

# ORAL CAVITY- A MAJOR TARGET OF COVID-19: PART-1

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## Abstract:

Since ages several viruses have been studied and said to be transmitted through saliva, such as herpes simplex virus, cytomegalovirus, etc. They are capable of infecting and replicating in the oral mucosa, leading to painful oral ulcers. Newer studies have described the oral manifestations of coronavirus disease 2019 (COVID-19). There is growing evidence that angiotensin-converting enzyme 2 (ACE2), the main host cell receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is highly expressed on the epithelial cells of the tongue and of the salivary glands. With this knowledge, it is important to understand if SARS-CoV-2 can infect and replicate in oral keratinocytes and fibroblasts, causing oral ulcerations and superficial necrosis. In this review of the available literature regarding different oral manifestations of COVID-19 and the role of ACE2 in SARS-CoV-2 cellular entry is described, thus bringing in new insights into oral keratinocytes and minor salivary glands as potential targets.

**Keywords:** ACE2, COVID-19, Oral Manifestations, SARS COV 2, Target organ in host.

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## INTRODUCTION:

The global pandemic burden has recently emerged by the human-to-human transmission of the novel coronavirus disease (COVID-19). Since its outbreak in December 2019, COVID-19 has affected more than 8,87,82,137 people worldwide as of 9th January 2021. (World Health Organization, 2020). The mode of infection spread, the resulting severe acute respiratory syndrome, and the global death toll. Coronavirus disease 2019 (COVID-19) has had a massive impact on health, wealth, and social aspects worldwide. Since the identification of this novel airborne infectious microorganism named severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] in Wuhan, China, millions of cases have been

diagnosed worldwide, with mortality rates ranging from 3% to 12%.<sup>1</sup>

Most of the cases of COVID-19 are mild (80%), whereas in 20% of cases, patients may develop severe disease, and 5% may become critically ill and develop pneumonia or acute respiratory distress syndrome that requires mechanical ventilation and intensive care unit hospitalization for the patient.<sup>1</sup> The most common symptoms of the disease are fever and dry cough and, in some cases, shortness of breath, dysosmia, and dysgeusia.<sup>2</sup> In addition to fever, fatigue, dry cough, myalgias, sore throat, breathing difficulties, and respiratory complications that often deteriorate to a severe acute respiratory syndrome, some patients infected by SARS-CoV-2

have developed a myriad of other local and systemic complications. They can be acute cardiac damage, acute renal failure, gastrointestinal complications, dysgeusia, anosmia, and rarely neurologic symptoms like Guillain-Barre syndrome.<sup>3-4</sup>

Some authors in Italy reported cases with the dermatologic implication in patients who suffered from SARS-CoV-2 infection.<sup>5</sup> Since then, there have been more reports describing dermatologic involvement, including lesions ranging from hands and feet to vasculitis, rash, urticaria, and varicella-like lesions.<sup>6</sup> Although SARS-CoV-2 is detected in saliva and oropharyngeal secretions, its routes of infection remain elusive, and little is known about the routes of transmission through the oral mucosa. Thus, more clinical evidence and research are needed to confirm the ability of SARS-CoV-2 to infect the oral tissues, and its pathogenic mechanisms in the oral and oropharyngeal mucosae need to be explored.

Hence, this review provides a comprehensive summary of oral manifestations in patients with COVID-19 by reviewing the relevant studies (PubMed, SAGE, IJOS, Oral Diseases, OOOO Journals, and some individual case reports) recently published concerning oral manifestations of COVID-19 to answer questions like:

### **What is the nature of the oral signs and symptoms in patients with COVID-19? Could the oral cavity be a target organ of COVID-19?**

Current research indicates that coronavirus invades human cells via the receptor angiotensin-converting enzyme 2 (ACE2) through scRNA-seq data analyses.<sup>7</sup> Therefore, cells with ACE2 receptor distribution may tend to become host cells for the virus<sup>8</sup> and cause an inflammatory response in related organs and tissues, such as the tongue mucosa and salivary glands.<sup>9</sup> SARS-CoV-2 interaction with ACE2 receptors has also been shown to impair taste bud sensitivity, which could induce dysfunctional gustatory responses.<sup>10</sup>

Some of the oral signs and symptoms related to COVID-19 are taste disorders, unspecific oral ulcerations, desquamative gingivitis, petechiae, and co-infections like candidiasis, as reported by some of the case reports.<sup>11</sup> However, it is still not sure

whether these manifestations could be a typical clinical pattern resulting from the direct SARS-CoV-2 infection or a systemic consequence due to the possibility of co-infections, impaired immune system, and adverse reactions of medical treatment of the disease itself.<sup>11</sup> Since the prevalence of clinical manifestations is still unknown, the range of COVID-19 presentations on the oral cavity as the virus's target is considered as broad and of current interest in this review.

