Dermatology Practical & Conceptual

Oral Mucosal Manifestations Associated with PCR Positivity in Patients with COVID-19

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ABSTRACT

Introduction: To date various oral manifestations in patients with coronavirus disease 2019 (COVID-19) have been reported.

Objectives: In the present study, we investigated the relationship between Polymerase Chain Reaction (PCR) positivity and oral signs in patients with suspected COVID-19.

Methods: A total of 383 patients who presented to the emergency department for the first time with any symptoms associated with COVID-19 were included in the study. Oral examinations were performed and the findings, PCR status, and thorax computerized tomography (CT) reports were recorded.

Results: Oral mucosa was involved in 246 (64.2%) patients. 175 (78,4%) of patients with COVID-19 confirmed the diagnosis with PCR test or CT results had oral manifestation. Dry mouth, microvesicles on the tonsils or pharynx, and petechiae in the oropharynx were significantly higher in patients with positive PCR tests ($P = 0.001$, $P < 0.001$, $P < 0.001$, respectively). The ratio of intact oral mucosa was statistically significantly higher in patients with negative PCR tests compared to those with positive PCR tests ($P < 0.001$). Microvesicles on the tonsils or pharynx were most associated with PCR positivity in patients without lung involvement ($P < 0.001$). Dry mouth, erythema of the tonsils and pharynx, petechiae in the oropharynx, and primary/secondary herpes infection are more related to PCR positivity in patients without lung involvement ($P < 0.05$). Lung involvement in patients with PCR positivity is related to only cheilitis ($P = 0.034$).

Conclusions: Our study revealed that especially microvesicles, petechiae, erythema on the tonsils or pharynx, and some other oral lesions such as dry mouth, oral aphthae, and primary/secondary herpes infection are associated with PCR positivity.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is a novel virus that generating coronavirus disease 2019 (COVID-19). The disease first started in China and spread rapidly all over the world in a short time. Transmission mainly happens through large droplets that occur during coughing and sneezing by symptomatic patients. Also contact with contaminated surfaces may be a risk for transmission [1]. The respiratory tract is the primary site of infection, with no symptoms or symptoms ranging from mild flu-like symptoms to fulminant pneumonia and potentially mortal respiratory distress [2]. The most common reported symptoms among patients with symptomatic COVID-19 are dry cough, myalgias, fever and headache. High fever (>38 °C) was found associated with COVID-19 PCR positivity [3].

Research shows that SARS-CoV-2 enters human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is detected in the cell membrane of many human organs and tissues, including the upper respiratory tract, epithelial cells of the tongue and salivary glands, and lungs. Thus, cells with ACE2 receptor distribution may become host cells for the virus and cause an inflammatory response [4]. The oral cavity is one of the main entryways for SARS-CoV-2. Various oral mucosal symptoms and signs such as vesiculobullous lesions, taste disorder, nonspecific oral ulcerations, cheilitis, desquamative gingivitis, petechiae, herpes virus infections, candidiasis and lingua villosa nigra due to COVID-19 have been reported in the literature 5-8. However, it is still unknown whether these manifestations in the oral cavity develop directly or indirectly [9].

Objectives

The gold standard for diagnosis of the disease is the finding of viral genome by real-time polymerase chain reaction (RT-PCR) in respiratory tract secretions [10]. Although many oral mucosal involvements associated with COVID-19 have been reported in the literature, there is no data on oral manifestations that may be associated with PCR positivity. In this study, we aimed to investigate oral mucosal signs and symptoms related to PCR positivity in patients with suspected COVID-19.

