Oral Manifestations of Asymptomatic and Mild-Symptomatic COVID-19 Patients

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Abstract

This study aimed to evaluate the possibility of whether specific oral manifestations could be regularly found in asymptomatic and mildly symptomatic COVID-19 patients.

Descriptive research had been conducted by selecting samples through simple random sampling. Sixty-five patients were registered and eligible in four quarantine buildings for special COVID-19 patients in Padang, West Sumatera, Indonesia. All patients were diagnosed with asymptomatic and mildly symptomatic COVID-19. The oral examination involved the entire surface of the oral mucosa, such as the lips, buccal mucosa, labial mucosa, tongue, floor of the mouth, palate, and gingiva.

There were no specific oral manifestations in all patients.

This study showed that there were no oral manifestations detected in any form as the primary lesions in asymptomatic or mildly symptomatic COVID-19 patients.

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Introduction

The coronavirus disease (COVID-19) has broken out and is rapidly spreading over the world. SARS-Cov-2 was a brand-new virus that was blamed for being the primary cause of the disease. This new virus was discovered in December 2019[1]. SARS-CoV-2 is conveyed mostly through droplets of saliva or nasal secretions from infected patients sneezing and coughing, according to the WHO[1,2]. SARS-CoV-2 can be transmitted to the body's mucous membranes (such as ocular, nasal, and oral) through direct or indirect contact[3,4,5].

SARS-CoV-2 primarily targets the mucosa of the upper respiratory tract[4]. SARS-CoV-2 spike protein can connect to specific cell membrane receptors and act as a crucial mediator for virus entry. Angiotensin-converting enzyme 2 (ACE2) has been identified as a SARS-CoV-2 receptor in previous research. After entering the cell membrane, the transmembrane protease serin 2 (TMPRSS2) and furin cleaved a subunit of the spike protein SARS-Cov-2, into S1 and S2[6,7]. The S1 protein interacts with ACE2, which functions as a receptor for the entrance of SARS-CoV-2 into cells. The S2 protein then helps to fuse the membranes of the virus and the host cell, allowing the virus to replicate and insert its viral material into the cell[7].

After the host was infected, several cellular enzymes were activated, such as ACE2, TMPRSS2, and furin. ACE2, TMPRSS2, and furin proteins are expressed in the tongue squamous epithelium, taste buds, gingival squamous epithelium, and submandibular glands[6]. ACE2 is a membrane-bound enzyme that is found almost in every human organ at varying levels[7,8]. Type 2 alveolar cells of the lungs, oral mucosa, particularly the tongue's epithelial cells, stratified oesophageal cells, columnar epithelial cells of the ileum and colon, cholangiocytes of the liver, proximal tubule cells of the kidney, bladder urothelial cells, and myocardial cells are among the cell surfaces that contain ACE2[7]. In the oral cavity, ACE2 receptors are more prevalent than in the lungs. ACE2 is abundant in epithelial cells of the tongue

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and also in other oral mucosal epithelial cells. The realities may show that SARS-CoV-2 susceptibility and infectivity are more apparent on the surfaces of the oral mucosa[1,9]. In the keratinized surface layer, TMPRSS2 is firmly communicated in separated squamous epithelium and is detected in salivary and tongue layer tests. Furin is found in the lowest layer of stratified squamous epithelium, is detectable in salivation, but does not remain in the tongue coating[6].

ACE2 was recognized as a receptor target for the novel SARS-CoV-2 as well as for previous SARS-CoVs[10]. ACE2 is a receptor functionally responsible for admitting the viral spikes and allowing the viruses to enter host cells[4]. SARS-CoV and SARS-CoV-2 also require TMPRSS2 as a serine protease and furin for invasion into the host[6,11,12].

