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COVID-19 and oral lesions: 2020–2024 outpatient case series and literature review

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Abstract

Data on oral lesions of coronavirus disease (COVID-19) are conflicting, and there are few evidence-based data on oral lesions directly caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The aim of this case series and literature review is to determine the prevalence of oral lesions associated with COVID-19 in outpatients and identify oral manifestations that are likely associated with COVID-19. We present 15 patients that came for their first specialist examination to the Oral Medicine Outpatient Clinic, Dental Clinic, Split, Croatia between November 2020 and January 2024. Their medical and dental history was taken following CARE guidelines. The prevalence of oral lesions associated with SARS-CoV-2 was 1.42% during the 4-year follow-up period. The most common oral lesions were nonspecific erosions, stomatitis, salivary flow disorders (xerostomia, oligosialia), salivary gland diseases (sialadenitis, chronic sialadenitis), candidiasis, pigmentation, aphthae, burning mouth syndrome, and geographic and fissured tongue. The mean latency period was 25.1 days. The site most commonly affected was the tongue (61.5%). Oral lesions associated with COVID-19 occurred in middle-aged patients, with an equal distribution by sex. They presented in a mild form and did not correlate with the severity of the clinical picture of COVID-19.

Keywords: aphthous, burning mouth syndrome, COVID-19, oral manifestations, xerostomia

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Introduction

The first case of coronavirus disease 2019 (COVID-19) diagnosed in Croatia was on 25 February 2020 in a 25-year-old man that had returned from Milan, Italy. Although respiratory symptoms are the primary indicators of the disease, investigations into extrapulmonary manifestations, such as those affecting the blood vessels, central nervous system (CNS), skin, gastrointestinal system, heart, kidneys, and liver, are ongoing (1–4). Literature data indicate that oral manifestations of COVID-19 affect both sexes equally, with a higher prevalence observed among the elderly and those with more severe forms of the disease (5, 6). Although various oral mucosal symptoms and signs have been reported, such as dysgeusia, which may indicate early COVID-19 infection, little is understood about oral lesions directly caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (7–17). Reported oral manifestations include ulcerative and vesiculobullous mucosal lesions, taste alterations, gingivitis, inflammation of Wharton's duct papillae, tongue plaques, dry mouth, bad breath, parotitis, aphthous ulcers, varicella-zoster virus infection, herpetic gingivostomatitis, recurrent herpes simplex virus (HSV) infection, angina bullosa hemorrhagica, Melkersson–Rosenthal syndrome, enlarged tongue, desquamative gingivitis, necrotizing periodontal disease (NPD), erythema exudativum multiforme, and burning mouth syndrome (BMS) (7–17). It remains uncertain whether these oral manifestations are directly caused by the novel coronavirus or result from side effects and drug interactions, immunosuppression, iatrogenic complications, stress, or concurrent conditions (6, 18–21).

SARS-CoV-2 is a mucotropic, neurotropic, and sialotropic virus (22). The angiotensin-converting enzyme 2 (ACE2) receptor is a protein that serves as the entry point for SARS-CoV-2 into the human body. ACE2 receptors are highly represented in the lungs, heart, esophagus, kidneys, bladder, ileum, and epithelial cells of the tongue and salivary glands (23–25). SARS-CoV-2 leads to alteration of the oral microbiome, which subsequently leads to opportunistic infections (26, 27). One hypothesis about the development of aphthous lesions in patients with COVID-19 speaks of an interaction between the ACE2 receptor and SARS-CoV-2 altering the epithelial barrier of keratinocytes and the salivary glands (19).

The bidirectional relationship between oral health and general health is well known. This was confirmed by a recent Cohrane review, which showed that regular tooth brushing and the use of chlorhexidine (CHX) antiseptics were effective in preventing ventilator-associated pneumonia and influencing the length of stay of patients in intensive care units (28, 29). Therefore, an oral medicine specialist should be part of a multidisciplinary medical team caring for these patients. On the other hand, dentists and physicians must be familiar with the oral lesions caused by SARS-CoV-2 in order to recognize the symptoms and signs of the disease early so that a timely diagnosis can be made and the spread of the infection in the population can be prevented.

