multiple reddish macules (hard palate)	Simultaneous	Chlorhexidine and topical mometasone furoate	INA
Riad et al. ²⁰	16 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	3 days after the PCR test	Paracetamol and chlorhexidine	INA
	69 M	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	43 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	24 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	19 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	29 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	47 M	Positive RT-PCR	Ageusia and ulcers (ventral and dorsum of the tongue)	3 days after the PCR test	Paracetamol and chlorhexidine	INA
	21 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	19 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	38 M	Positive RT-PCR	Ulcers (ventral and dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA

Table 1 Continued

Author	Age/sex	Diagnostic test	Oral manifestations/ anatomical location	Latency	Management of oral manifestations	Skin lesions
	25 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	36 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	29 M	Positive RT-PCR	Ageusia and ulcers (ventral and dorsum of the tongue)	Same day of the PCR test	Paracetamol and chlorhexidine	INA
	70 F	Positive RT-PCR	3 ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	68 M	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	42 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	29 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	37 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	31 M	Positive RT-PCR	Ageusia and ulcers (ventral and dorsum of the tongue)	Same day of the PCR test	Paracetamol and chlorhexidine	INA
	19 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	29 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	37 M	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	57 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
	41 M	Positive RT-PCR	Ulcers (dorsum of the tongue)	4 days after the PCR test	Paracetamol and chlorhexidine	INA
	50 M	Positive RT-PCR	Ulcers (dorsum of the tongue)	3 days after the PCR test	Paracetamol and chlorhexidine	INA
	32 F	Positive RT-PCR	Ulcers (dorsum of the tongue)	5 days after the PCR test	Paracetamol and chlorhexidine	INA
Díaz Rodríguez and Jimenez ²¹	43 F	Positive RT-PCR	Dysgeusia, aphthous-like lesions, burning sensation, and tongue depapillation	INA	Corticosteroids	INA
	53 M	Positive RT-PCR	Dysgeusia, angular cheilitis, and burning sensation	After hospital discharge	Neomycin, nystatin, and triamcinolone acetonide	INA
	78 F	Positive RT-PCR	Pseudomembranous candidiasis (tongue and palate), angular cheilitis, and dry mouth	During the hospitalization	Neomycin, nystatin, and triamcinolone acetonide	INA
Bezerra et al. ³⁹	33 M	IgG positive	Ageusia, ulcers (floor of the mouth, buccal mucosa and labial mucosa)	70 days after the onset of symptoms	Triamcinolone acetonide and chlorhexidine	INA
Soares et al. ²²	23 F	Positive RT-PCR	Vesiculobullous lesions (lips)	3 days after the onset of symptoms	Dexamethasone	INA
Riad et al. ²³	47 F	Positive RT-PCR	Candidiasis (dorsal surface of the tongue and hard palate) and burning sensation	2 weeks after the onset of symptoms	INA	INA

Table 1 Continued

Author	Age/sex	Diagnostic test	Oral manifestations/ anatomical location	Latency	Management of oral manifestations	Skin lesions
Riad et al. ²⁴	29 M	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	52 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	45 F	Positive RT-PCR	Halitosis	INA	Chlorhexidine	INA
	72 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	19 F	Positive RT-PCR	Halitosis	INA	Chlorhexidine	INA
	32 M	Positive RT-PCR	Halitosis	INA	Chlorhexidine	INA
	42 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	29 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	50 F	Positive RT-PCR	Halitosis and ageusia	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	37 F	Positive RT-PCR	Halitosis	INA	Chlorhexidine	INA
	18 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	29 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	26 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	38 M	Positive RT-PCR	Halitosis	INA	Chlorhexidine	INA
	26 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	25 F	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA
	29 F	Positive RT-PCR	Halitosis	INA	Chlorhexidine	INA
34 M	Positive RT-PCR	Halitosis	INA	Lidocaine, chlorhexidine, and prednisolone	INA	
Kämmerer et al. ³⁷	46 M	Positive RT-PCR	Ulcers resembling HSV (buccal mucosa)	3 days after extubation	Acyclovir	No
Askin et al. ³³	INA	Positive RT-PCR	Enanthema	INA	INA	Yes
	INA	Positive RT-PCR	Aphthous stomatitis and enanthema	INA	INA	Yes
Binois et al. ³⁸	INA	Positive RT-PCR	Aphthous stomatitis	INA	INA	Yes
	57 M	Positive RT-PCR	Bilateral ulcers (tongue and lips – erythema multiforme major) and ageusia	8 days after the onset of symptoms	Amoxicillin/clavulanic acid and antiviral drugs	No
Cebeci Kahraman et al. ²⁵	67 F	Positive RT-PCR	Thick-crusted hemorrhagic necrosis (lips)	INA	Subcutaneous low- molecular-weight heparin, and eculizumab	No
Riad et al. ²⁶	50 F	Positive RT-PCR	Ageusia, mucositis (all over the mouth), and depapillation of the tongue	0 day after the PCR test	Paracetamol	No
	34 M	Positive RT-PCR	Mucositis (palate and buccal mucosa) and depapillation of the tongue	1 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	56 F	Positive RT-PCR	Mucositis (hard and soft palate) and depapillation of the tongue	1 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	62 M	Positive RT-PCR	Mucositis (all over the mouth) and depapillation of the tongue	2 days after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No