### **Oral manifestations can be broadly divided into three groups:**

1. Oral mucosal lesions.
2. Oral osseous lesions.
3. Taste disorders.

### **ORAL MUCOSAL LESIONS**

Several viruses are transmitted through saliva, such as herpes simplex virus, cytomegalovirus, and Zika virus, which are capable of infecting and reflecting in the oral mucosa, leading to painful oral ulcers. Though the virus is said to be "Novel Coronavirus," a few impactful studies have described the oral manifestations of this coronavirus disease 2019 (COVID-19). There is also growing evidence that angiotensin-converting enzyme 2 (ACE2) is the primary host cell receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is highly expressed in the epithelial cells of the tongue and of the salivary glands. This may explain the development of dysgeusia in patients with COVID-19. Hence, it is vital to recognize whether SARS-CoV-2 can infect and replicate in oral keratinocytes and fibroblasts, causing oral ulcerations and superficial necrosis. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is also detected in the cell membrane of numerous other human organs and tissues. These may include the lungs, kidneys, liver, epithelial cells of the tongue and salivary glands, upper respiratory tract, nervous system, and skeletal muscle.<sup>7</sup>

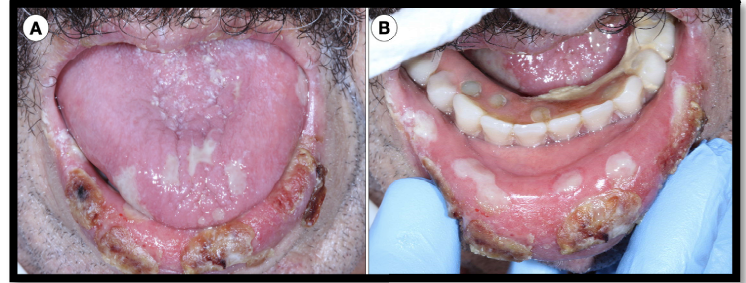
Although SARS-CoV-2 can be detected in saliva and oropharyngeal secretions, its routes of infection remain elusive, and very little is known about the routes of its transmission through the oral

mucosa. Thus, more clinical evidence and research are needed to confirm the ability of SARS-CoV-2 to infect the oral tissues and its pathogenic mechanisms in the oral and oropharyngeal mucosae. Hence in this review, we have tried to describe different presentations of Covid-19 in the oral environment by compiling other cases from various case reports and case series available in the recent literature on Covid-19.

## CLINICAL PRESENTATION OF ORAL MUCOSAL LESIONS

### CASE PRESENTATION 1:-

An 81-year-old man reported with cough and progressive chest tightness present for ten days. The patient had a medical history of well-controlled hypertension and chronic obstructive pulmonary disease. The patient had signs of dysgeusia, chills, and fever. The patient also developed a dry cough and mild dyspnoea afterward and was treated using azithromycin and ceftriaxone for seven days. The diagnosis of COVID-19 infection was made on real-time Reverse Transcriptase-Polymerase Chain Reaction (rRT-PCR) amplification of the viral DNA from a collected pharyngeal sample. Head and neck examination did not identify any asymmetries, swellings, or enlarged cervical lymph nodes. Still, the oral examination revealed multiple shallow aphthous-like ulcers of varying sizes and irregular margins covered with mucopurulent membrane, suggesting superficial necrosis in the upper and lower lip mucosa as well as the anterior dorsal tongue (*Figures 1A and 1B*). The lesions were painful on palpation. Herpes simplex virus (HSV-1) was detected in the saliva sample by PCR. The patient was immediately started on intravenous acyclovir 250 mg/m 3 times a day for ten days, but there was no clinical improvement. To manage the pain associated with the oral ulcers, a trained dentist administered daily photobiomodulation therapy (PBMT) for ten consecutive days. After 16 days in the intensive care unit (ICU) and 14 additional days in a critical care unit, the patient's clinical course and respiratory status showed an improvement, so he was discharged.<sup>12</sup>



**Fig. 1. A, Clustered ulcers 1 to 1.5 cm in diameter covered with crusts occurring on the lower lip (vermilion). Ulcerative painful lesions with superficial necrosis affecting the anterior dorsal tongue. B, Lower lip mucosal ulcers covered with a mucopurulent membrane and the so-called aphthous-like pattern.**