The objective of this case series and literature review was to recognize oral lesions potentially linked to COVID-19 and assess their prevalence among outpatients. Additionally, we aimed to review existing knowledge regarding oral lesions associated with COVID-19. It's important to note that while our findings suggest a probable association, the absence of comprehensive diagnostic tests and further research means that causality remains speculative.

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Methods

In this case series, we present 15 patients that underwent their initial specialist examination at the Oral Medicine Outpatient Clinic at the Dental Clinic in Split, Croatia, which serves as the teaching base for the School of Medicine's Dental Medicine Program at the University of Split. The examinations occurred from November 2020 to January 2024. All patients had previously tested positive for SARS-CoV-2, confirmed by reverse transcription-polymerase chain reaction (RT-PCR). A single oral medicine specialist conducted clinical oral examinations for all patients. Exclusion criteria included patients without confirmation of COVID-19 through RT-PCR testing. Medical and dental histories were obtained following the CARE guidelines for case reports and in accordance with the Declaration of Helsinki for medical research involving human subjects (30, 31). Informed consent was obtained from all study participants.

Results

An equal number of women and men (60% women, 40% men) participated in this case series. The sample of COVID-19 patients consisted of 15 subjects 24 to 85 years old, median 49.0 (interquartile range [IQR] 37.0 to 60.0). The median age of the women was 40.0 years (IQR 34.0 to 68.0). The median age of the men was 49.0 (IQR 46.0 to 53.0). The general and main clinical characteristics of the outpatients are listed in Table 1.

The prevalence of oral lesions associated with SARS-CoV-2 was 1.42% during the 4-year follow-up period. The most common oral lesions were nonspecific erosions, stomatitis, salivary flow disorders (xerostomia, oligosialia), salivary gland diseases (sialadenitis, chronic sialadenitis), candidiasis, pigmentation, aphthae, BMS, and geographic and fissured tongue.

Case 1

An 85-year-old female patient came to her first specialist examination due to changes in the oral mucosa. The latency period for the oral lesions was 14 days. Biochemical findings showed elevated urate (345 µmol/l; reference values: 134–337 µmol/l) and total cholesterol (5.1 mmol/l; reference values: 3.5–5.0 mmol/l). Her medical history included diabetes mellitus (DM), glaucoma, external hemorrhoids, and hypertension. She was taking metformin, bisoprolol fumarate, and antidepressants. She denied an allergy to the medication. She was a nonsmoker. Clinically, there were multiple, shallow erosions covered by pseudomembranes on the upper and lower jaw (generalized). She was prescribed local therapy with an oral antiseptic (CHX 0.12%, twice daily for 14 days) and dexamethasone drops (10 drops three times daily for 14 days). A follow-up examination (after 14 days) showed significant improvement with complete regression of the lesions within 3 weeks.

Case 2

A 57-year-old female patient came to her first specialist examination for changes in the oral mucosa accompanied by burning and pain. The latency period for the oral lesions was 14 days. Her COVID-19 infection presented with fever up to 39.0 °C, shallow breathing, headache, myalgia, joint pain, hypogeusia, and hyposmia. Her medical history included reactive arthritis (ReA) and chronic gastritis. She was not taking any medication. She had no allergies and no drug allergies. She was a nonsmoker. Her complete blood count (CBC), biochemistry, antinuclear antibodies (ANA), extractable nuclear proteins (ENA), and urine culture results were noncontributory. Human leukocyte antigen (HLA) typing showed a positive result for the HLA B-27 antigen. She denied gastrointestinal and urogenital problems. Clinical oral examination revealed multiple shallow erosions on both sides (more pronounced on the right) in the anterior region of the hard palate mucosa on an extremely erythematous background. She was prescribed local therapy with an oral antiseptic (0.12% CHX digluconate and 0.05% cetylpyridine chloride, twice daily) and dexamethasone drops (10 drops three times daily) for 2 weeks. The oral lesions regressed within 10 days. Based on the test results and the medical history (the patient stated that she had had such lesions previously, during immunosuppression), we can speculate that the patient had oral manifestations of ReA triggered by the immunosuppression caused by SARS-CoV-2.

