Oral Manifestations of Coronavirus Disease 2019 (COVID-19)

A Comprehensive Clinicopathologic and Immunohistochemical Study

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents rapid transmission and significant mortality worldwide. It is responsible for coronavirus disease 2019 (COVID-19). The disease presents diverse clinical symptoms, including fever, cough, dyspnea, and pneumonia. However, other manifestations associated with COVID-19 need to be clarified, leading specialists to an early diagnosis and better prognosis. We describe the spectrum of clinicopathologic COVID-19-related oral lesions that can be the first and/or the unique manifestation of the disease. Fourteen patients with a mean age of 58 years (range: 23 to 88 y) with oral lesions were included. All patients were confirmed to be infected with SARS-CoV-2 by reverse transcription polymerase chain reaction testing. Patients demonstrated mild symptoms, including dysgeusia, anosmia, fever, and headache. The lesions were recognized and classified into 2 groups: (1) lesions caused by ischemia and/or hemorrhage and (2) lesions secondary to inflammatory events associated with viral load. The palate was most affected (n = 8), followed by the tongue (n = 4), and both the lip and palate (n = 2). Histologic analysis demonstrated thrombosis of small arteries and capillaries, associated with areas of hemorrhage and chronic inflammatory infiltrate. Immunohistochemistry showed positive staining for spike protein (SARS-CoV and SARS-CoV-2) and angiotensin-converting enzyme 2 in the surface epithelium, salivary glands, inflammatory cells, and endothelial cells. Although the incidence of oral lesions among patients infected with SARS-CoV-2 appears to be uncommon, these findings suggest that the oral mucosa can also be a target organ for SARS-CoV-2.

Key Words: SARS-CoV-2, COVID-19, oral lesions, thrombosis

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan (China) and has now spread to all countries of the world, reaching ~216 million cumulative cases by August 2021.[1–3] Worldwide epidemiological data show at least 4.5 million deaths directly attributed to COVID-19 since the start of the pandemic, and this number is expected to rise with the ongoing pandemic.[4,5] Brazil represents the second most affected country with ~20 million confirmed cases and more than 570,000 deaths because of the disease, and this number is still increasing dramatically.[6,7]

SARS-CoV-2 enters the cells by binding to angiotensin-converting enzyme 2 (ACE2), expressed mainly in type II alveolar cells, macrophages, smooth muscle cells, and perivascular pericytes.[8,9] Clinical manifestations include fever and respiratory symptoms such as shortness of breath.[10–12] In severe cases, SARS-CoV-2 can lead to pneumonia, multiple organ failure, and death.[13,14] Systemic disease is significantly associated with enhanced concentrations of inflammatory mediators (interferonγ-induced protein 10, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, macrophage inflammatory proteins 1A, interleukins,[2,6,7] tumor necrosis factor-α, and lactate dehydrogenase), causing hyperinflammation syndrome and the induction of a cytokine storm, besides activating the coagulation cascade and thrombotic phenomena.[8–11] Cell infection and viral replication cause systemic inflammation, endothelial cell apoptosis, and microvascular prothrombotic effects in vital organs such as the lung, brain, kidney, and liver.[14–16]

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Since COVID-19 has been established as a systemic disease, a significant effort has been made to understand the alterations in the skin and oral cavity, which can appear as the first (or only) symptoms of this condition. Oral manifestations of COVID-19 include dysgeusia, ulcers, petechiae, and reddish macules.[17–19] However, the nature of these lesions is controversial, as some reports also describe lesions clinically befitting herpes simplex, candidiasis, and geographic tongue. As these oral conditions are commonly seen in patients with psychiatric problems, stress, medication use, and systemic diseases, it is difficult to establish the pathogenesis of these lesions and determine if they are a true manifestation of the disease or an accompanying manifestation. Although some oral lesions have been reported in the context of COVID-19, data regarding histopathological descriptions are still scarce.

In this study, we report a case series of 14 COVID-19-associated oral lesions, considering the histopathologic and immunohistochemical features, and emphasize microthrombosis and the detection of viral proteins.

PATIENTS AND METHODS

This retrospective study included 14 patients with oral lesions associated with COVID-19 from 2 oral and maxillofacial pathology diagnostic centers (Oral Pathology and Stomatology Clinics, Private Clinics, Rio Grande do Norte, Brazil; and Department of Stomatology, A.C. Camargo Cancer Center, São Paulo, Brazil). Biopsies were obtained, and histologic sections were stained with hematoxylin-eosin. The clinicopathologic features were retrieved from the patients' medical files and included age, sex, lesion location, clinical presentation, time of evolution, treatment used, and follow-up. All patients tested positive for SARS-CoV-2 using reverse transcription polymerase chain reaction. Other potential causes of lesions with similar characteristics were carefully analyzed to exclude the possibility of drug-induced reactions and infections. This study was approved by the Ethical Committee of the Dental Piracicaba School, University of Campinas.

