

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.e-jds.com](http://www.e-jds.com)

Review article

# Review of oral ulcerative lesions in COVID-19 patients: A comprehensive study of 51 cases

Yu-Hsueh Wu<sup>a,b†</sup>, Yang-Che Wu<sup>c,d†</sup>, Ming-Jane Lang<sup>e</sup>,  
Yi-Pang Lee<sup>e</sup>, Ying-Tai Jin<sup>f,g\*\*</sup>, Chun-Pin Chiang<sup>e,h,i\*</sup>



<sup>a</sup> Department of Stomatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>b</sup> Institute of Oral Medicine, School of Dentistry, National Cheng Kung University, Tainan, Taiwan

<sup>c</sup> School of Dentistry, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan

<sup>d</sup> Department of Dentistry, Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfare, New Taipei City, Taiwan

<sup>e</sup> Department of Dentistry, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

<sup>f</sup> Department of Pathology, Taiwan Adventist Hospital, Taipei, Taiwan

<sup>g</sup> Department of Pathology, National Cheng Kung University Hospital, Tainan, Taiwan

<sup>h</sup> Department of Dentistry, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

<sup>i</sup> Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, Taipei, Taiwan

Received 6 July 2021

Available online 15 July 2021

## KEYWORDS

COVID-19;  
SARS-CoV-2;  
Oral manifestation;  
Oral ulcerative  
lesions;  
Recurrent aphthous  
stomatitis

**Abstract** Numerous oral manifestations of COVID-19 have been reported in the literatures. Common oral lesions in COVID-19 patients included ulcerations, xerostomia, dysgeusia, gingival inflammation, and erythema. Among them, oral ulceration is the most frequent finding and is present as various but distinct patterns. Thus, we conducted a comprehensive review of 51 COVID-19 patients with oral ulcerative lesions to further analyze the various oral ulcerative lesions in COVID-19 patients. There were a median age of 41.4 years and a slight female predilection in these patients. Most oral lesions manifested as an aphtha-like ulceration but lack of an evidence of recurrent aphthous stomatitis. Some of them were present as herpetiform ulcerations without HSV infection. Widespread ulcerations accompanied with necrosis were observed in the more severe and immunosuppressed older patients. Although some reported patients were asymptomatic, most of them had systemic symptoms concurring or slightly preceding the oral ulcerative lesions and the latency from the onset of systemic symptoms to oral ulcerative lesions were under 10 days, suggesting that oral ulceration was one of the early

\* Corresponding author. Department of Dentistry, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 707, Section 3, Chung-Yang Road, Hualien 970, Taiwan.

\*\* Corresponding author. Department of Pathology, Taiwan Adventist Hospital, No. 424, Section 2, Bade Road, Taipei 10556, Taiwan.  
E-mail addresses: [yingtaijin@gmail.com](mailto:yingtaijin@gmail.com) (Y.-T. Jin), [cpchiang@ntu.edu.tw](mailto:cpchiang@ntu.edu.tw) (C.-P. Chiang).

† These two authors contributed equally to this work.

<https://doi.org/10.1016/j.jds.2021.07.001>

1991-7902/© 2021 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

symptoms of COVID-19. Therefore, the oral ulcerative lesions may be considered as oral markers for early diagnosis of the underlying COVID-19 infection in the asymptomatic patients. © 2021 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

In the end of 2019, an acute respiratory illness appeared abruptly and soon spread worldwide, which was officially named coronavirus disease-19 (COVID-19), and the virus responsible for this disease was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO). The common clinical presentations of COVID-19 included fever, cough, sore throat, runny nose, myalgia, fatigue, and dyspnea. Less frequently, sputum production, headache, and diarrhea were also observed.<sup>1</sup> Wang et al.<sup>2</sup> reported the hematological and radiographic alterations in the patients infected by SARS-CoV-2 in their study. Lymphopenia is found in 70.3% patients, and prolonged prothrombin time occurs in 58% patients. Chest computed tomography shows patchy opacities or “ground-glass” pattern in lungs. The median age of the diagnosed patients is 56 years, while the patients treated in the intensive care unit (ICU) are even older. About one fourth patients are transferred to the ICU due to complications, such as acute respiratory distress syndrome or shock.<sup>2</sup>

Localized involvements of COVID-19, like skin rash, sore throat, hyposmia, anosmia, and oral lesions, have also been mentioned in some literatures.<sup>3,4</sup> The common oral lesions of COVID-19 include ulcerations, xerostomia, dysgeusia, gingival inflammation, and erythema.<sup>4–6</sup> According to the associated studies, the most frequent oral finding was oral ulceration, and there were distinct clinical patterns observed in different case studies.<sup>7–17</sup> Despite growing literatures investigating oral presentations in COVID-19 patients, few of them provide deep insight into oral ulcerative lesions, the most frequent but diverse one. The detailed clinical features, histological findings, immune profile, and the possible underlying pathogenetic mechanism of the oral ulcerative lesions are still lacking. Therefore, we conducted a comprehensive review of 51 COVID-19 patients with oral ulcerative lesions to further analyze the various oral ulcerative lesions in COVID-19 patients.