Case 3

A 46-year-old male patient came to his first specialist examination because of changes to the oral mucosa. The latency period for the oral lesions was 9 days. He reported a poor general condition (malaise) and subfebrile condition (37.3 °C) 2 days before the lesions appeared. The medical history was noncontributory. He was not taking any medication. He had no allergies and no drug allergies. He was a nonsmoker. Clinical oral examination revealed hyperplastic gingiva on the palatal side unilaterally (regions 21–22), two erosions on the left buccal mucosa (retrocommissural), one erosion on the mucosa of the dorsum of the tongue (unilateral left, middle third), and erythematous operculum (region 38; Fig. 1). The patient was diagnosed with a subclinical form of primary herpetic gingivostomatitis (PHGS), which was considered a working diagnosis. He was prescribed local therapy (hexetidine and dexpanthenol liquid, lidocaine spray) three times a day for 14 days, and the lesions regressed completely. The diagnosis was further supported by serological tests for HSV (HSV1/HSV2 IgM 116, reference values: < 20 U/ml, and IgG 347, reference values: < 20 U/ml), performed 3 weeks later. However, to confirm the diagnosis, a baseline serology test with negative antibodies before the described episode would be necessary.

Case 4

A 24-year-old female patient came to her first specialist examination because of gum problems. The latency period for the oral lesions was 14 days. The medical history was noncontributory. She was not taking any medication. She had no allergies and no drug allergies. She was a nonsmoker. Clinical oral examination revealed diffuse erythematous mucosa of the cheeks on both sides and three shallow erosions on the attached gingiva (regions 13–15; Fig. 2). The patient was prescribed a local CHX antiseptic 0.12% (twice daily) and dexamethasone drops (10 drops three times daily) for 2 weeks, after which the lesions disappeared completely. We can suggest that the patient had nonspecific COVID-19 oral lesions, erosions (gingiva), and stomatitis.

Case 5

A 40-year-old female patient came to her first specialist examination for dry mouth. The latency period for the xerostomia was

28 days. She denied dryness of the eyes, skin, and other mucous membranes. Her medical history included a duodenal ulcer (2005), pulmonary embolism (2012), sinus surgery (2019), and hypothyroidism. She was only taking levothyroxine (50 µg). Clinical oral findings were normal. Unstimulated whole saliva (UWS) was measured, which showed oligosialia (0.3 ml/min). Stimulated whole saliva (SWS) was 0.5 ml/min, indicating reactivity of the salivary glands to stimulation, but still below reference values. The patient was recommended local measures to stimulate salivation (sufficient fluid intake 2.0 l, sugar-free chewing gum, mildly acidic drinks without sugar, and marshmallow root tea). At the 3-month follow-up, her condition improved significantly.

Case 6

A 53-year-old male patient came to his first specialist examination because of a painful swelling in front of the right ear. The latency period for the oral lesions was 40 days. COVID-19 was accompanied by anosmia, ageusia, heaviness in the chest, and fever up to 39.1 °C. The swelling subsided after he was prescribed antibiotic therapy (amoxicillin and clavulanic acid) for the first time. After that he suffered a relapse. He was diagnosed with elevated serum amylase (368 U/l, reference values: 23–91 U/l) and urine amylase (1,748 U/l, reference values: < 400 U/l) 7 days prior to the examination. In his medical history he stated cardiac and gastric diseases. He was taking the following medications: bisoprolol, ramipril, and pantoprazole. He was a nonsmoker. On inspection, we noticed a swelling on the right side of his face. On palpation, we found an oval, painful, mobile lesion in front of the right ear with a diameter of 5.0 mm. We found cloudy saliva at the excretory duct of the right parotid gland. The UWS was measured, which showed oligosialia (0.3 ml/min). The SWS was 0.5 ml/min, indicating reactivity of the salivary glands to stimulation, but still below reference values. The patient was prescribed antibiotic therapy (amoxicillin and clavulanic acid) for 10 days, with the recommendation to massage the right parotid gland externally over the facial skin, drink mildly acidic drinks, and drink sufficient fluid. At the follow-up examination after 2 weeks, the clinical oral findings were normal.