Immunohistochemical reactions were performed in 3 μm sections from formalin-fixed, paraffin-embedded tissues that were dewaxed with xylene and then hydrated in a descending ethanol series. Endogenous peroxidase activity was blocked with 10% hydrogen peroxide in a single bath for 15 minutes. After washing in PBS buffer (pH 7.4), the sections were incubated for 2 hours with primary antibodies and then exposed to highly sensitive horseradish peroxidase reagents (ADVANCE, Dako, Carpinteria, CA) and diaminobenzidine tetrahydrochloride (DAB; Sigma-Aldrich, St Louis, MO). The slides were counterstained with Carazzi's hematoxylin for 3 minutes.

All cases were submitted to the same immunohistochemical panel, including the antibodies Ki67, caspase-3, CD34, CD31, D240, CD105, ACE2, and spike proteins (SARS-CoV and SARS-Cov-2). Detailed information about the immunohistochemistry (IHC) antibodies and the methods used in the reactions are shown in Table 1. Negative and positive controls were used (fibrous hyperplasia and lung tissue of patients who died of COVID-19, respectively).

TABLE 1. Antibodies Utilized in This Study

Antibody	Source/Clone	Dilution	Antigen Retrieval
Ki67	Dako/Mib-1	Prediluted	EFTRS-L
CD34	Dako/QBEnd10	Prediluted	EFTRS-H
CD105	Dako/SN6h	Prediluted	EFTRS-H
CD31	Dako/JC70A	Prediluted	EFTRS-H
D240	Dako/Podoplanin	Prediluted	EFTRS-H
Caspase-3	Abcam/Polyclonal	1:300	Citrate buffer (pH 6.0)
ACE2	Santa Cruz/E-11	1:200	Citrate buffer (pH 6.0)
Spike protein	BioSB/BSB-134	1:200	Citrate buffer (pH 6.0)

ACE2 indicates angiotensin-converting enzyme 2; EFTRS-H, EnVision FLEX target retrieval solution, high pH; EFTRS-L, EnVision FLEX target retrieval solution, low pH.

RESULTS

The mean age of the 14 patients was 58 years (range: 23 to 88 y), and 10 were men (71.5%) and 4 were women (28.5%). All patients had mild symptoms that included dysgeusia, anosmia, fever, and headache. None of the patients included in this study were intubated. The oral lesions were classified into 2 groups, although a combination of both occurred in the majority of cases:

(1) Lesions presenting as ecchymosis, purplish areas, and petechiae. These alterations were most commonly observed in the palate and tongue.
(2) Vesiculobullous lesions or ulcerations with ischemic aspects, occurring in any location of the oral mucosa, but mainly on the lips, buccal mucosa, and tongue.

Of the 14 patients, 8 had lesions only in the palate (57.1%), 4 had tongue lesions, and 2 presented lesions in either the lip or palate (14.3%). The clinical aspects included petechia, ecchymosis, reddish macules, and chronic ulcers with more than 7 d of evolution, and some patients presented with vesiculobullous eruptions in the lip, palate, and buccal mucosa (Figs. 1 and 2). Table 2 summarizes the clinical, laboratory, and histopathologic findings of the patients. Most patients with chronic ulcers were treated with topical corticosteroids and the lesions resolved after 1 to 2 weeks. No treatment was used for patients with only vascular lesions, and there was complete resolution within 2 weeks of the initial consultation.

Histologically, the lesions presented epithelial vacuolization with occasional exocytosis, and in the subjacent connective tissue, a chronic inflammatory infiltrate composed mainly of mononuclear cells (lymphocytes and macrophages) of variable intensity was evident. In only 2 cases, polymorphonuclear neutrophils predominated (Figs. 3–5). Thromboses of small arteries and capillaries were also commonly found, showing thrombi in different stages, including newly fibrin-coated thrombi, all associated with areas of hemorrhage. Some studies have reported reorganization processes associated with angiogenesis. Fibrinoid necrosis of the vessels was noted in many cases, mainly in patients with extensive areas of