Table 1 Continued

Author	Age/sex	Diagnostic test	Oral manifestations/ anatomical location	Latency	Management of oral manifestations	Skin lesions
	45 F	Positive RT-PCR	Mucositis (all over the mouth) and depapillation of the tongue	1 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	57 F	Positive RT-PCR	Mucositis (buccal mucosa) and depapillation of the tongue	0 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	49 M	Positive RT-PCR	Ageusia, mucositis (all over the mouth), and depapillation of the tongue	0 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	39 F	Positive RT-PCR	Ageusia, mucositis (all over the mouth), and depapillation of the tongue	0 day after the PCR test	Paracetamol	No
	46 M	Positive RT-PCR	Mucositis (buccal mucosa) and depapillation of the tongue	2 days after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	62 F	Positive RT-PCR	Mucositis (all over the mouth) and depapillation of the tongue	1 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No
	55 M	Positive RT-PCR	Mucositis (gingiva) and depapillation of the tongue	2 days after the PCR test	Paracetamol	No
	61 F	Positive RT-PCR	Ageusia, mucositis (buccal mucosa), and depapillation of the tongue	0 day after the PCR test	Paracetamol	No
	48 F	Positive RT-PCR	Mucositis (all over the mouth) and depapillation of the tongue	1 day after the PCR test	Lidocaine, chlorhexidine, and prednisolone	No

F, female; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INA, information not available; M, male; RT-PCR, reverse transcription polymerase chain reaction.

^a4 patients, all women, with an average age of 64.25 years, average latency time of 19.5 days, but only 3 had oral manifestations.

^b6 patients, 4 women, and 2 men, aged 40–69 years.

course of the infection and persist for a longer time, a positive result indicates that the patient had COVID-19 in the recent past and does not allow us to state that the virus was present when the lesions were reported.

The latency of oral manifestations, from the onset of symptoms (as mentioned in 82 cases), ranged from two days before onset of systemic symptoms to 70 days after these symptoms. In 18 (16.4%) patients, cutaneous manifestations of COVID-19 associated with oral lesions were mentioned.^{9–11,13,16,18,33,35,36}

The presence of ulcerated lesions was the most common intraoral finding in patients with COVID-19 (50.9%/n = 56).^{6–8,11,13,15–17,20–22,33–39} Petechiae, macules, hemorrhagic blisters, pustular enanthem, mucositis (30.0%/n = 33),^{6,9,10,13,16,19,26,33,36,40} and halitosis (17.3%/n = 19)^{14,24} were also frequently oral manifestations described. Regarding anatomical location of the lesions, tongue was the most affected site (53.6%/n = 59),^{6–8,12,15,16,18–21,23,26,34–36,38} followed by

palate (22.7%/n = 25),^{6–13,19,21,23,26,36,40} and lips/labial mucosa (14.5%/n = 16).^{6,11,13,15–18,21,22,25,36,38,39} Table 2 summarizes oral manifestations and anatomical location of the lesions described in this review.