Figure 1 | Primary herpetic gingivostomatitis (PHGS) depicted by an erosion on the left buccal mucosa (near the back corner of the mouth) and erosion on the mucosa of the dorsum of the tongue (unilateral, left side, middle third).

Case 7

A 37-year-old male patient came to his first specialist examination because of painful changes in the oral cavity. The latency period for the oral lesions was 7 days. COVID-19 was accompanied by fever up to 38.4 °C, back pain, and cough. Subjectively, he had pain, a burning sensation, and difficulty swallowing. He had taken three 500 mg doses of azithromycin. He denied diseases in his medical history. He was not taking any medication. He had allergies to amoxicillin (he was hospitalized because he developed aphthous stomatitis after taking amoxicillin at age 18), pollen, and grass. He was a nonsmoker. Clinically, the entire oral cavity was covered with extensive erosions with pseudomembranes (Fig. 3). He also noted two sores on the genital mucosa. He denied any changes to the skin. He was prescribed systemic corticosteroid therapy with methylprednisolone at an initial dose of 40 mg, gradually reducing the dose by 8 mg every 2 days. Local therapy for the oral cavity included a combination of CHX antiseptic 0.12%, dexamethasone drops, and lidocaine spray, three times daily for 14 days. A follow-up after 2 days showed a marked regression of symptoms and completely normal clinical findings after 2 weeks. The patient was recommended an allergy test for antibiotics (amoxicillin, azithromycin); that is, a patch test and a cellular allergen stimulation test enzyme-linked immunosorbent assay (CAST ELISA) with examination by a clinical pharmacologist.

Figure 2 | Stomatitis and erosions (gingiva): a) diffuse erythematous mucosa on the right buccal mucosa, b) diffuse erythematous mucosa on the left buccal mucosa, c) shallow erosions on the attached gingiva (regions 13–15).

Figure 3 | Bullous oral eruption attributed to azithromycin.

Case 8

A 31-year-old female patient came to her first specialist examination because of changes at the corners of the lips. The latency period for the oral lesions was 7 days. Subjectively, she had a burning sensation and a feeling of tightness. COVID-19 was accompanied by left-sided pneumonia, and she was prescribed infusions, gastroprophylaxis, thromboprophylaxis, parenteral clindamycin and cefuroxime, oral azithromycin, methylprednisolone, and remdesivir. As a result of the polytherapy, she developed pseudomembranous enterocolitis caused by *Clostridioides difficile*. She mentioned seborrhea in her medical history. She was not on chronic therapy. She had been a smoker for 6 years and smoked up to 15 cigarettes per day. On inspection, yellowish crusts with erythema were visible at the corners of the lips bilaterally. Brown pigmentation was visible on all the teeth. She underwent treatment involving local therapy for the lips, including a 1% boric acid compress and a combination cream of betamethasone, clotrimazole, and gentamicin applied to the corners of the lips three times a day for 14 days. In addition, oral treatment included miconazole gel administered four times daily for 14 days, and oral probiotics in the form of one lozenge daily for 1 month. A follow-up examination after 2 weeks revealed normal clinical oral findings.

Case 9

A 35-year-old female patient came to her first specialist examination for aphthae. The latency period for the oral lesions was 3 days. COVID-19 was accompanied by fever up to 37.9 °C, headache, and back and joint pain. She denied changes to her eyes and other mucous membranes. She denied intestinal problems. In her medical history, she reported hypothyroidism. She was only taking beta-glucan. She denied allergies. She had been a smoker for 15 years (up to 10 cigarettes a day). Clinically, herpetiform aphthae were visible on the ventral side of the tongue on both sides and on the mucosa of the lower lip. The patient's CBC and differential blood count, serum iron, unsaturated iron-binding capacity (UIBC), total iron binding capacity (TIBC), ferritin, folic acid, and vitamin B12 were noncontributory. CHX antiseptic 0.12% (twice daily for 14 days) and betamethasone dipropionate in orabase (three times daily for 14 days) were prescribed as local therapy. The patient continues to have regular follow-ups because the aphthous eruptions occur approximately every 2 months. She was instructed to use local corticosteroid therapy for recurrent aphthae to improve her quality of life.