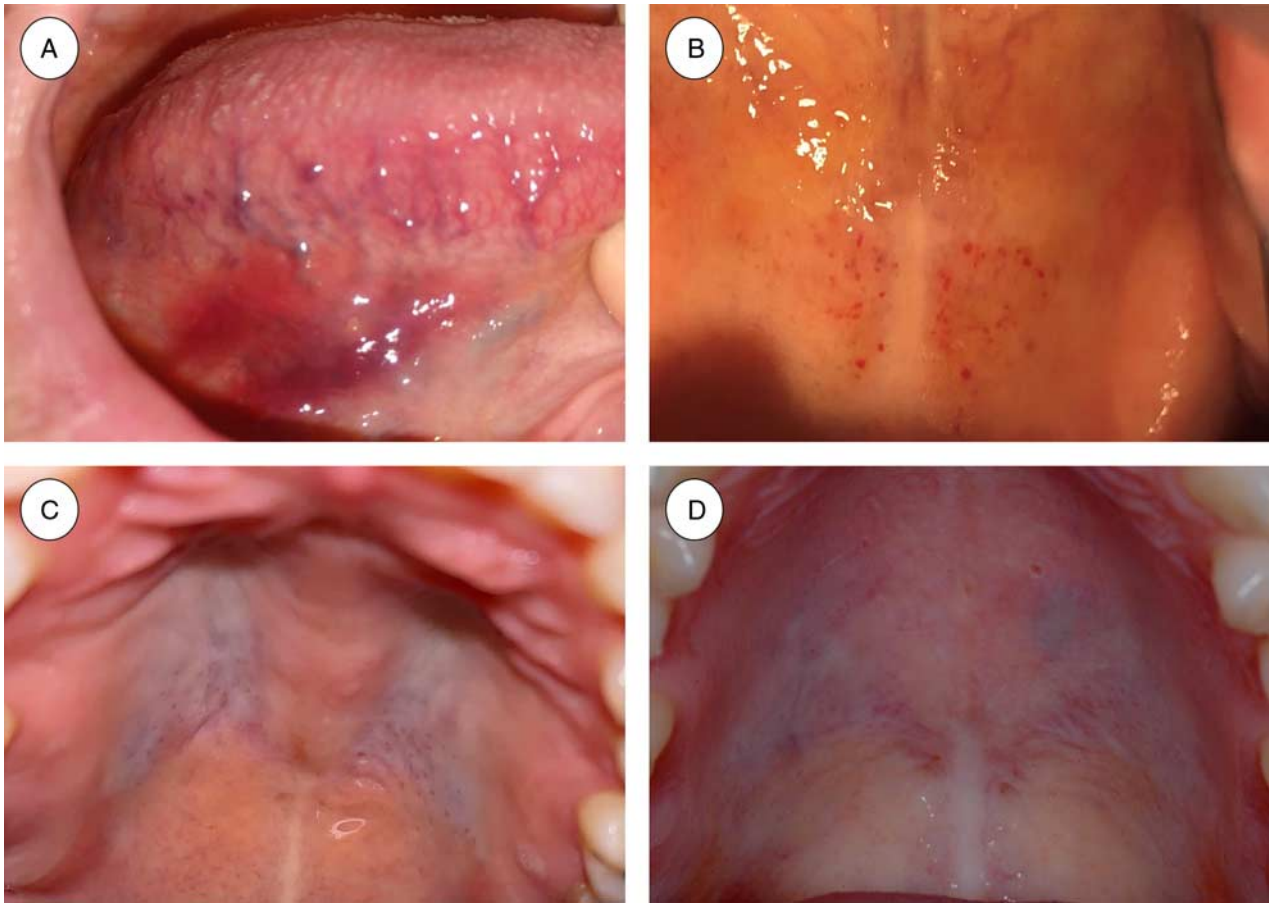

FIGURE 1. Vascular lesions in patients with coronavirus disease 2019. A, Extensive area of ecchymosis on the tongue. B–D, Areas of petechiae associated with ischemic mucosa on the palate.

ecchymosis. In all cases, extravasated erythrocytes were remarkable, confirming ubiquitous hemorrhage.

In the biopsies of the lip and palate, salivary glands showed a moderate inflammatory process (chronic sialadenitis) with acinar atrophy and ductal ectasia, causing fibrosis in some cases. Thrombogenic vasculopathy and necrosis of the vessels were also observed in the glandular stroma.

All but one of the cases were positive for spike protein, demonstrating granular cytoplasmic staining mainly in the endothelial, inflammatory, and epithelial cells. In the salivary glands, positive staining was observed in both the acinar and ductal cells. Strong positivity for spike protein was also detected in the thrombi, suggesting a direct correlation between SARS-CoV-2 infection and the occurrence of thrombotic phenomena. Interestingly, in 8 cases, vacuolated cells of the superficial layers of the epithelium were also positive for this protein, probably representing a direct cytopathic effect.

The endothelial cells surrounding the areas of thrombosis were positive for CD105 and Ki67, indicating neovascularization. Endothelial cells intermingled with thrombotic tissue were positive in the nucleus for caspase-3, denoting a process of apoptosis; most of them were also positive for CD34 and CD31, and negative for podoplanin (D240). ACE2 was strongly positive in endothelial cells, acinar and ductal cells of the salivary glands, and in areas of thrombosis. In the epithelium, weak-to-moderate ACE2 positivity was observed.

DISCUSSION

COVID-19 has emerged as a pandemic associated with the SARS-CoV-2;[1–9] Brazil has presented a dramatic number of cases and deaths.[20] In this context, it is very important to understand how this disease manifests and affects different organs. In the oral region, studies of SARS-CoV-2 are limited to case reports, and clinicopathologic analyses of patients with oral lesions are lacking. Therefore, this study presents a spectrum of the clinicopathologic characteristics of 14 patients with COVID-19 who presented with oral lesions to elucidate the effects of SARS-CoV-2 in the oral cavity.