The greater predominance of lesions on the tongue may be because of the higher expression of ACE2 in this region.²⁸ Fifty percent of the lesions on the buccal mucosa (n = 4)^{15,36,37,39} and 67.8% of the lesions on the tongue (n = 40)^{6,7,15,16,18,20,21,34,35,38} were manifested as ulcers, whereas 72.0% of lesions on the palate (n = 18)^{6,9,10,13,19,26,36,40} were manifested as macular lesions, petechiae, hemorrhagic blisters, pustular enanthem, and mucositis. Three clinical patterns were observed among the ulcerated lesions: ulcers resembling herpes simplex virus (HSV), aphthous ulcers, and erythema multiforme-like. In two studies, authors classified ulcers as nonspecific.^{35,36} Within the lesions with herpetiform aspect, there were reports of

Table 2 Oral manifestations observed in patients with COVID-19 and anatomical location of the lesions

	Number of patients (%)
Oral manifestations	
Ulcers	56 (50.9)
Macules, petechiae, hemorrhagic blisters, pustular enanthem, and mucositis	33 (30.0)
Halitosis	19 (17.3)
Tongue depapilation	15 (13.6)
Candidiasis	5 (4.5)
Burning mouth	5 (4.5)
Dry mouth	3 (2.7)
Pigmented lesion	1 (0.9)
Hairy tongue	1 (0.9)
Geographic tongue	1 (0.9)
Necrotizing ulcerative gingivitis	1 (0.9)
Desquamative gingivitis	1 (0.9)
Crusted hemorrhagic necrosis	1 (0.9)
Anatomical location of the lesions	
Tongue	59 (53.6)
Palate	25 (22.7)
Vermilion zone of the lip/Labial mucosa	16 (14.5)
Buccal mucosa	8 (7.3)
All over the mouth	7 (6.4)
Gingiva	5 (4.5)
Others ^a	3 (2.7)

^aAnterior tonsillar pillar, mucosa above the mucogingival junction, and floor of the mouth.

presentations similar to primary infection by HSV¹⁸ and the recurrence of HSV on the lip,¹⁷ palate,^{7,8} tongue,^{7,20,34} and buccal mucosa.³⁷

It is estimated that more than 70% of the population aged 25 years old has already been exposed to HSV, and this rate may be even higher in developing countries. The HSV has the ability, after primary infection, to remain in latency in the host cells. The secondary or recurrent infection of HSV occurs with the virus's reactivation triggered by numerous factors, such as old age, physical or mental stress, ultraviolet light, and respiratory diseases, among others.⁴¹ Kämmerer et al.³⁷ reported a case of a 46-year-old patient who developed ulcerated lesions with a herpetiform pattern on the buccal mucosa three days after extubation. The patient had a history of recurrent HSV infection.³⁷ Although the localization in nonkeratinized mucosa is not the preference for oral manifestation of HSV recurrence, biopsy and histopathological examinations showed central ulcerations with apoptotic keratinocytes, while the immunohistochemical examination demonstrated positivity for HSV 1 and 2, and the diagnosis was recurrent herpes simplex infection.³⁷ Immunosuppression and the stress of prolonged hospitalization caused by COVID-19 were identified as triggering agents.³⁷

In the other reported cases of COVID-19 with a clinical aspect of herpetiform ulcer, the lack of histopathological studies

complemented by immunohistochemical studies and PCR did not exclude the possibility of infection by HSV. Therefore, there is a question as to whether SARS-CoV-2 directly causes the lesions observed in these patients or whether they are a recurrence of HSV secondary to the immunodysregulation caused by COVID-19, stress, or other triggering factors.^{42,43} The absence of a history of previous herpes, cited by some studies,^{11,17} does not rule out the possibility of recurrent herpetic infection since the primary infection is commonly asymptomatic.⁴¹ The use of serological tests to rule out HSV infection, mentioned by one of the studies,⁷ is not considered the test of choice for diagnosing active lesions.⁴⁴⁻⁴⁶ The presence of the virus in patients' saliva is not enough to attribute the etiology of the lesions to HSV, considering that studies show the possibility of asymptomatic oral shedding of HSV in the saliva at least once a month.⁴⁷