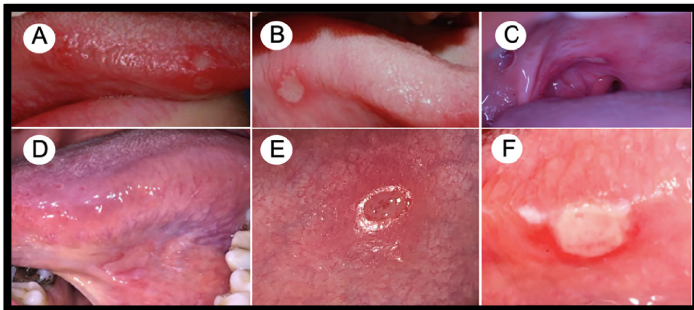
### CASE PRESENTATION 2:-

An 83-year-old female patient reported for abdominal distension and mild dyspnea. Her past medical history was significant for obesity, Parkinson's disease, hypertension, pancreatitis, and chronic obstructive pulmonary disease. Lung CT showed discrete hyperdense areas in both lungs. rRT-PCR for SARS-CoV-2 yielded positive results, and the patient was placed in an isolation ward. Head and neck examination results were negative. The intraoral examination identified a 1.5 X 1.5 cm ulcer on the right lateral border of the tongue and a discrete area in the anterior hard palate affected by a petechia and a shallow necrotic area (*Figures 2A and 2B*). Both lesions were painful and developed simultaneously to hospital admission. PCR of saliva was negative for HSV-1. The patient started receiving PBMT according to the standard protocol of the hospital. Complete pain control was achieved after five days of light therapy. Because of the mild respiratory symptoms, the patient was placed in a critical care unit and showed improvement after ten days of hospitalization.<sup>12</sup>



**Fig. 2. A: Painful ulcer on the right lateral border of the tongue. B: Focal erythema/petechia and a shallow necrotic area on the anterior hard palate.**

Several other similar presentations have been reported in the literature. (Fig. 3)<sup>12</sup>



**Fig. 3. Lesions are presenting an aphthous-like pattern. A, B, Patient presenting with multiple shallow ulcers at the tongue's apex and anterior lateral border. C. Patient with an isolated peritonsillar major aphthous-like ulcer. D. Patient showing solitary, painful ulcer in the ventral portion of the tongue. E. Patient with ulcerated lesion with slightly elevated and a marked erythematous halo. F, Patient has an aphthous-like ulcer covered by a necrotic membrane on the tongue's lateral border.**

#### APHTHOUS ULCERATIONS AND DESQUAMMATIVE GINGIVITIS DURING COVID PANDEMIC (Cases courtesy- Dr. Om Baghele)

It has been observed by some of the authors that, the incidence of major aphthae and desquamative gingivitis-like lesions was higher during the lockdown period because of Covid-19, especially during the month of April to August 2020. This was the period when even dental clinics were closed apart from urgent case management. Many calls for telephonic consultations were regarding oral

ulcerations may or may not be associated with pharyngeal inflammation. Many of these cases refused to undergo Covid testing for obvious apprehensions. We also found it is difficult to follow up such cases (telephonic consultations) for pre- or post-covid exposures. We asked for photographs to be taken with their mobile phones, whenever possible and submit for further diagnosis and management. Many of these patients were experiencing these ulcerations for the first time. When there is no corroborative Covid history these patients were treated with regular established management for aphthous ulcerations and desquamative gingivitis.

Although we can't say whether these lesions were because of SARS CoV-2 infections, definitely there prevalence has increased during the lockdown period. The tension and uncertainty of Covid, job losses or reduced pay packages, restrictions on activities and increased cost of living may have triggered forced behavioural changes leading to stress. Both these disorders are found to be positively associated with stress, nutritional deficiencies and immunocompromised states.



**Fig 4: Few photographs sent through telephonic consultations are presented here, few are also showing pre- and post-treatment clinical picture. (Photographs courtesy- Dr Om Baghele)**

The living systematic review aimed to summarize evidence on the prevalence of oral signs and symptoms in patients with COVID-19 was reviewed. Oral mucosal lesions showed various clinical aspects, varying in localization, size, color appearance, and quantity. Patients presented blisters, ulcers, erosion, macule, and plaques. Four patients showed oral mucosal lesions in a localized area, while the lesions were diffuse in 3 patients, and data were not

reported for one patient. Tongue mucosa was affected in 5 cases, while injuries on the lips and palate were reported in 3 points each, and buccal mucosa and gingiva were described once in different patients (Table 1).