The most important finding of the present study was the confirmation of the thrombotic process that occurs in oral lesions, as reported previously by our group.[18,19] In summary, our results provide new insights of oral lesions that occur in the context of COVID-19, and we are convinced that some

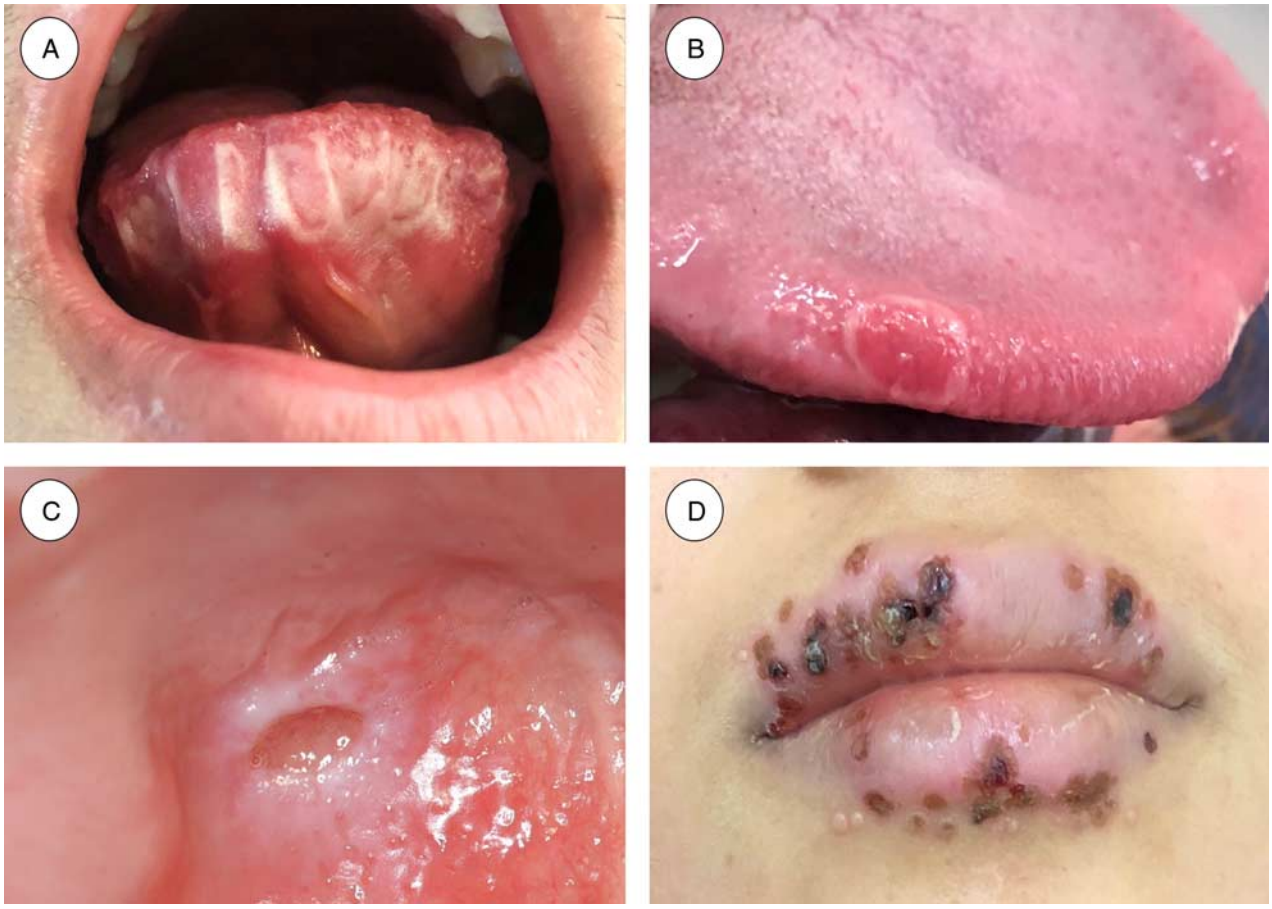

FIGURE 2. Ulcerated lesions in patients with coronavirus disease 2019. A, Extensive areas of ischemic mucosa of the tongue. B, Chronic ulcer with 20 days of evolution, not responsive to treatment with corticoids. C, Ulceration of the palate, with ischemic halo and central areas with white pseudomembrane. D, Vesiculobullous lesions in the lip that evolved to ulceration and sanguinolent crust formation in a young patient.

lesions might represent a real cytopathic effect of SARS-CoV-2 in the oral mucosa. We demonstrated the presence of the virus in the vacuolated cells of the surface epithelium and also in the salivary glands, indicating possible viral transmission by salivary droplets.[21,22] These preliminary results corroborate the hypothesis that salivary secretions may represent the main source of the contagion.[23–25] In fact, coronaviruses other than SARS-CoV-2 have been detected previously in saliva and salivary glands, which are considered a reservoir for several viruses, and saliva has emerged as a promising noninvasive specimen for diagnosis, monitoring, and infection control of patients with SARS-CoV-2 infection.[26,27]

Oral manifestations of COVID-19 have been previously reported and encompass a broad spectrum of clinical presentations, including maculopapular-petechial eruption, painful ulcers, and vesiculobullous lesions.[28–30] Most of these are considered to be nonspecific signs of the disease. However, in previous studies, we have confirmed the presence of SARS-CoV-2 spike protein in salivary glands, endothelium, and in the oral epithelium, confirming an association between COVID-19 and oral lesions. The ulcers occurring in the context of COVID-19 have a particular appearance, with ischemic borders and a central area with a fibrinous pseudomembrane, with the patients reporting a time of evolution of ~21 to 28 days. These lesions must be differentiated from conventional ulcers associated with trauma, which generally show an erythematous halo and complete their resolution in ~7 to 14 days.[18,19]