ACE2 binds with SARS-CoV and SARS-CoV-2 by spike protein, and ultimately the viruses enter and infect cells. TMPRSS2 protease acts to activate the virus fully in the host cell and bind to the ACE2 receptor[12]. In addition, previous studies demonstrated that the serine protease of TMPRSS2 connects with S-protein, assisting the spike of protein to cleave and regulating the entire mechanism of viral invasion. Some proteases are also involved in this mechanism[13]. Furin is entangled in viral infections, develops specific viral envelope glycoproteins, and finally, the fusion of viruses to host cells elevates the potential[14].

Human flu infections and other SARS coronaviruses infect ferrets' upper and lower respiratory tracts (SARS-CoV-1). SARS-CoV-2 is unique in that it replicates in the nasal turbinates, soft palate, and tonsils of the respiratory system. SARS-CoV-2 also actively infects and replicates in the gastrointestinal tract. The viral RNA was discovered in the rectal rectum, but no virus was isolated in the lung lobe[15,16].

Fever, tiredness, dry cough, myalgia, and dyspnea are some of COVID-19's most well-known adverse effects. Several patients may have headaches, dizziness, muscle pain, nasal obstruction, runny nose, sore throat, diarrhea, nausea, and vomiting. It can also cause pneumonia, severe acute respiratory syndrome, kidney failure, and passing out in severe cases[5, 17-19].

COVID-19 positive patients have been reported to have oral manifestations such as recurrent herpes simplex, candidiasis, geographic tongue, unspecified ulcers, blisters, white plaque on the tongue dorsum, taste disturbances, burning sensation, and difficulty swallowing, according to several case reports. However, all patients had a history of severe disease and comorbidities[5, 20-22]. These findings still cannot confirm whether the manifestations are a characteristic pattern of direct COVID-19 virus infection. The possibility exists that oral lesions might result from systemic damage, considering the chance of astute contamination and unfavorable responses to treatment[21,23].

Since the oral mucosa can be the first infected area for SARS-CoV-2, an oral mucosal lesion is assumed to be the first sign of COVID-19 if it is considered a sign of COVID-19[20,23]. Most of the oral manifestations in SARS-CoV-2 patients did not provide evidence, even though the clinical signs showed positive symptoms of COVID-19[5]. Whereas the third fact is that SARS-CoV receptor-2 is widely available in oral mucosa[1,6,9]. Until now, there have been no reports of clinical features of the oral mucosa in COVID-19 patients that were symptomatic, mild, or asymptomatic.

The aim of this study was to evaluate oral manifestations in symptomatic and mildly symptomatic COVID-19 patients treated in four special quarantine buildings for COVID-19 patients in Padang, West Sumatra, Indonesia.

Materials and methods

Descriptive research was carried out in this study, conducted from June to September 2020. Patients were registered and eligible in four quarantine buildings for special COVID-19 patients in Padang, West Sumatera, Indonesia. All patients were diagnosed with asymptomatic and mildly symptomatic COVID-19. A simple random sampling was used in this study.

Before participating in the study, all subjects gave their informed consent for consideration. To acquire informed consent, all subjects were given a full explanation of the study's aim and their rights to confidentiality. The study was directed as per the Declaration of Helsinki, and the convention was supported by the Universitas Baiturrahmah's Health Research Ethics Committee.

Inclusion criteria included patients diagnosed with asymptomatic and mild-

symptomatic COVID-19. A positive nasopharyngeal swab result for SARS-CoV-2 RNA amplification using reverse transcription polymerase chain reaction (RT-PCR). Exclusion criteria included patients who refused to undergo oral examinations. An oral examination was performed by a dentist and involved the entire surface of the oral mucosa, such as the lips, buccal mucosa, labial mucosa, tongue, floor of the mouth, palate, and gingiva. The data were analyzed using descriptive analysis.