**Table 1. Oral Lesion Characterization in Patients with COVID-19 (n = 7 Studies)<sup>13</sup>**

Study	Oral Signs and Symptoms	Location on Oral Mucosa	History of Appearance	Duration and Recovery	Reported Diagnosis
<b>Amorim dos Santos (2020), Brazil</b>	1) White plaque. 2) Multiple pinpoint yellowish ulcers. 3) Nodule. 4) Severe geographic tongue + fissured tongue. 5) Extremely viscous saliva	1) Tongue dorsum 2) Tongue dorsum. 3) Lower lip	On the 24th day of hospitalization, the white plaque was persistent and associated with yellowish ulcers. Two weeks later, severe geographic tongue was observed	14 d after the first oral examination, the lesions on the tongue dorsum resolved almost completely. Severe geographic tongue improved to moderate within approximately 17 days after its appearance	1) Fungus infection. 2) Herpetic recurrent oral lesion. 3) Fibroma. 4) Geographic tongue. Authors suggested that oral lesions, coinfections, and secondary manifestations may be due to systemic condition of the patient
<b>Ansari (2020), Iran</b>	Several painful ulcers, with irregular margins and varying sizes in red and nonhemorrhagic background	Case 1: Hard palate. Case 2: Anterior region of the tongue	Case 1: 5 d after the onset of symptoms. Case 2: 1 week after hospitalization	Approximately 7 d of duration until complete recovery	Diffuse edema with desquamation, granulation, and ulceration under the mucosa, with invasion of mononuclear and neutrophilic cells, indicating a secondary bacterial infection. Negative serologic tests for herpes simplex virus type 1 and 2. Authors suggested that oral lesions are due to COVID-19
<b>Cebeci Kahraman (2020), Turkey</b>	1) Largely erythematous surface. 2) Few petechiae. 3) Numerous pustular enanthema (1 to 3 mm in	1) Oropharynx and hard palate. 2) Palate midline. 3) Near soft palate border, more prominent on the left side	10 d after the onset symptoms	After a few days of therapy	Diffuse oropharyngeal erythema, petechia, and pustule formation. Authors suggested that oral mucosal may be involved in COVID-19 symptoms

	diameter)				
<b>ChauxBodard (2020), France</b>	Irregular ulcer	Dorsal side of the tongue	First symptom: a painful inflammation of a tongue papilla. 24 h later: erythematous macula. After, the lesion turned to an irregular and asymptomatic ulcer	10 days of duration until complete recovery	COVID-19 is associated with inflammatory reactions, such as vascular inflammation. The ulcer observed after a macular erythematous lesion could be explained by vasculitis. Authors suggested that these oral ulcers could be an inaugural symptom of COVID-19
<b>Martin Carreras-Presas (2020), Spain</b>	1) Pain. 2) Small blisters. 3) Desquamative gingivitis	1) Tongue. 2) Internal lip mucosa. 3) Gingiva	1) With first symptoms. 2 and 3) 1 mo after first symptoms	3 days of duration and treatment until recovery	Suggestive of erythema multiforme. Authors suggested that SARS-CoV-2 may provoke exanthematic lesions
<b>Putra (2020), Indonesia</b>	Stomatitis aphthous	Not reported	7 d after the first symptom (fever)	3 days of duration until recovery	Stomatitis aphthous. Authors suggested a diagnosis of hand, foot, and mouth disease
<b>Soares (2020), Brazil</b>	1) Painful ulceration. 2) Multiple reddish macules of different sizes	1) Buccal mucosa. 2) Scattered along the hard palate, tongue, and lips	Not reported	21 days of duration until complete recovery	Diffuse chronic inflammatory infiltrate with focal areas of necrosis and hemorrhage in the lamina propria. Intense lymphocytic infiltration in adjacent minor salivary glands. Negative IHC reactions against HHV-1, HHV-2, CMV, treponema pallidum, and EBV. Authors suggested that oral mucosal may be involved in COVID-19 symptoms

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HHV: Human herpesvirus; IHC: Immunohistochemical.