The oral lesions appear concomitant to the increase in SARS-CoV-2 binding with ACE2. When the infection occurs, the interaction between SARS-CoV-2 and ACE2 may cause disruption of the epithelial lining of oral mucosa, leading to the permeability of the mucosa to foreign pathogens, generating ulcers, and necrosis.[21]

Evidence of the direct infection of the oral tissues is presented: (1) the immunohistochemical identification of viral spike protein in oral lesions of COVID-19 patients; and (2) the elevated expression of ACE2 (the enzyme that facilitates entry of the virus into the cell) in the minor salivary glands.[31] In fact, several authors have demonstrated the presence of the virus against the SARS-CoV-2 spike protein in endothelial cells, pneumocytes,[32] small bowel submucosa,[33] and sweat glands of the skin using

TABLE 2. Clinical, Laboratory, and Histopathologic Findings of the Patients

ID	Sex	Age	Oral RT-PCR	Nasal RT-PCR	Oral lesions	Localization	Systemic Symptoms	Comorbidity and Risk Factors	Histopathology	IHC—Spike Protein
1	M	63	+	+	Extensive ecchymosis	Tongue	Fever and cough, cutaneous rash	Hypertension and diabetes	Thrombi in different stages, hemorrhage and intense inflammation	+, surface epithelium, vessels and SG
2	M	71	+	+	Ischemic mucosa and petechiae	Palate	Headache and anosmia	Diabetes	Ulcer with fibrinoid necrosis of the vessels	+, surface epithelium
3	M	88	−	+	Chronic ulcer	Tongue	Dry cough and loss of taste	None	Ulcer with chronic inflammatory infiltrate and thrombosis	Negative
4	F	39	+	+	Ischemic mucosa and chronic ulcer	Palate	Only cough	NA	Chronic sialadenitis, mild inflammatory infiltrate, epithelial vacuolization	+, ductal and acinar cells of the SG
5	F	23	+	−	Vesiculobullous lesions and petechiae	Lip and palate	Asymptomatic	None	Chronic sialadenitis, microthrombosis	+, surface epithelium and SG
6	M	64	+	+	Ischemic extensive ulcer	Palate	Only fever (up to 39°C)	Hypertension	Intense vasculitis, thrombosis and chronic inflammatory infiltrate	+, vessels and inflammatory cells
7	M	31	+	−	Vesiculobullous lesions and petechiae	Lip and palate	Asymptomatic	None	Chronic sialadenitis, microthrombosis	+, surface epithelium and SG
8	M	56	+	−	Multiple minor ulcers and petechiae	Tongue	Fever and dyspnea	Hypertension	Endothelial proliferation, microthrombosis	+, vessels and surface epithelium
9	F	53	+	+	Reddish macule and chronic ulcer	Palate	Only dyspnea	COPD	Thrombosis and vasculitis, epithelial vacuolization	+, vessels and surface epithelium
10	M	45	+	+	Extensive areas of ischemic mucosa	Tongue	Headache and anosmia	None	Microthrombosis, vasculitis and mild inflammation	+, diffuse in SG and inflammatory cells
11	M	69	+	+	Chronic ulcer and ecchymosis	Palate	Asthenia and fever	None	Fibrinoid necrosis of the vessels, thrombosis and hemorrhage	+, vessels
12	M	72	+	+	Painful chronic ulcers and reddish macules	Palate	Dry cough and dyspnea	Hypertension and diabetes	Intense vacuolization of the surface epithelium, thrombosis and hemorrhage	+, vessels and surface epithelium
13	F	70	NA	+	Reddish macules and chronic ulcer	Palate	NA	None	Disseminated microthrombosis, mild inflammation	+, vessels and surface epithelium
14	M	66	+	+	Petechiae	Palate	Only dry cough	None	Hemorrhage and microthrombosis	+, diffuse in SG and surface epithelium

COPD indicates chronic obstructive pulmonary disease; F, female; M, male; NA, not available; RT-PCR, reverse transcription polymerase chain reaction; SG, salivary glands.

IHC.[32,34] The tropism of these viruses for glands in general is not surprising, and it is well known that viral infections can manifest as parotid enlargement, for example, human immunodeficiency virus and cytomegalovirus.[32] These findings support the hypothesis that salivary glands can be a natural reservoir for the virus.

Nevertheless, the clinical and microscopic characteristics of these oral lesions raise some controversial points. Herein, we describe the microscopic characteristics of biopsies of oral lesions related to COVID-19, including perivascular infiltrate, chronic sialadenitis, and thrombogenic vasculopathy, findings that were shared by most of the clinical presentations. In the lungs, the alveolar walls are expanded and multiple fibrinous microthrombi in the alveolar capillaries are observed.[35] The present findings are also observed in oral lesions and might be suggestive—but not conclusive for—COVID-19. These features can also be seen in a number of other inflammatory conditions unrelated to COVID-19, such as reactive, vascular, and inflammatory diseases but they also share similarities with histologic descriptions of skin lesions associated with COVID-19.[36,37] Thus, COVID-related lesions must be evaluated while correlating the concurrent clinical, histologic, immunohistochemical, and laboratory findings.