## Clinical features of 51 COVID-19 patients with oral ulcerative lesions

Age, sex, locations, and other clinical descriptions of the 51 COVID-19 patients with oral ulcerative lesions reported in the literature are shown in Table 1. The age of the 51 patients ranged from 16 years to 83 years with a mean age of 41.4 years. A slight female predilection was observed in the reported cases with a female-to-male ratio of 1.22:1 (28 females, 23 males). The sites of the lesion were not reported in two cases. There were 43 cases with single

involved site, while there were 6 cases with involvement of more than one site in their oral cavities. The common sites of involvement in descending order were lip and labial mucosa (28.6%), tongue (25%), palate (16.4%), buccal mucosa (16.4%), gingiva (8.9%), and tonsil (3.6%). The lesion sizes were measured from 1 mm to 17 mm in the 27 reported cases and 88.9% of these lesions were under 1 cm in greatest dimension. Pain was mentioned in 40 of 41 cases and the remaining 10 cases did not report the pain symptom.

The clinical presentations of the oral ulcerations were various, from aphthous stomatitis-like lesions to widespread ulcerations with necrosis or crusting. Like aphthous stomatitis, most of the lesions showed solitary or multiple punched-out ulcerations, which were covered by a yellowish membrane and surrounded by an erythematous halo (case 1–25, 37, 38, 41, 43, and 45).<sup>9–13,17</sup> Some of these lesions (case 31, 32, 40 and 42) showed herpetiform pattern, with resemblance to herpes infection, but rendered a negative result to the test for herpes simplex virus (HSV).<sup>13,14</sup> Patients in case 34, 35, and 50 showed the lesions resembling recurrent herpetic infection but all of them did not have any previous history of herpetic infection.<sup>15,16</sup> Although the lesions looked like aphthous ulcerations, patients in these reported cases usually lacked the history of recurrent aphthous stomatitis (RAS), oral inflammatory diseases, or allergy.<sup>10,13,18</sup> Besides, some possible etiologic conditions of RAS, such as deficiencies of vitamin B12, folate, and iron were also excluded.<sup>13</sup>

The 71-year-old-female in case 26 and the 81-year-old male in case 28 possessed severe clinical presentations of COVID-19 and were admitted to intensive care unit (ICU). Their oral examination showed multiple oral ulcerations with focal necrosis and crusting, and HSV-1 was detected in the saliva sample by performing PCR.<sup>10</sup> The patient in case 33 was also admitted to the ICU and underwent invasive mechanical ventilation. Multiple ulcerations over his oral mucosa were positive for HSV-1 DNA, and HSV-1 reactivation was also proved by the serum tests before and after inpatient care.<sup>18</sup> The patient in case 47 had a past medical history of kidney transplant and took immunosuppressants regularly. He was admitted to ICU for supplemental O<sub>2</sub>, and his oral lesions exhibited herpes-like ulcers on the dorsal tongue as well as candidiasis. However, no HSV test was performed to confirm the herpes infection.<sup>19</sup> These extensive ulcerations with necrosis, or co-infection of other pathogens were almost observed in the immunocompromised or older individuals, and usually accompanied with more severe clinical symptoms.

The patients in case 2, 3, 6, 8, 11, 16, 18, 20 and 38 showed oral ulcerations, independent of any systemic symptoms. However, most reported cases showed systemic