Previous studies have also pointed out the ability of SARS-CoV-2 to trigger an unregulated activation of immune system, causing an excessive release of cytokines. This storm of cytokines causes defense cells to migrate to the affected area. Without a feedback mechanism to control this process, the action of the immune system begins to cause damage to the patient's tissues.⁴⁸ It has been suggested that the pathogenesis of the recurrent aphthous stomatitis is associated with an immune reaction mediated by T cells and an increase in cytokines as the tumor necrosis factor-alpha.⁴⁹ Therefore, the production of cytokines triggered by the virus may induce an immune reaction that culminates in destruction of oral mucosa. However, recurrent aphthous ulcers are common lesions and can be triggered by numerous factors, including stress. It is still not possible to establish whether these injuries are caused directly by the virus, whether they are related to immunocompromised status associated with the disease, or if they are secondary to other predisposing factors.

Several studies have described skin lesions similar to erythema multiforme in patients with COVID-19^{5,9,50}; however, only two oral manifestation cases similar to erythema multiforme were reported in this review.^{11,38} Erythema multiforme is a rare, acute inflammatory disorder that affects skin and mucous membranes. It usually occurs in young adults, with a peak of presentation between 20 and 40 years, with 20% of cases occurring in children. Its etiology is still uncertain, but it is believed to be an immunologically induced response by exposure to certain microorganisms and drugs. Viral infections are reported as triggering factors, with HSV identified in 70% of patients with erythema multiforme. Many medications have also been associated with the development of this condition, such as non-steroidal anti-inflammatory drugs, chemotherapeutic agents, cephalosporins, penicillin, sulfonamides, allopurinol, barbiturates, carbamazepine, and phenytoin, among others. Of the mucous surfaces, oral mucosa is the most frequently affected, especially in cases associated with medications.⁵¹ Lesions typically occur on lips and on oral nonkeratinized mucosa, not bound to bone, presenting as erythematous plaques that evolve

to diffuse, painful erosions and ulcers with irregular borders, and with associated necrosis. The formation of hemorrhagic crusts on lips is common. Associated skin lesions may be present, usually macules or erythematous papules, which develop into a concentric erythematous pattern (target lesions).⁵²

This review included only two (1.8%) cases with an erythema multiforme-like presentation.^{11,38} One patient used several medications such as antibiotics, lopinavir-ritonavir, hydroxychloroquine, and corticosteroids during hospitalization for the treatment of COVID-19, developing, after hospital discharge, an erythematous rash on the trunk and genital region, blisters on the mucosa of the lower lip, desquamative gingivitis, and crusts on the vermilion portion of the lower lip.¹¹ Oral manifestations were observed approximately 30 days after the onset of COVID-19 symptoms.¹¹ Only the skin lesion was biopsied, showing nonspecific findings with some viral rash criteria and urticarial dermatitis with slight blood extravasation. Based on the time elapsed between the diagnosis of COVID-19 and oral manifestations, it is more likely that those injuries were because of a drug reaction.¹¹ The other patient, 5 days after the first symptoms (cough, headache, myalgia, and fever), was hospitalized, and physical examination found ulcers of the mouth and glans, and erythematous conjunctivitis, and these findings were consistent with erythema multiforme major.³⁸ Swabs of the mouth ulcers, glans, and conjunctiva were negative for herpes simplex virus, varicella-zoster virus, and COVID-19.³⁸ Human immunodeficiency virus antigen and antibodies were negative, cytomegalovirus and Epstein-Barr virus serologies only found IgG, and mycoplasma pneumoniae nasopharyngeal polymerase chain reaction was negative.³⁸ These findings suggest mucosal damages were more likely to result from deleterious immune responses towards self-tissues rather than a cytopathic effect directly caused by the virus.³⁸