Results

Oral examinations have been carried out on asymptomatic and mildly symptomatic non-hospitalized patients who were located in the COVID-19 quarantine building in Padang city, West Sumatera, Indonesia. Oral examination, which included examination of the lips, tongue, buccal mucosa, lingual mucosa, gums, and palate, was carried out in 65 COVID-19 patients. Sixty-five participants consist of 22 males (18–55 years of age; the average age was 29.5 years) and 43 females (14–55 years of age; the average age was 30.05 years); the age range was 14–55 years. The participants' average age was 29.86 years old. The results showed that there were no specific oral manifestations in all patients. Almost all of the oral mucosa was apparently normal. Five (7.7%) patients (1 male and 4 females) had mild tongue coatings (Table 1). All patients had no complaints in their oral cavity. There was also no patient who complained of impaired function of smell and taste, xerostomia, burning sensation, or difficulty swallowing. During the quarantine period, the patient is given therapy in the form of vitamin C and zinc every day.

Gender	Number and Percentage (%)	Oral manifestation	
		Yes	No
Male	22 (33.8)	1 (mild tongue coating)	21
Female	43 (66.150	4 (mild tongue coating)	39
Total	65	5	60

Table 1. Oral Manifestations in COVID-19 Patients.

Discussion

The oral cavity is a significant entry point for microorganisms. SARS-CoV-2 is thought to enter human cells via numerous routes. Because it promotes viral infectivity, the protease receptor-mediated entry route is crucial. ACE2, TMPRSS2, and furin are the three molecules required for SARS-CoV-2 infection. They are very scattered on the oral mucosa[6]. Because the oral mucosa is the first region to be infected with SARS-CoV-2, an oral mucosal lesion could be the first symptom of COVID-19[23]. The oral cavity was identified as a potential source of SARS-CoV-2 infection susceptibility[18].

This study showed that no oral manifestations were found to be associated with SAR-COV2 infection in a total of 65 asymptomatic and mildly symptomatic COVID-19 patients. Only five (7.7%) out of 65 patients had tongue coatings. The production of tongue coating is a common occurrence in good health, with the majority of coating occurring on the posterior third of the tongue[24]. Viruses are facilitated by the spike (S) protein of coronaviruses to enter target cells. The S-protein surface unit ties to cell receptors and mediates virus attachment to the surface of target cells. ACE2, TMPRSS2, and furin are functional receptors that facilitate the SARS-CoV-2 virus's binding to the target cell surface[4,6,15,16,25-27].

ACE2 is a unique and useful receptor for SARS-CoV-2[8]. TMPRSS2 activity can be inhibited by plasminogen activator inhibitor type 1, and serpin B8 has been accounted for as a furin inhibitor. The harmony among protease and protease inhibitors is accounted for as one more prerequisite for viral contamination. Moreover, RNase in saliva acts as an anti-RNA infection factor. Therefore, even though there is a SARS-CoV-2 disease factor in the oral cavity, the real circumstances in the oral cavity are extremely convoluted[6].

Although the oral cavity may be the virus's entry site, other components in saliva, such as protease inhibitors, which are abundant in saliva, should be considered[6]. As a complex fluid, saliva is the first line of defense against the infection of viruses, especially for the innate immune system. As a physical barrier, the surface of the mouth mucosal membrane becomes damaged if the secretion of saliva decreases. On the other side, the viruses adhere to the host membrane and enhance colonization. Decreased salivary secretion likewise forestalls the emission of antimicrobial peptides and proteins[28].

Many types of proteins in saliva participate as antivirals, such as IgA, lysozyme,

mucin, cathelicidin (LL-37), peroxidase, lactoferrin, salivary agglutinins (gp340, DMBT1), alpha-defensins, cystatins, and beta-defensins. Several proteins are potent inhibitors of virus replication, particularly SARS-CoV-2[28].

IgA is the most widely generated antibody by the human body, and it is found in high numbers in mucus on the mucosal epithelium's surface. IgA is one of the mucosal defense mechanisms. IgA is functionally involved in the body's defense mechanism as the frontline to inhibit viral and bacterial infections that attack mucosal epithelial cells, such as influenza[6,29]. The incidence of a particular IgA deficiency and the COVID-19 infection rate per population had a strong positive correlation. The low selective IgA deficiency enhances the mortality rate of patients infected with COVID-19 in Japan[29].