Case 10

A 49-year-old male patient came to his first specialist examination in the context of diagnosis of Sjögren's disease. Subjective dryness of the oral cavity, eyes, and skin had been present for years, but this worsened considerably after COVID-19 complicated by bilateral pneumonia. The latency period for the oral lesions was 60 days. He used eye drops three times a day. He did not report difficulty swallowing solid dry food. ANA and ENA results were noncontributory. The Schirmer test result showed an extremely dry eye (2.0 mm and 6.0 mm; reference values: > 10.0 mm). In his medical history, he mentioned a lumbar spine operation (2009) and cervical spine complaints. He was not taking any medication. He was allergic to acetylsalicylic acid (anaphylactic reaction). He was a nonsmoker. Clinical oral findings were normal. UWS (Qs = 0.2 ml/min) and SWS (Qss = 0.6 ml/min) were measured. A biopsy of the minor labial salivary glands was performed. The histopathological findings showed that the chronic inflammatory infiltrate did not fulfil the qualitative or quantitative criteria of chronic sialadenitis in the context of systemic connective tissue disease. The patient was given instructions for the treatment of dry mouth: moisturize the oral cavity with small sips of liquid during the day, chew sugar-free gum (three times a day for 30 minutes), sip mild acidic drinks without sugar (e.g., lemonade), and use marshmallow root tea as a mouthwash.

Case 11

A 60-year-old female patient came to her first specialist examination because of a burning sensation in the lips, and the edges and the tip of the tongue (visual analogue scale, VAS 8/10). The latency period for the oral symptoms was 30 days. The burning pain increased toward evening. There was no discomfort when eating. She denied any change in taste. COVID-19 was accompanied by pneumonia, dry cough, and fever up to 40.0 °C. In her medical history, she mentioned an adnexectomy (2019) and thyroid disease. She was not taking any medication. She denied drug allergies. She was a nonsmoker. Clinical oral findings were normal. The sialometric findings showed normosialia (Qs = 0.4 ml/min). The patient was informed in detail about BMS, a neuropathic pain disorder with a highly probable neuropathic etiology. The limited therapeutic options were explained, and she is followed up regularly once a year.

Case 12

A 76-year-old female patient came to her first specialist examination because of a burning sensation on the tip of the tongue and lack of saliva. The latency period for the oral symptoms was 15 days. The burning sensation on the tongue is of the same in-

tensity throughout the day (VAS 6/10). There was no discomfort when eating. She denied any change in taste. In her medical history, she reported thyroid disease, hypertension, hypercholesterolemia and dizziness. After COVID-19, she was monitored for elevated blood glucose levels. She was taking an antihypertensive (calcium channel blocker), atorvastatin, and betahistine. She denied drug allergies. She was a nonsmoker. The clinical oral findings were normal. UWS (Qs = 0.4 ml/min) and SWS (Qss = 0.8 ml/min) were measured. The sialometric findings showed proper salivary gland function during stimulation. The patient received instructions for dry mouth therapy. At the 3-month follow-up, the patient had normal blood glucose levels. The sialometric results improved, and the subjective feeling of dry mouth decreased. The burning sensation at the tip of the tongue was still present, and so she was informed about BMS and is followed up once a year.

Case 13

The 69-year-old male patient came because of a burning sensation on the tongue. The latency period for the oral lesions was 15 days. In his medical history, he mentioned prostatitis and liver lesions, which he checked regularly. He was taking a combination of dutasteride and tamsulosin. He denied allergies. He was a nonsmoker. Clinically, a geographic and fissured tongue was visible on the mucosa of the dorsum of the tongue. The patient was informed that this was a morphological change in the mucosal structure and not a pathological change. The diagnosis, prognosis, and therapeutic options were explained in detail to relieve the patient of unnecessary worries.