The presence of macules, petechiae, hemorrhagic blisters, pustular enanthem, and mucositis was reported in 33 (30.0%) patients in this review.^{6,9,10,13,16,19,26,33,36,40} We found that 42.4% of these patients also had associated skin lesions ($n = 14$),^{9,10,13,16,33,36} signaling the possibility that these changes represent a viral enanthema. In some cases, the presence of low platelet count and/or elevation of the D-dimer was highlighted.^{10,13} The pathophysiology by which COVID-19 causes thrombocytopenia is not yet completely understood, but, it is believed to be associated with the interference in hematopoiesis, excessive destruction of platelets by antibodies, and platelet consumption because of hypercoagulability.⁵³ In three studies of this review, the authors performed a histopathological examination of the lesions and observed microscopic characteristics of hemorrhages and thrombi formation in the small vessels.^{19,22,36} These findings have similarities with cutaneous vasculitis and thrombotic complications reported in cutaneous biopsies of patients with COVID-19.⁵³ In two of these studies, the authors complemented the histopathological analysis with immunohistochemical exam for HSV-1, HSV-2, cytomegalovirus

(CMV), *Treponema pallidum*, and *in situ* hybridization for Epstein-Barr virus (EBV) with a negative result for all reactions.^{22,36} In one of these studies, based on clinical characteristics, histopathological and immunohistochemical findings suggested that patients' lesions were a direct result of SARS-CoV-2 infection.³⁶ In the other study, immunohistochemistry for spike SARS-CoV-2 protein was positive in endothelial cells, keratinocytes, acinar and ductal cells of the minor salivary glands, which proved the presence of virus at the time of lesions.²²

Halitosis or "bad breath" is a condition that is characterized by an unpleasant odor coming from the mouth. About 80–85% of all halitosis cases are of intraoral origins, such as gingival and periodontal diseases (e.g., acute necrotizing ulcerative gingivitis, herpetic gingivitis, periodontitis, pericoronitis, and periodontal abscess), deep caries lesions, exposed necrotic pulp, poorly adapted dentures and orthodontic appliances, biofilm on the tongue, and candidiasis, among others.⁵⁴ Riad et al.²⁴ reported that 18 patients diagnosed with COVID-19, confirmed by PCR and without any relevant medical history, presented halitosis during the course of infection. The authors also reported that most of the study participants had oral hygiene at a "reasonable" level, and only one participant had intraoral ulcers associated with halitosis.²⁴ The halimeter examination showed that all patients had physiological halitosis.²⁴ The authors suggested that SARS-CoV-2 may cause possible epithelial changes on the dorsal tongue surface because of ACE2 receptors, which are deeply located in abundance in this site.²⁴ This hypothesis was reinforced by the study of Watanabe,⁵⁵ which found that the severity of halitosis was strongly associated with epithelial changes in the keratinized mucosa of the tongue. The other halitosis case was described in a patient who also had edema and gingival erythema, necrosis of the interdental papillae, and bleeding from the gingival sulcus.¹⁴

The presence of candidiasis was reported in five (4.5%) patients in this review.^{16,21,23,34} Candidiasis is the most common fungal infection in the oral cavity, and it is associated, among other factors, with the patient's immune status and the oral mucosa microenvironment.⁵⁶ In the cases reported in this review, there was a recent history of antibiotic therapy,^{16,23,34} use of corticosteroids,²³ and/or hospitalization.^{8,34} Therefore, it is likely that the candidiasis cases observed here do not represent a manifestation related to COVID-19 but are secondary to the use of medications and the patients' immunosuppression status.

Five (4.5%) patients in this review reported complaints of burning mouth.^{12,19,21,23} Along with this symptom, patients also presented complaints of dysgeusia, dry mouth, tongue depapillation, and/or candidiasis. As the patients presented candidiasis and tongue depapillation, burning mouth could be related to these conditions.⁵⁷ Three (2.7%) patients had dry mouth.^{12,16,21} Fantozzi et al.⁵⁸ found that xerostomia might present as a prodromal or as the sole manifestation of COVID-19, although more than 400 medications can cause salivary gland dysfunction, and 80% of the most commonly prescribed medications

have been reported to cause hyposalivation.⁵⁹ It has been found that the incidence and severity of the hyposalivation are directly proportional to the number of medications that the patient is taking.⁵⁹