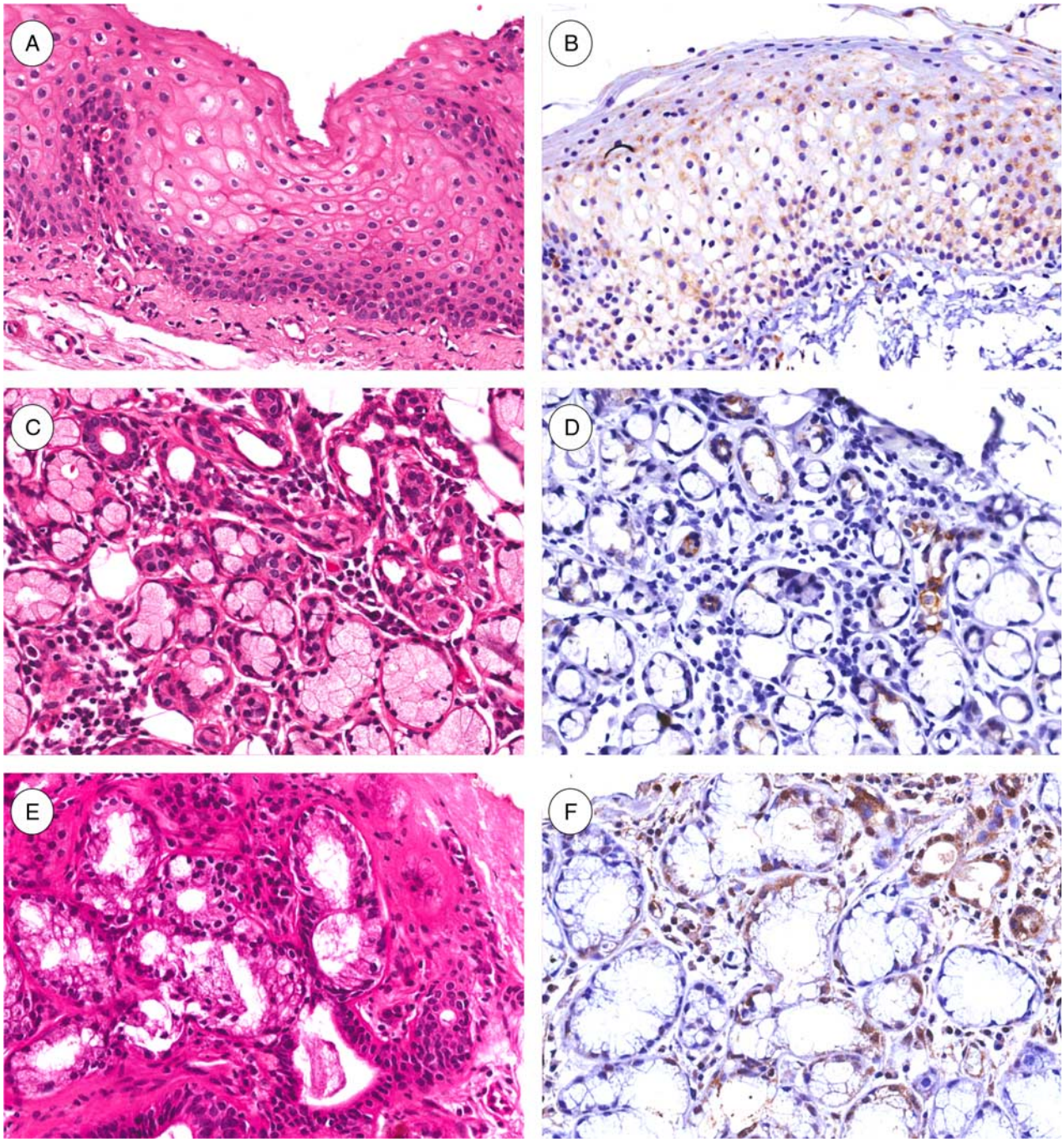

FIGURE 3. Histopathologic and immunohistochemical findings of oral lesions in patients with coronavirus disease 2019. A, Epithelium demonstrating vacuolization of the superficial layers. B, These vacuolated cells were positive for spike protein, confirming the presence of the viral material. C, Chronic sialadenitis in a patient with an ulcerated lesion in the palate. D, Focal positivity for spike protein in the ductal structures. E, Fibrosis in the salivary gland of a patient with lesions on the tongue. F, Immunohistochemistry for spike protein demonstrated intense positivity in acinar and ductal cells.

Nevertheless, some points remain unclear: Are the oral cavity and salivary glands relevant target organs for COVID-19? Are the lesions caused directly by SARS-CoV-2, or do these lesions represent only the side effects of the hyperinflammatory status and the use of drugs?