Several case reports demonstrated that positive patients with COVID-19 experienced manifestations in their oral cavity, but all patients had a history of severe disease and were also comorbid. Amorim dos Santos et al., (2020)[20] reported that oral manifestations were found in a positive patient with COVID-19, for example, candidiasis, geographic tongue, and recurrent herpes simplex. The oral circumstances that were found in those patients were concluded to be secondary lesions resulting from the deterioration of systemic health or as a result of COVID-19 treatments.

Sinjari et al., (2020)[5] found several oral manifestations in the form of 30% xerostomia, 25% of patients reported detailed weakened taste, 15% burning sensation, and 20% difficulty swallowing in hospitalized patients. Ninety-five percent of patients have systemic disorders such as hypertension, diabetes, obesity, and thyroid disorders and were prescribed lopinavir, ritonavir, and/or hydroxychloroquine, as well as additional medications for the several fundamental diseases they displayed.

Taste changes were the most commonly reported oral manifestations related to COVID-19 positivity, mild/moderate severity, and female gender. Various clinical viewpoints demonstrate the presence of coinfection, decreased immunity, and side effects compared to primary oral mucosal infection, which was mainly caused by SARS-CoV-2[21].

Xerostomia was also a symptom of COVID-19, as were hypogeusia and chemosensory changes. In fact, xerostomia has been discovered in the majority of COVID-19 patients due to the neuroinvasive and neurotrophic capabilities of SARS-CoV-2. Xerostomia could likewise be instigated by various medication treatments, for example, antidepressants, antipsychotics, anticholinergics, antihypertensives, allergy medicines, and tranquilizers[5].

Acute COVID-19 infection has the potential to cause abnormalities in the oral mucosa associated with systemic administration of experimental antiviral drugs as well as systemic failures in patients[20,30]. Due to the fact that the study is still ongoing and intraoral examinations have not been considered as early screening for this disease, considerable study and more literature are required to understand the mechanisms underlying oral findings in COVID-19 patients. Thus, there was very little evidence to confirm the oral findings reported in previous studies as a direct manifestation of SARS-CoV-2 infection[31]. There is no scientific evidence in the literature to show which oral manifestations of SARS-CoV-2 could really cause disease[5]. Associated systemic disease and/or poor oral health may contribute to oral manifestations[31].

Many studies assumed that the ACE-2 protein was abundant in the oral mucosa as the port of entry for SARS-Cov-2. On the other hand, based on tissue biopsy from 15 different human organs, we found that in the oral mucosa, strong staining of ACE2 protein was observed in the vascular endothelium, vascular smooth muscle cells, and basal layer of the epithelium. It was different from lung epithelial cells. In normal lung tissue, positive staining for ACE2 is present on alveolar epithelial cells and capillary endothelium. That is a possible reason why lesions in the oral mucosa are uncommon[32].

There is different regulation of the expression of the ACE-2 protein for both severe and non-severe clinical symptoms. According to Baker et al[33], ACE-2 protein expression is upregulated in patients with severe clinical symptoms who require mechanical ventilation; however, ACE-2 protein expression does not change in patients with non-severe clinical symptoms. Our patients were asymptomatic and had mild clinical symptoms; this could be the reason why the oral mucosa of our patient was almost free of any lesion[33]. The other reason why oral lesions almost disappeared in our study was

the transmission of SARS-Cov-2. The most common viral transmission is via infected respiratory droplets. Li et al.[26] have found the positive detection rate of the RNA virus SARS-Cov-2 in nasopharyngeal swabs was the highest (54.05%), trailed by anal swabs (24.32%), and the positive location rate in saliva was just 16.22%.

Conclusions

This study showed that there were no oral manifestations detected in any form as the primary lesions in asymptomatic or mildly symptomatic COVID-19 patients.

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Declaration of Interest

The authors report no conflict of interest.

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