**Table 1** Summary of 51 reported cases of oral ulcerative lesions in COVID-19 patients.

Case No.	References (Year of publication)	Age	Sex	Lesion site	Clinical features	Lesion size	Pain	General symptoms	Onset (day)	Confirmation of COVID-19
1	Riad et al. <sup>9</sup> (2021)	16	F	Upper lip	Solitary ulcerative white halos with well-defined erythematous margins	1 mm	+	Cough	0	+
2	Riad et al. <sup>9</sup> (2021)	17	F	Buccal mucosa	Same as above	1 mm	+	Asymptomatic	0	+
3	Riad et al. <sup>9</sup> (2021)	19	M	Buccal mucosa	Same as above	1 mm	+	Asymptomatic	0	+
4	Riad et al. <sup>9</sup> (2021)	20	M	Palate	Same as above	2 mm	+	Anosmia	0	+
5	Riad et al. <sup>9</sup> (2021)	20	F	Buccal mucosa	Same as above	2 mm	+	Anosmia	0	+
6	Riad et al. <sup>9</sup> (2021)	24	F	Tongue	Same as above	1 mm	+	Asymptomatic	0	+
7	Riad et al. <sup>9</sup> (2021)	25	F	Upper gingiva	Same as above	2 mm	+	Anosmia	0	+
8	Riad et al. <sup>9</sup> (2021)	26	F	Buccal mucosa	Same as above	2 mm	+	Asymptomatic	0	+
9	Riad et al. <sup>9</sup> (2021)	27	F	Upper lip	Same as above	2 mm	+	Cough	0	+
10	Riad et al. <sup>9</sup> (2021)	27	F	Palate	Same as above	2 mm	+	NR	0	+
11	Riad et al. <sup>9</sup> (2021)	31	M	Lower lip	Same as above	2 mm	+	Asymptomatic	0	+
12	Riad et al. <sup>9</sup> (2021)	31	F	Tongue	Same as above	2 mm	+	NR	0	+
13	Riad et al. <sup>9</sup> (2021)	36	F	Palate, upper and lower gingiva	Same as above	4 mm	+	Anosmia, fever, cough	0	+
14	Riad et al. <sup>9</sup> (2021)	37	M	Buccal mucosa	Same as above	2 mm	+	Anosmia	1	+
15	Riad et al. <sup>9</sup> (2021)	38	F	Buccal mucosa	Same as above	1 mm	+	Fever	0	+
16	Riad et al. <sup>9</sup> (2021)	38	F	Tongue	Same as above	1 mm	+	Asymptomatic	0	+
17	Riad et al. <sup>9</sup> (2021)	39	F	Upper lip	Same as above	4 mm	+	Cough	0	+
18	Riad et al. <sup>9</sup> (2021)	42	F	Lower lip	Same as above	3 mm	+	Asymptomatic	0	+
19	Riad et al. <sup>9</sup> (2021)	46	F	Upper gingiva	Same as above	2 mm	+	Fever	1	+
20	Riad et al. <sup>9</sup> (2021)	48	F	Lower lip	Same as above	2 mm	+	Asymptomatic	0	+
21	Riad et al. <sup>9</sup> (2021)	56	F	Buccal mucosa	Same as above	2 mm	+	Cough	0	+
22	Brandão et al. <sup>10</sup> (2021)	28	M	Upper and lower labial mucosa, tongue	Aphtha-like ulcerations	NR	NR	Anosmia, cough, fever, headache, myalgia, chills	8	+
23	Brandão et al. <sup>10</sup> (2021)	29	M	Tongue	Same as above	10 mm	+	Anosmia, fever, cough, headache, dyspnea on exertion, malaise	8	+
24	Brandão	32	F	Tongue	Same as above	3–4 mm	NR	Anosmia, fever, cough,	10	+

Table 1 (continued)