In the 2 cases, first oral manifestations developed in association with the initial systemic symptoms (Chaux-Bodard et al. 2020; Martin Carreras-Presas et al. 2020). Also, patients with severe COVID-19 infection developed late lesions

between the 7th and 24th day after symptom onset (Amorim dos Santos et al. 2020; Ansari et al. 2020; Cebeci Kahraman and Caşkurlu 2020; Martin Carreras-Presas et al. 2020; Putra et al. 2020). In all patients, the lesions healed within 3 to 21 d through topical treatments, by oral hygiene, or spontaneously. Two patients presented negative serological test results for herpes simplex virus type 1 and 2 antibodies (Ansari et al. 2020), and 1 showed negative immunohistochemical reactions against herpes simplex virus types 1 and 2, cytomegalovirus, *Treponema pallidum*, and Epstein-Barr virus (Soares et al. 2020). However, other infectious, inflammatory, and autoimmune disorders could not be excluded from the diagnosis. Therefore, oral mucosal lesions seemed to develop as secondary manifestations and co-infections related to the patients' weakened systemic condition.

## DISCUSSION

This review presented several cases of SARS-CoV-2 infection, with oral manifestations developing during the infectious period of the disease. Of importance, the oral presentations appeared concomitant with the loss of taste and smell. The oral lesions were more severe and widespread in older patients with more severe COVID-19 infection. The observed lesions presented two well-defined and distinct patterns, one resembling aphthous-like ulcers in young patients with mild cases of COVID-19 and another with more widespread patterns resembling HSV-1 necrotic ulcers in the more severe and immunosuppressed older individuals<sup>14</sup> (Table 2).

**Table 2. Clinical features of the oral ulcers in patients with COVID-19**

Patient	Gender	Age	COVID-19 severity	Anosmia	Dysgeusia/Ageusia	Oral lesion	Time to onset (days)	Duration
1	M	81	Severe	No	Yes	Aphthous-like + necrosis	5	11
2	F	71	Severe	No	Yes	Hemorrhagic ulcerations with necrotic areas	4	> 15
3	F	83	Mild	No	No	Aphthous-like + necrosis	2	5
4	M	72	Mild	No	No	Aphthous-like + necrosis	5	7
5	F	32	Mild	Yes	Yes	Aphthous-like	10	5
6	M	35	Moderate	Hyposmia	Yes	Aphthous-like	6	8
7	M	29	Mild	Yes	Yes	Aphthous-like	8	5
8	M	28	Mild	Yes	Yes	Aphthous-like	8	6

COVID-19, coronavirus disease 2019; M, male; F, female.

The recently published tropism of SARS-CoV-2 to the tongue and salivary gland epithelium are essential, suggesting that the virus may target the

oral mucous membrane. This leads us to speculate that the development of oral manifestations in these patients may be directly associated with the COVID-19 infection. Whether the lesions are caused directly by the virus or are an associated manifestation resulting from the patient's severely compromised state remains to be determined. Nevertheless, considering that the distribution of ACE2 receptors may determine the route of SARS-CoV-2 infection, the presence of ACE2 receptors on the tongue and salivary glands, as recently described, suggests that the epithelial cells of the tongue and the salivary glands may be involved in COVID-19 infection and the dysfunction caused by it. This could lead to the development of dysgeusia and oral mucosal ulcerations, and necrosis. Thus, the interaction between SARS-CoV-2 and ACE2 might disrupt the function of oral keratinocytes and the epithelial lining of salivary glands ducts, resulting in painful oral ulcers. Therefore, understanding the pathogenesis of COVID-19 infection is vital for developing robust infection control in dental offices and hospitals. After infection of the oral keratinocytes/glandular tissues, there is an increase in the cell walls' permeability to foreign pathogens and viral replication in the cells lining the oral mucosa, leading to ulcers and necrosis.

Unlike taste disorders, oral mucosal lesions were described in only a few case reports, to understand whether this type of condition is directly caused by SARS-CoV-2 or represents secondary manifestations disorderly taste responses is inconclusive. Thus, it is important to carry out clinical oral examination of patients with infectious diseases in the intensive care unit, given the need for support, pain control, and quality of life in Covid-19 patients.

## CONCLUSION

Oral symptoms are not frequently described in clinical studies related to COVID-19. This review suggests a new etiopathogenic mechanism between ACE2 and SARS-CoV-2 may exist in the oral cavity. Hence additional clinical and epidemiologic data are required to validate this hypothesis. Awareness of such oral manifestations is essential because the lesions may precede the typical respiratory

symptoms by several days, and the oral lesions' worsening may precede a more serious clinical scenario. Additional studies need to investigate whether SARS-CoV-2 infection directly causes oral ulcerations or whether oral lesions are a coincidental event with COVID-19 progression. Dentists working in the hospital setting or ICUs should perform careful oral and oropharyngeal examinations and document suspicious oral lesions in patients with COVID-19, especially in those who complain of loss of taste and smell.

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