Case 14

A 37-year-old female patient came because of a dry tongue. The latency period for the oral symptoms was 60 days. She denied subjective dryness of the eyes. The ANA, ENA, and Schirmer test results were noncontributory. She did not mention any diseases in her medical history. She was only taking replacement therapy with vitamin D drops. She denied allergies to medication. She has been a smoker for 15 years, smoking up to 10 cigarettes per day. Clinical oral examination revealed discrete, protruding filiform papillae on the mucosa of the dorsum of the tongue (*lingua villosa alba*). UWS (Qs = 0.2 ml/min) and SWS (Qss = 0.4 ml/min) were measured. The sialometry values indicated hyposalivation. The patient was given instructions to treat dry mouth, instructions to clean the mucosa of the dorsum of the tongue with a tongue cleaner (or a special soft brush) once or twice a week, and instructions to stop smoking.

Case 15

A 49-year-old male patient came for a burning sensation on the front half of the tongue (VAS 7/10). The latency period for the oral symptoms was 60 days. COVID-19 was accompanied by pneumonia. The burning sensation on the tongue occurred every day for more than 2 hours. The tongue burning worsened in the evening; cold relieved his discomfort. He also mentioned the occasional dysgeusia (saltiness). CBC, blood iron, UIBC, TIBC, ferritin, blood glucose, folic acid, and vitamin B12 were normal. In his medical history he denied any diseases. He was not taking any medication. He was allergic to penicillin. He was a nonsmoker. Clinical oral findings were normal. UWS (Qs = 0.5 ml/min) and SWS (Qss = 0.9 ml/min) were measured and showed normosialia. The patient was informed about BMS, symptomatic therapy was explained to him (melting small ice cubes in the oral cavity), he was given instructions for the treatment of dry mouth, and he is followed up regularly once a year.

Discussion

Symptoms such as dysgeusia and anosmia are clearly associated with SARS-CoV-2 due to their pathophysiological mechanism (32). However, the data on oral lesions associated with SARS-CoV-2 are confusing. The aim of this case series and literature review was to highlight oral lesions in outpatients that have recovered from a mild and severe form of COVID-19. Therefore, oral lesions in outpatients associated with SARS-CoV-2 can be divided into four categories: 1) true oral lesions directly caused by SARS-CoV-2, 2) opportunistic infections in immunocompromised patients, 3) drug-induced reactions, and 4) their combination.

We presented 15 case series with a mild and severe form of COVID-19, of which 93.3% showed a mild pattern of oral lesions. Only one patient had a severe pattern, and this was a drug-induced bullous oral eruption caused by azithyromicin. We also found no difference in the occurrence of mild and severe patterns of oral lesions between the age groups; that is, the milder clinical picture of oral lesions was equally distributed in younger and older age groups. Moreover, the severity of oral lesions did not correlate with the severity of the clinical picture of COVID-19. Our results are not consistent with those of Brandão et al. They presented eight case series with a mild pattern of oral lesions due to COVID-19 in younger patients (mild COVID-19) and a severe pattern in older patients (severe COVID-19) (19).

The most common clinical entities probably directly caused by SARS-CoV-2 included salivary flow disorders (xerostomia and oligosialia) and salivary gland diseases (sialadenitis and chronic sialadenitis). Our findings are consistent with the results of the systematic review by Amorim Dos Santos et al. and an update of this review conducted 6 months later, in which xerostomia was the main oral manifestation of COVID-19 (1, 33). One of our patients had parotitis (Case 6). This was shown by Lechien et al. who described parotitis caused by SARS-CoV-2 in three patients (34). The pathophysiological mechanism can be explained by the significantly higher number of ACE2 receptors on the salivary glands (including the minor salivary glands) compared to the lungs (35). The prevalence of salivary gland–related symptoms is high, as shown by the results of our case series (36).

Nonspecific erosions and stomatitis are lesions that we tentatively consider true COVID-19 oral lesions (i.e., directly caused by SARS-CoV-2 in our case series). The possible pathophysiological mechanism of the erosions relates to direct damage to the oral mucosa when SARS-CoV-2 binds to keratinocytes and nonkeratinocytes. In addition, the inflammation can be local or systemic and lead to the production of inflammatory cytokines and tumor necrosis factor alpha (TNF-α). As a result, chemotaxis of neutrophils to the site of inflammation occurs, causing nonspecific oral erosions and ulceration (2).