Case No.	References (Year of publication)	Age	Sex	Lesion site	Clinical features	Lesion size	Pain	General symptoms	Onset (day)	Confirmation of COVID-19
	et al. <sup>10</sup> (2021)							headache		
25	Brandão et al. <sup>10</sup> (2021)	35	M	Tonsillar pillar	Same as above	5 mm	NR	Hyposmia, fever, cough, sore throat, malaise	6	+
26	Brandão et al. <sup>10</sup> (2021)	71	F	Upper and lower lips, tongue	Oral ulceration with focal necrosis, hemorrhagic crusting	NR	+	Cough, dysgeusia, fever, mild dyspnea, CT showing "ground-glass" pattern in both lungs	4	+
27	Brandão et al. <sup>10</sup> (2021)	72	M	Upper and lower lips	Same as above	NR	+	Fever, dyspnea	5	+
28	Brandão et al. <sup>10</sup> (2021)	81	M	Upper and lower labial mucosa, tongue	Same as above	10–15 mm	+	Cough, chest tightness, chills, fever, dyspnea, CT showing "ground-glass" pattern in both lungs	5	+
29	Brandão et al. <sup>10</sup> (2021)	83	F	Tongue and palate	An aphtha-like ulcer with focal necrosis	15 mm	+	Abdominal distension, mild dyspnea	2	+
30	Cicarese et al. <sup>6</sup> (2021)	19	F	Lips	Ulcerations with crusting	NR	–	Fever, fatigue, hyposmia	7	+
31	Ansari et al. <sup>14</sup> (2021)	56	F	Palate	Ulcerations with irregular margins	NR	+	Fever, shortness of breath	5	+
32	Ansari et al. <sup>14</sup> (2021)	75	M	Tongue	Several small ulcers with irregular margins	NR	+	Hypoxia	7	+
33	Kämmerer et al. <sup>18</sup> (2021)	46	M	NR	Multiple sharply circumscribed ulcerations	NR	+	Fatigue, dry cough, fever, respiratory distress, CT showing "ground-glass" pattern in both lungs	15	+
34	Martín Carreras-Presas et al. <sup>15</sup> (2021)	56	M	Palate	Multiple ulcerations with unilateral affection	NR	+	Fever, hyposmia, enlarged lymph nodes	NR	NR (pending the result)
35	Martín Carreras-Presas et al. <sup>15</sup> (2021)	58	M	Palate	Multiple small ulcerations with unilateral affection	NR	+	NR	NR	NR
36	Martín Carreras-Presas et al. <sup>15</sup> (2021)	65	F	Labial mucosa	Blisters and ulcerations	NR	+	High fever, diarrhea, skin rash, bilateral pneumonia	NR	+
37	Al-Khanati et al. <sup>11</sup> (2020)	24	M	Lower labial mucosa	Multiple aphtha-like ulcerations	15–17 mm	+	Headache, fatigue, fever, dizziness, nausea, sore throat	NR	–
38	Corchuelo and Ulloa <sup>12</sup> (2020)	40	F	Tongue, attached gingiva of tooth 34	Aphtha-like ulcers	NR	+	Asymptomatic	NR	+

(continued on next page)

Table 1 (continued)

Case No.	References (Year of publication)	Age	Sex	Lesion site	Clinical features	Lesion size	Pain	General symptoms	Onset (day)	Confirmation of COVID-19
39	Malih et al. <sup>35</sup> (2020)	38	M	Left tonsil	Aphthous stomatitis-like lesions	NR	NR	Fatigue, anosmia, fever, skin rash, malaise	NR	+
40	Dominguez-Santas et al. <sup>13</sup> (2020)	19	M	Lower labial mucosa	Four clustered aphthae	NR	NR	Anosmia, fever, headache, malaise, and dyspnea	0	+
41	Dominguez-Santas et al. <sup>13</sup> (2020)	33	M	Upper gingiva	An aphtha-like ulcers	NR	NR	Anosmia, fever, headache, malaise, dyspnea, pneumonia of right lower pulmonary field, mild lymphopenia	3	+
42	Dominguez-Santas et al. <sup>13</sup> (2020)	37	M	Tongue (right ventral side)	Seven aphtha-like ulcers	NR	NR	Anosmia, fever, headache, malaise, and dyspnea	5	+
43	Dominguez-Santas et al. <sup>13</sup> (2020)	43	F	Buccal mucosa (right)	An aphtha-like ulcer	NR	NR	Anosmia, fever, headache, malaise, dyspnea, bilateral pneumonia, mild lymphopenia	4	+
44	Eghbali Zarch et al. <sup>36</sup> (2020)	56	F	Lower labial mucosa	Preceding vesicles	NR	+	High fever, fatigue	2	+
45	Soares et al. <sup>17</sup> (2020)	42	M	Buccal mucosa	A "punched-out" ulcer	NR	+	Fever, cough, shortness of breath, skin petechia-like and small vesicobullous lesions	NR	+
46	Putra et al. <sup>3</sup> (2020)	29	M	NR	Aphthous stomatitis-like lesions	NR	+	Fever, cough, anosmia, skin petechia-lesions, sore throat	7	+
47	Amorim Dos Santos et al. <sup>19</sup> (2020)	67	M	Tongue	Multiple pinpoint yellowish ulcers	NR	NR	Dyspnea, fever, diarrhea, CT showing "ground-glass" pattern in both lungs	24	+
48	Chérif et al. <sup>37</sup> (2020)	35	F	Upper lip	Ulcerations	NR	NR	Fever, myalgia, dyspnea, cough, vomiting, diarrhea, rash	NR	+
49	Sinadinos and Shelswell <sup>16</sup> (2020)	56	M	Palate	Recurrent herpes-like stomatitis	NR	+	Sore throat	NR	NR (pending the result)
50	Sinadinos and Shelswell <sup>16</sup> (2020)	58	M	Palate	Unilateral palatal ulcerations	NR	+	NR	NR	NR (pending the result)
51	Sinadinos and Shelswell <sup>16</sup> (2020)	65	F	Tongue	Erythema multiform-like ulcerations	NR	+	Bilateral pneumonia	NR	+

NR: not reported.