In this review, we found that geographic and hairy tongue (0.9%/n = 1, for each other)^{8,34} were also alterations described for COVID-19 patients. Both conditions are common and can be found in the oral mucosa's routine clinical examination,^{60,61} which weakens a possible correlation with COVID-19. Also, the hairy tongue's predisposing factors are poor general condition, poor hygiene, and the use of medications that reduce salivary flow, which are common in hospitalized patients or who have had a recent systemic infection.⁶¹

Four authors reported gingival involvement in patients with COVID-19 in this review.^{11,13,14,16} A case of desquamative gingivitis detected 30 days after the diagnosis of COVID-19 and after a prolonged hospitalization period was reported in a patient who further developed a skin rash and vesicle-erosive eruption in the oral cavity.¹¹ As previously discussed, because of the great latency time between oral manifestations and the diagnosis of COVID-19, it is more likely that the injuries reported in this patient are because of the drug reaction. In another study, a case of necrotizing gingivitis was reported in a patient suspected of COVID-19.¹⁴ The suspicion was based solely on the reported symptoms of fever and lymphadenopathy, which could be justified by oral infection, making the correlation with COVID-19 infection questionable. One (0.9%) case of gingival petechiae was observed in a patient with COVID-19 who had severe thrombocytopenia.¹³ Finally, the case of a patient who had asymptomatic COVID-19, diagnosed through a positive IgG test performed three weeks earlier, developed a pigmented lesion on the gums.¹⁶ As IgG antibodies' presence indicates past infection, possibly, this pigmented lesion is not associated with COVID-19. A variety of medications, including chloroquine, quinine, minocycline, zidovudine, chlorpromazine, and ketoconazole, are known to cause melanin pigmentation in the oral mucosa.⁶² However, the patient did not use any of these medications. Only the use of vitamin D2 and azithromycin for five days have been reported.

The etiology of oral lesions seen in patients with COVID-19 is still uncertain. The small number of cases with oral manifestations, associated with rare histopathological, immunohistochemical studies, and molecular biology techniques to rule out other infectious agents' hypotheses in the reported cases, makes it difficult to affirm whether SARS-CoV-2 has induced these lesions. Although only one author identified the SARS-CoV-2 spike protein in immunohistochemistry, many authors noted that the resolution of oral lesions occurred in parallel with the cure of COVID-19. Interestingly, the two main clinical manifestations observed in patients with COVID-19 in this review (ulcers and macular-petechial enanthema) are findings commonly reported in other viral diseases that present oral manifestations. Nevertheless, it is possible that some findings observed

in the physical examination of these patients are not directly associated with the disease, representing secondary alterations to the immunocompromised patients caused by the infection or induced by the medications used in the treatment of COVID-19.

As happens with any scientific study, our integrative review had some limitations. One of them was because of the reviewed articles' methodological weaknesses since most of the publications analyzed were case reports. In three of the patients, there was no laboratory confirmation for COVID-19 using PCR testing, and in three cases,^{16,39,40} there was confirmation of past infection through serology. In addition, because of the suspension of in-office appointments, many patients were followed up through telemedicine, which made it difficult to obtain further investigation for better characterization of oral lesions. Thus, there is a need for prospective longitudinal studies with many more patients to assess the incidence of oral manifestations in these cases. Additional studies should be associated with histopathology, immunohistochemistry, and molecular techniques for a better understanding of these lesions. The low number of publications correlating COVID-19 to oral manifestations may be because of these manifestations' rarity or underreporting because of the lack of an adequate oral clinical examination. Many of the cases reported in this review were of critically ill hospitalized patients, supporting the importance of including an oral surgeon in the multidisciplinary hospital team. As we are dealing with a new virus, we expect that new publications will further point to new evidence that will help us to understand the presentation spectrum of this disease.

Conclusion

Based on current scientific evidence, it was not possible to state that the oral lesions seen in patients with COVID-19 were induced by the virus or were secondary to the deterioration of systemic health and the drugs used in treatment of the disease. Healthcare professionals should be aware of COVID-19-related oral symptoms, and, whenever possible, patients with COVID-19 should undergo an intraoral examination.

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