Due to the recognized neurotropic effect of the novel coronavirus, BMS could similarly be regarded as a potential direct consequence of SARS-CoV-2. In our case series, three patients developed BMS after COVID-19 (two women and one man), two of whom recovered from the severe form of COVID-19 and one patient from the mild form. Our results are consistent with those of

Katz et al. and the systematic review and meta-analysis by Williams et al. (37, 38).

In our case series, there are several clinical entities potentially associated with immunosuppression caused by SARS-CoV-2: palatal lesions of ReA, PHGS, aphthae, and geographic tongue. However, aphthae and geographic tongue could also have a dual etiology; that is, directly caused by SARS-CoV-2 and immunosuppression. Oral lesions of ReA are rare and have been described by Glavina et al. (39). It's crucial to distinguish this clinical entity to avoid misattributing oral lesions solely to SARS-CoV-2. PHGS and reactivation of HSV due to immunosuppression by SARS-CoV-2 have also been described in the literature (40, 41). A retrospective cross-sectional study speaks of a strong association between aphthae and COVID-19 (42).

Only one patient had candidiasis (acute atrophic) and overcame a severe form of COVID-19. *Candida albicans* is known to be a commensal of the oral cavity. However, *C. albicans* can cause infections of the oral mucosa and skin as well as systemic infections in immunocompromised patients such as COVID-19 patients (43). The oral candidiasis in the patient (Case 8) is a consequence of the combination of immunosuppression and treatment of COVID-19 and is not directly caused by SARS-CoV-2. A retrospective study conducted in Italy on 27 children showed that acute pseudomembranous candidiasis was the most common form of oral fungal infection (44). We can probably conclude that opportunistic oral fungal infections in COVID-19 are the result of immunosuppression, medications, and poor oral hygiene (2).

Only one of our patients had geographic tongue (Case 13; 6.67%). Our results are consistent with the results of a Spanish study conducted on 666 patients. Nuno-Gonzalez et al. showed the prevalence of geographic tongue in 3.9% of COVID-19 patients (45). The existence of "COVID tongue" is still of great interest in the research community. We believe that geographic tongue has a dual etiology (a combination of the direct cause of SARS-CoV-2 and immunosuppression) due to the following facts: 1) high expression of the ACE2 receptor on the dorsum of the tongue, 2) ACE2 is the cellular receptor responsible for coronavirus entry into cells, 3) geographic tongue has an immunological basis (among others), and 4) COVID-19 is characterized by impaired regulation of cytokines; that is, increased levels of interleukin 6 (IL-6) and IL-17 (5, 46, 47). SARS-CoV-2 could be a trigger and a direct cause for the occurrence of geographic tongue, but it is not yet a pathognomonic sign of early infection with COVID-19. Due to the small number of studies conducted, "COVID tongue" is still a suggestive hypothesis and not a clinical reality.

The most common sites for oral lesions possibly associated with SARS-CoV-2 were the tongue (61.5%), the entire oral cavity (30.8%), the gingiva (23.1%), and the buccal mucosa (15.4%). Our results are partially consistent with those of Rueda et al. In their case series, the lips were the main site for the occurrence of oral lesions in COVID-19, whereas in our case series it was the tongue (48). The latency period of oral lesions associated with SARS-CoV-2 in our case series was 25.1 days. Our results are consistent with those of the case series of hospitalized patients by Rueda et al., for whom the latency period was 22.5 days (48). Wu et al. and Mahmoud et al. reported a significantly shorter latency period; that is, an average of 3.2 days and a maximum of 14 days from the onset of COVID-19 (49, 50).

The limitation of our case series was the lack of a histopathological diagnosis. This decision resulted from several reasons: 1) most lesions were mild, 2) performing an oral biopsy would not modify the therapy for oral lesions, 3) it exposes the patient to unnecessary surgical risk, 4) it introduces additional unnecessary concerns, and 5) it was not in accordance with ethical principles.