CT: chest computed tomography.

symptoms concurring or slightly preceding the oral lesions. The latency period from the onset of systemic symptoms to oral lesions were under 10 days, except two cases (case 33 and 47).<sup>9,10,13–15,18,19</sup> The mean of the latency period in the

40 reported cases was 3.2 days (Table 1). The mean incubation period of COVID-19 in several studies was reported to be a maximum 8 days and their pooled mean incubation period was 6.2 days.<sup>20</sup> These findings suggest that the oral

ulceration may be one of the early symptoms of COVID-19. In addition, the oral ulcerations may sometimes appear in the asymptomatic patients so that oral ulcerations may be the hint to warn us about the underlying infection in those asymptomatic COVID-19 patients.

### Histological findings and immune profile of oral ulcerative lesions in COVID-19 patients

Based on the current literatures, it seems that there are no pathognomonic findings in these oral ulcerative lesions histologically. The biopsy results revealed non-specific ulcerations with granulation tissue base and diffuse chronic inflammatory cell infiltration. Residual surface epithelium showed edematous change and neutrophilic exocytosis.<sup>14</sup> In addition to the above findings, focal areas of necrosis and hemorrhage were observed in case 45. Besides, both superficial and deep small blood vessels were obliterated by thrombi, which was mainly composed of endothelial cells (positive for CD34) and fibrin. Adjacent minor salivary glands exhibited an intense lymphocytic infiltration. Immunohistochemically, CD3 and CD8 positivities were observed in most inflammatory cells in basal cell layer of the epithelium, in the connective tissue, and in salivary gland tissue. Some other inflammatory cells demonstrated positivities for CD4, CD20, CD68, CD138, and CD163. This immunohistochemical pattern indicates that the components of the inflammatory cells are mainly CD3-positive and CD8-positive T lymphocytes.<sup>17</sup> However, biopsy was lack in many cases, so further studies are needed to explore the microscopic details of these oral ulcerative lesions.

### Concomitant infections or symptoms in 51 COVID-19 patients with oral ulcerative lesions

The concomitant infections or symptoms in 51 COVID-19 patients with oral ulcerative lesions are shown in Table 2. For the concomitant infections in 51 COVID-19 patients with oral ulcerative lesions, 4 (7.8%) patients had HSV infection and 2 (3.9%) patients had oral candidiasis. Regarding the concomitant symptoms in 51 COVID-19 patients with oral ulcerative lesions, anosmia or hyposmia (17 patients, 33.3%) was the most common concomitant symptoms, followed by dysgeusia, ageusia or hypogeusia (9 patients, 17.6%), xerostomia (2 patients, 3.9%), and COVID tongue (geographic tongue-like lesion, 2 patients, 3.9%).

**Table 2** Concomitant infections or symptoms in 51 COVID-19 patients with oral ulcerative lesions.

Concomitant infection or symptom	Patient number (%)
Herpes simplex virus infection	4 (7.8)
Candidiasis	2 (3.9)
Anosmia or hyposmia	17 (33.3)
Dysgeusia, ageusia, or hypogeusia	9 (17.6)
Xerostomia	2 (3.9)
COVID tongue (geographic tongue-like lesion)	2 (3.9)

### Discussion

The clinical presentations of the oral ulcerative lesions in COVID-19 patients are various but distinct. Some may look like aphthous ulcerations (minor or herpetiform type), while there is no evidence of RAS in these patients. These aphtha-like oral lesions occur predominantly in relatively young patients with mild symptoms. Widespread oral ulcerations accompanied with necrosis are observed in the more severe and immunosuppressed older individuals. This difference may be related to the way by which SARS-CoV-2 infects cells. SARS-CoV-2 enters the cells by the synergy of its own spike protein, angiotensin-converting enzyme 2 (ACE2) on the surface of host cell, and transmembrane protease serine 2 (TMPRSS2). The viral spike protein can recognize ACE2 on the host cell surface, and then TMPRSS2 is triggered to cleave the spike protein for priming cell membrane fusion.<sup>21,22</sup> The levels of ACE2 and TMPRSS2 are found to be positively correlated with age and the disease severity, which may explain why the elderly tend to possess high risk for severe diseases and why the elderly usually show more widespread and serious oral lesions.<sup>21</sup>