Thrombotic phenomena are well described in several organs in the context of COVID-19 (lung, kidney, and skin).[37–39] In fact, this disease primarily involves the lungs, but it represents a systemic disease, with endothelial cells as important target cells of SARS-CoV-2.[12,15,39] Thus, any

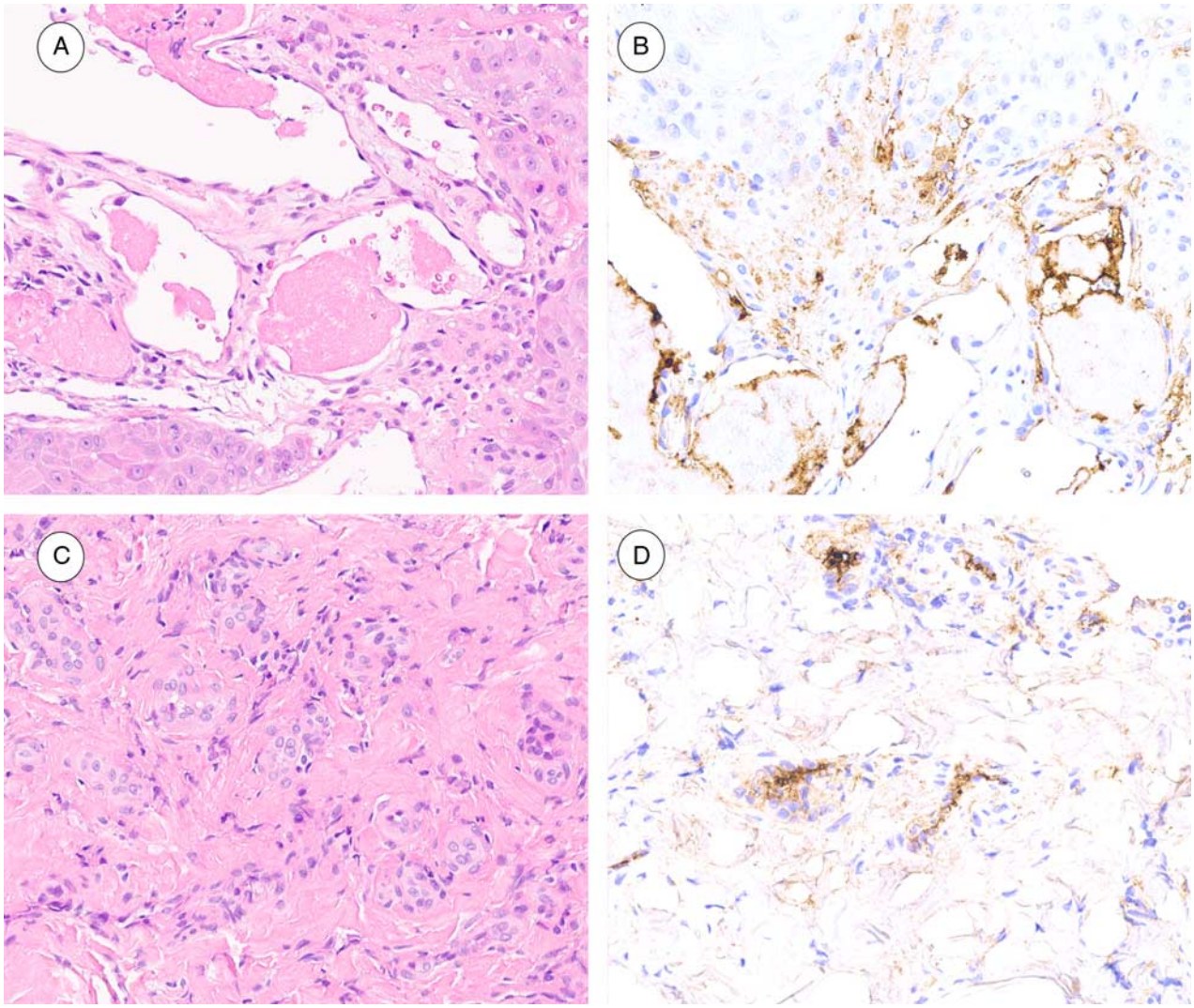

FIGURE 4. Histopathologic and immunohistochemical findings of lesions on the palate of a patient with coronavirus disease 2019. A, Vessels with fibrin thrombi. B, Positivity for spike protein in endothelial cells. C, Vessels appear to be in proliferation, showing some endothelial cells with ample cytoplasm and nuclei; these cells were positive for CD105 and spike protein (D).

organ, depending on the systemic involvement, can be affected by thrombotic disease. In the oral tissues, we observed thrombi of diverse morphology and different times of evolution, ranging from fibrin thrombi and recanalized thrombi to vessels with fibrinoid necrosis. These events corroborate the IHC findings, where apoptotic markers were positive in endothelial cells, suggesting a role in the pathogenesis of the lesions.[32–34] We hypothesize that vessel damage causes activation of the coagulation cascade with consequent consumption of coagulation factors favoring the appearance of vascular, vesiculobullous lesions, and chronic ulcers in the oral cavity.