Conclusions

Oral lesions likely associated with COVID-19 might be categorized into two groups: 1) oral lesions possibly directly caused by SARS-CoV-2 (nonspecific erosions, stomatitis, salivary flow disorders, salivary gland diseases, BMS, aphthae, and geographic tongue), and 2) other oral lesions potentially linked to SARS-CoV-2 (oral manifestations of ReA, PHGS, drug-induced reactions, cheilitis angularis, candidiasis, and pigmentation). In our cases, oral lesions associated with COVID-19 occurred in middle-aged patients, with an equal distribution by sex. The oral lesions were mild and did not correlate with the severity of the clinical picture of COVID-19. Most oral lesions resolved within 2 weeks. Our small case series suggests that the prevalence of oral lesions caused by and associated with SARS-CoV-2 was low during the 4-year follow-up period. Nevertheless, understanding and identifying the oral lesions potentially linked to COVID-19 during its latency period is crucial for accurately diagnosing and managing both oral and systemic manifestations of the disease.

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Table 1 | **General and main clinical characteristics of outpatients.**

Case	Sex	Age	COVID-19 severity	Latency (days)	Cutaneous/mucous membrane manifestations	Clinical oral findings	Oral symptoms	Location	Suggested etiology
1	F	85	Mild (fever up to 39.4 °C, myalgia)	14	—	Erosions	Burning, pain	Gingiva	Nonspecific erosions
2	F	57	Mild (fever up to 39.0 °C, shallow breathing, headache, myalgia, joint pain, hypogeusia, hyposmia)	14	—	Erosions	Burning, pain	Hard palate	Palatal lesions of ReA triggered by SARS-CoV-2
3	M	46	Mild (fever up to 37.3 °C, malaise)	9	—	Hyperplastic gingiva, erosions, erythematous operculum	Burning, pain	Gingiva, buccal mucosa, tongue (dorsum)	PHGS
4	F	24	Mild (lymphadenopathy)	14	—	Erythema, erosions	Pain	Buccal mucosa, gingiva	Stomatitis, nonspecific erosions
5	F	40	Mild (headache, joint pain, hypogeusia)	28	—	Xerostomia	Dryness	Whole oral cavity	Oligosialia
6	M	53	Mild (anosmia, ageusia, fever up to 39.1 °C, heaviness in the chest)	40	—	Swelling on the right side of the face	Pain while eating	Preauricular	Sialadenitis (parotitis)
7	M	37	Mild (fever up to 38.4 °C, back pain, cough)	7	Genital mucosa	Erosive stomatitis	Pain, burning, difficulty swallowing	Whole oral cavity	Bullous oral eruption caused by azithromycin
8	F	31	Severe (left-sided pneumonia)	7	—	Yellowish crusts, erythema, pigmentation	Burning, tightening	Bilateral corner lip, mucosa of whole mouth, teeth	Cheilitis angularis, acute atrophic candidiasis, tooth pigmentation
9	F	39	Mild (fever up to 37.9 °C, headache, back and joint pain)	3	—	Multiple small round erosions covered by a pseudomembrane and surrounded by an erythematous halo	Pain	Tongue (ventral side), mucosa of lower lip	Herpetiform aphthae
10	M	49	Severe (bilateral pneumonia)	60	Eyes, skin	Xerostomia	Dryness	Whole oral cavity	Chronic sialadenitis
11	F	60	Severe (pneumonia, dry cough, fever up to 40.0 °C)	30	—	Healthy oral mucosa	Burning (VAS 8/10)	Lips, tongue (lateral edges bilaterally, tip)	BMS
12	F	76	Mild (back pain)	15	—	Healthy oral mucosa	Burning (VAS 6/10), dryness	Tongue (tip)	BMS
13	M	69	Mild (malaise)	15	—	Exfoliated areas, fissures	Burning	Tongue (dorsum)	Geographic and fissured tongue
14	F	37	Mild (joint pain)	60	—	*Lingua villosa alba*	Dryness	Tongue (dorsum)	Oligosialia
15	M	49	Severe (pneumonia)	60	—	Healthy oral mucosa	Burning (VAS 7/10), dysgeusia (saltiness)	Tongue (anterior half)	BMS

BMS = burning mouth syndrome, F = female, M = male, PHGS = primary herpetic gingivostomatitis, ReA = reactive arthritis, VAS = visual analogue scale.