The development of the oral ulceration could be possibly associated with the pathogenesis of COVID-19 as well. Because oral epithelial cells have proved to express ACE2, the disruption of oral epithelial cells may occur when the SARS-CoV-2 spread to these epithelial cells.<sup>10</sup> Besides, increased cytokines, such as interleukin 6 (IL-6) and interleukin 10 (IL-10), in COVID-19 patients may lead to chemotaxis of lymphocytes and neutrophils to the lesion site, and thus neutrophilic exocytosis and CD3-positive and CD8-positive lymphocytes are observed in the reported cases.<sup>23</sup> Patients with RAS have been proved to have increased levels of CD8-positive T lymphocytes and/or decreased CD4-positive T lymphocytes by Wardhana and Datau.<sup>24</sup> Pedersen et al. have also found that the proportion of CD8-positive T lymphocytes is significantly increased in the active RAS, though the total counts of CD4-positive and CD8-positive T lymphocytes are significantly lower in the patients than in the control subjects.<sup>25</sup> However, the immunopathological responses in COVID-19 are complicated and have not been thoroughly studied, either systemic or local, and lack of sufficient biopsy samples of the oral ulcerative lesions even makes them full of unknowns.

In addition, necrosis and co-infection of HSV or candida are also noted in some severe cases. The expression of ACE2 on endothelial cells may be involved in the tissue necrosis in these lesions. The expression of ACE2 on endothelial cells makes the viral particles prone to aggregation in the endothelia at the lesion sites. Recruitment of immune cells, either by direct viral infection of the endothelial cells or immune-mediated, can lead to extensive endothelial dysfunction and cause endotheliitis, giving rise to the necrosis of infected tissue.<sup>26</sup>

There are two types of HSV: type 1 (HSV-1) and type 2 (HSV-2). HSV-1 usually infects the oral, facial, and ocular areas as well as skin above the waist. The natural history of HSV infection includes primary infection, latency, and recurrent infection. Primary HSV-1 infection typically occurs at a young age and often is asymptomatic. After primary HSV-1 infection is established, the virus is taken up by



sensory nerves, and often transported to the associated sensory ganglia where the virus remains in a latent state. The most common site of latency for HSV-1 is the trigeminal ganglion. The virus uses the axons of the sensory neurons to travel back and forth to the skin or mucosa and usually infects the epithelium supplied by the sensory ganglion when reactivated. Recurrent (secondary) herpes infection occurs with reactivation of the virus. Old age, physical or emotional stress, fatigue, severe systemic disease, and malignancy have been associated with reactivation.<sup>27,28</sup> Therefore, the COVID-19-induced immunocompromised status is probably the etiological factor causing concomitant HSV infection. Moreover, HSV reactivation is also common in non-immunocompromised patients with prolonged mechanical ventilation in ICU.<sup>29</sup>

Oral candidiasis is a kind of opportunistic infection in immunocompromised patients. It often occurs in patients with immune deficiency diseases, specific nutritional deficiencies and malnutrition, endocrine disorders, malignancies, xerostomia, and in patients taking corticosteroids or broad-spectrum antibiotics.<sup>27</sup> In COVID-19 patients, immunocompromised status, xerostomia, administration of corticosteroids in patients with severe COVID-19, and taking antibiotics in patients with bacterial pneumonia co-infection may play important roles in causing concomitant oral candidiasis. Moreover, Le Balc'h et al. also found that COVID-19 patients with acute respiratory distress syndrome usually tend to have bacterial, fungal, or viral co-infections.<sup>29</sup>

Moreover, xerostomia or dry mouth, the common symptom in COVID-19 patients, may also play a role in causing oral ulcerations in COVID-19 patients. Loss of the protection and lubrication of saliva may easily lead to mucosal trauma and local microbial infections.<sup>30</sup> The occurrence of xerostomia may be attributed to the expression of ACE2 and TMPRSS2 on the salivary gland cells. The infection of salivary gland cells by SARS-CoV-2 finally results in destruction of salivary acinar cells and the impaired saliva-production function.<sup>31</sup> In addition to the salivary gland cells, taste bud cells and olfactory supporting cells are another cells that can express ACE2 and TMPRSS2.<sup>32,33</sup> Thus, when these cells are infected by SARS-CoV-2, destruction of taste bud cells and olfactory supporting cells may subsequently lead to dysgeusia (or ageusia and hypogeusia) and anosmia (or hyposmia), respectively.<sup>31,32</sup> The neurotropism of SARS-CoV-2 (i.e., this may result in easy infection of sensory nerves by SARS-CoV-2 and dysfunction of these infected sensory nerves) and the alterations of cytokines in COVID-19 patients may also play pivotal roles in causing dysgeusia (or ageusia and hypogeusia) and anosmia (or hyposmia).<sup>32,33</sup> Interestingly, the close relation between xerostomia and dysgeusia as well as the synergy of gustatory and olfactory systems make the interaction between these oral involvements sophisticated.<sup>33</sup>