In addition to hyperinflammation and the eventual side effects of drugs, the direct cytopathic effect of the virus, as occurs in other organs such as the lungs, should also be considered in the pathogenesis of oral lesions.[37] In fact, we confirmed the presence of spike protein in the surface epithelium and also in the salivary glands.[19] Thus, oral lesions could be a result of diverse mechanisms, such as direct effects of the virus, hyperinflammation, side effects of drugs, or trauma. To date, we do not know the frequency of the incidence of oral lesions or the association with viral load or clinical status of the patients. These lesions appear to be more common in patients with moderate disease but can also occur in asymptomatic individuals. Patients with severe COVID-19 also have oral lesions, which are more likely to be associated with trauma because of intubation and appear to be not associated with cytopathic effects.[21]

In conclusion, although the incidence of oral lesions among patients infected with SARS-CoV-2 remains unclear, the detection of viral proteins in the oral mucosa and the presence of thrombotic vessels and hemorrhage elucidate COVID-19 pathogenesis in the oral mucosa. Moreover, surveillance of oral lesions and other oral symptoms in patients with COVID-19 can assist in the early diagnosis of the disease.

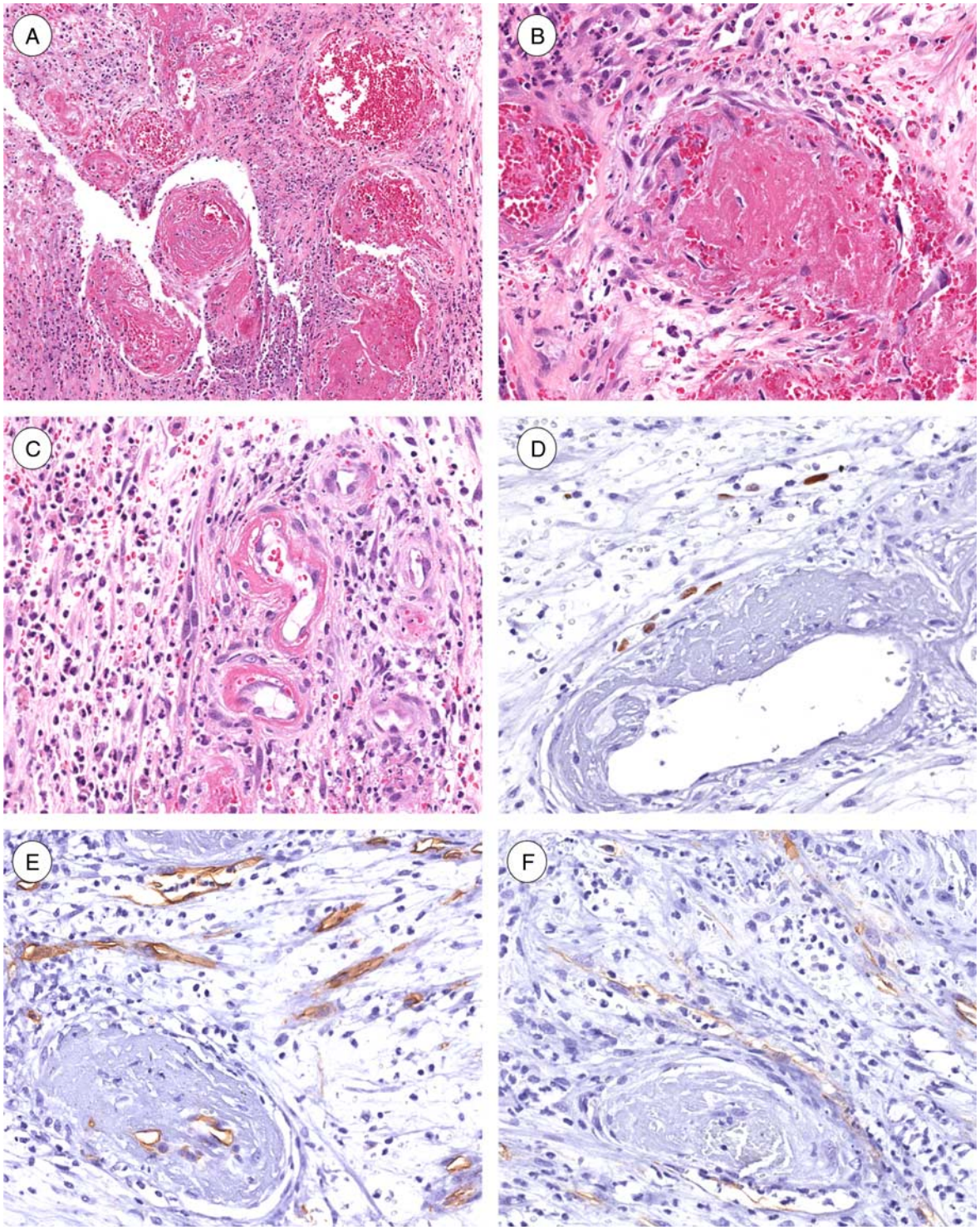

FIGURE 5. Histopathologic and immunohistochemical findings of lesions in a coronavirus disease 2019 positive patient with extensive ecchymosis. A, Vessels of different sizes with fibrin thrombi associated with areas of hemorrhage. B, In detail, some thrombi demonstrate a reorganization process, with new vessels in the interior of the thrombi. C, Some vessels demonstrate fibrinoid necrosis, which was also a common finding. D, The endothelial cells were positive for caspase-3, indicating apoptosis. The great majority of the vessels were positive for CD34 (E) and negative for D240 (F), indicating that the virus has a particular tropism for blood vessels while lymphatic vessels appear to be not involved in the pathogenesis.

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