Fantozzi et al. conducted a survey of 326 COVID-19 patients with confirmed SARS-CoV-2 infection and reported that dysgeusia was the most common symptom (59.5%), followed by xerostomia (45.9%) and olfactory alterations (hyposmia/anosmia, 41.4%).<sup>4</sup> The most frequently concomitant symptoms in our reported 51 COVID-19 patients with oral ulcerative lesions is anosmia or hyposmia

(33.3% of 51 COVID-19 patients), but other symptoms such as dysgeusia (17.6%) and xerostomia (3.9%) were relatively uncommon (Table 2). The relatively-high frequency of the olfactory alterations in our reported cases might also be due to that anosmia or hyposmia was an annoying symptom for the patients and thus the patients usually reported it to the caring physicians. On the contrary, the 51 COVID-19 patients in our study might think that dysgeusia and xerostomia were less disturbing symptoms and thus they forgot to report them to the caring physicians. Besides, COVID tongue, a geographic tongue-like lesion, is not a well-reported and universally-recognized lesion in COVID-19 patients (2 cases in our 51 COVID-19 patients); therefore, the lower occurrence rate of COVID tongue in our 51 COVID-19 patients is understandable. The higher expression of ACE2 and TMPRSS2 on the tongue epithelial cells may result in easy destruction and depapillation of filiform and fungiform papillae from the dorsal surface of the tongue when the patients are infected with SARS-CoV-2, and this may explain why there is geographic tongue-like lesion on the dorsal surface of the tongue in COVID-19 patients and why some of the COVID-19 patients may have hypogeusia because taste cells are contained in the shedding fungiform papillae on the dorsal and lateral borders of the tongue.<sup>34</sup>

Taken together, the pathogenetic mechanism may play an important role in the clinical presentations of COVID-19. The distribution and levels of ACE2 and TMPRSS2 in human cells determine which tissue or organ is prone to be infected and what clinical manifestations may be present. In this comprehensive review, the 51 COVID-19 patients with oral ulcerative lesions showed a mean age of 41.4 years and a slight female predilection. Most oral ulcerative lesions are manifested as aphtha-like ulcerations measuring less than 1 cm in greatest dimension or forming clusters, but there is no previous history or other etiological factors of RAS involved in the formation of oral ulceration. Some oral lesions are present as widespread ulcerations accompanied with necrosis, which are mainly observed in the more severe and immunosuppressed older patients. There are usually systemic symptoms concurring or slightly preceding the oral lesions and the latency from the onset of systemic symptoms to oral lesions are under 10 days, with the mean of 3.2 day. The incubation periods of COVID-19 are almost under 16 days, so the findings suggest that oral ulceration is one of the early symptoms of COVID-19.<sup>20</sup> Besides, the oral ulcerations may sometimes appear in the asymptomatic patients. Therefore, the presence of oral ulcerative lesions may be helpful for early diagnosis and detection of the underlying COVID-19 infection in those asymptomatic patients.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

## References

- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.

2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *J Am Med Assoc* 2020;323:1061–9.
3. Putra BE, Adiarto S, Dewayanti SR, Juzar DA. Viral exanthem with “Spins and needles sensation” on extremities of a COVID-19 patient: a self-reported case from an Indonesian medical frontliner. *Int J Infect Dis* 2020;96:355–8.
4. Fantozzi PJ, Pampena E, Di Vanna D, et al. Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. *Am J Otolaryngol* 2020;41:102721.
5. Iranmanesh B, Khalili M, Amiri R, Zartab H, Aflatoonian M. Oral manifestations of COVID-19 disease: a review article. *Dermatol Ther* 2021;34:e14578.
6. Ciccarese G, Drago F, Boatti M, Porro A, Muzic SI, Parodi A. Oral erosions and petechiae during SARS-CoV-2 infection. *J Med Virol* 2021;93:129–32.
7. de Sousa FACG, Paradella TC. Considerations on oral manifestations of COVID-19. *J Med Virol* 2021;93:667–8.
8. La Rosa GRM, Libra M, De Pasquale R, Ferlito S, Pedullà E. Association of viral infections with oral cavity lesions: role of SARS-CoV-2 Infection. *Front Med (Lausanne)* 2021;7:571214.
9. Riad A, Kassem I, Stanek J, Badrah M, Klugarova J, Klugar M. Aphthous stomatitis in COVID-19 patients: case-series and literature review. *Dermatol Ther* 2021;34:e14735.
10. Brandão TB, Gueiros LA, Melo TS, et al. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? *Oral Surg Oral Med Oral Pathol Oral Radiol* 2021;131:e45–51.
11. Al-Khanati NM, Riad A, Sahloul ME, Klugar M. Aphthous-like stomatitis of COVID-19 patients: case report and review of evidence. *Braz J Oral Sci* 2020;19:e201354.
12. Corchuelo J, Ulloa FC. Oral manifestations in a patient with a history of asymptomatic COVID-19: case report. *Int J Infect Dis* 2020;100:154–7.
13. Dominguez-Santas M, Diaz-Guimaraens B, Fernandez-Nieto D, Jimenez-Cauhe J, Ortega-Quijano D, Suarez-Valle A. Minor aphthae associated with SARS-CoV-2 infection. *Int J Dermatol* 2020;59:1022–3.
14. Ansari R, Gheitani M, Heidari F, Heidari F. Oral cavity lesions as a manifestation of the novel virus (COVID-19). *Oral Dis* 2021;27:771–2.
15. Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. *Oral Dis* 2021;27(Suppl 3):710–2.
16. Sinadinos A, Shelswell J. Oral ulceration and blistering in patients with COVID-19. *Evid Based Dent* 2020;21:49.
17. Soares CD, Carvalho RA, Carvalho KA, Carvalho MG, Almeida OP. Letter to Editor: Oral lesions in a patient with Covid-19. *Med Oral Patol Oral Cir Bucal* 2020;25:e563–4.
18. Kämmerer T, Walch J, Flaig M, French LE. COVID-19-associated herpetic gingivostomatitis. *Clin Exp Dermatol* 2021;46:174–6.
19. Amorim Dos Santos J, Normando AGC, Carvalho da Silva RL, et al. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? *Int J Infect Dis* 2020;97:326–8.
20. Dhoubi W, Maatoug J, Ayouni I, et al. The incubation period during the pandemic of COVID-19: a systematic review and meta-analysis. *Syst Rev* 2021;10:101.
21. Yang J, Petitjean SJL, Koehler M, et al. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun* 2020;11:4541.
22. Dong M, Zhang J, Ma X, et al. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. *Bio-med Pharmacother* 2020;131:110678.
23. Tan M, Liu Y, Zhou R, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *Immunology* 2020;160:261–8.
24. Wardhana, Datau EA. Recurrent aphthous stomatitis caused by food allergy. *Acta Med Indones* 2010;42:236–40.
25. Pedersen A, Hougen HP, Kenrad B. T-lymphocyte subsets in oral mucosa of patients with recurrent aphthous ulceration. *J Oral Maxillofac Pathol* 1992;21:176–80.
26. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–8.
27. Neville B, Damm DD, Allen C, Chi A. Viral infections and allergies and immunologic diseases. In: Neville BW, Damm DD, Allen CM, Chi AC, eds. *Oral and maxillofacial pathology*. 4th ed. St Louis: Elsevier, 2016. 191–199, 218–224.
28. Tovu S, Parlatescu I, Tovu M, Cionca L. Primary herpetic gingivostomatitis in children and adults. *Quintessence Int* 2009;40:119–24.
29. Le Balc’h P, Pinceaux K, Pronier C, Seguin P, Tadié J-M, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. *Crit Care* 2020;24:530.
30. Turner MD, Ship JA. Dry mouth and its effects on the oral health of elderly people. *J Am Dent Assoc* 2007;138:S15–20.
31. Sakaguchi W, Kubota N, Shimizu T, et al. Existence of SARS-CoV-2 entry molecules in the oral cavity. *Int J Mol Sci* 2020;21:6000.
32. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: identification of cell types and trends with Age. *ACS Chem Neurosci* 2020;11:1555–62.
33. Mahmoud MM, Abuhashish HM, Khairy DA, Bugshan AS, Khan AM, Moothedath MM. Pathogenesis of in COVID-19 patients: a scoping review. *Eur Rev Med Pharmacol Sci* 2021;25:1114–34.
34. Hathway RW. COVID tongue. *Br Dent J* 2021;230:114.
35. Malih N, Hajinasrollah G, Zare M, Taheri M. Unexpected presentation of COVID-19 in a 38-year-old male patient: a case report. *Case Rep Dermatol* 2020;12:124–31.
36. Eghbali Zarch R, Hosseinzadeh P. COVID-19 from the perspective of dentists: a case report and brief review of more than 170 cases. *Dermatol Ther* 2021;34:e14717.
37. Chérif MY, de Filette JMK, André S, Kamgang P, Richert B, Clevenbergh P. Coronavirus disease 2019-related Kawasaki-like disease in an adult: a case report. *JAAD Case Rep* 2020;6:780–2.