Methods

All patients were recruited from the COVID-19 emergency service in the Erzurum City Hospital, the only pandemic hospital in the province, between 01 Januar-30 June 2020. Adult patients who presented to the emergency department for the first time with any symptoms in terms of COVID-19 were included in the study. Patients with complaints for a maximum of 14 days were enrolled, as PCR test may become negative. The patients were questioned in terms of sore throat, loss of taste and smell, presence of back and chest pain, headache, and dry mouth sensation (xerostomia). The oral mucosa of patients was examined by a dermatologist and the findings (erythema, xerosis, vesicle, crypt, candida, tonsillar hypertrophy, leukoplakia, geographic tongue, scrotal tongue, herpes simplex infections, aphthae/ulcer, other) were recorded. These disorders were diagnosed clinically. All necessary data such as age, gender of the patients, complaints, oral mucosal findings, PCR status, and thorax computerized tomography (CT) reports were anonymized and obtained from the electronic database and patient follow-up forms. Behçet disease, recurrent aphthous stomatitis, inflammatory bowel diseases, and collagen tissue disease such as systemic lupus erythematosus which may cause oral aphthae. In diabetes mellitus, anticholinergic drugs lead to dryness in the oral mucosa. Various infection diseases such as hand, foot, and mouth disease, herpangina, and tularemia can cause oral mucosal ulceration. Some drugs such as isotretinoin may be a reason for cheilitis. Oral lichen planus clinically presents as reticular, erosive or ulcerative lesion with whitish streak or white, lacy patches. The patients who have the above-mentioned diseases and use drugs that may cause disorders of oral mucosa and also those with dermatological diseases such as oral lichen planus and bullous diseases with oral mucosal involvement were excluded from the study. Moreover, patients without CT were not included.

The study protocol was approved by the ethics committee of the Erzurum Regional Training and Research Hospital (reference no. 2021/12-187). An informed consent form was obtained from all participants. The study was performed as per the latest version of the Helsinki Declaration and the Guidelines for Good Clinical Practice.

Statistical Analysis

All procedures were performed using Statistical Package for Social Sciences (SPSS Inc. v21.0) software. After checking the normality distribution of scale variables by Kolmogorov - Smirnov test, the Pearson chi-square, and the Fisher exact tests were used for the categorical variables where appropriate. Examination findings related to PCR results were evaluated with univariate and multivariate logistic regression analysis. Multivariate analysis was performed using the "Backward: Wald" method. A two-sided P value less than 0.05 was considered statistically significant.

Results

A total of 383 patients with any symptoms associated with COVID-19 were included in the study. Oral mucosal involvement was present in 246 (64.2%) of all patients. The PCR

Table 1. Distribution of oral mucosal examinations of patients evaluated for COVID-19 according to PCR and CT results.

		PCR negative, N (%)		PCR positive, N (%)	
		CT: normal/ unknown	CT: COVID-19 pneumonia	CT: normal/ unknown	CT: COVID-19 pneumonia
Oral mucosa examination	Total N = 383	(N =160)	(N = 13)	(N = 168)	(N = 42)
Normal oral mucosa findings	137 (35.8%)	89 (55.6%)	5 (38.5%)	35 (20.8%)	8 (19.0%)
Erythema of tonsils and pharynx	187 (48.8%)	62 (38.8%)	6 (46.2%)	97 (57.7%)	22 (52.4%)
Dry mouth sensation (Xerostomia)	41 (10.7%)	11 (6.9%)	3 (23.1%)	22 (13.1%)	5 (11.9%)
Micro vesicles on tonsils or pharynx	77 (20.1%)	7 (4.4%)	1 (7.7%)	57 (33.9%)	12 (28.6%)
Cryptic tonsillitis	24 (6.3%)	3 (1.9%)	1 (7.7%)	15 (8.9%)	5 (12.2%)
Oral candidiasis (Suspected)	74 (19.3%)	24 (15.0%)	5 (38.5%)	37 (22.0%)	8 (19.0%)
Tonsillar hypertrophy	57 (14.9%)	18 (11.3%)	4 (30.8%)	25 (14.9%)	10 (23.8%)
Petechiae in the oropharynx	100 (26.1%)	19 (11.9%)	3 (23.1%)	60 (35.7%)	18 (42.9%)
Geographic tongue	7 (1.8%)	5 (3.1%)	1 (7.7%)	1 (0.6%)	0 (0.0%)
Scrotal tongue	33 (8.6%)	12 (7.5%)	1 (7.7%)	13 (7.8%)	7 (16.7%)
Primary/secondary herpes infection	22 (5.8%)	3 (1.9%)	0 (0.0%)	15 (9.0%)	4 (9.5%)
Oral aphthae	66 (17.2%)	15 (9.4%)	4 (30.8%)	34 (20.2%)	13 (31.0%)
Cheilitis or angular cheilitis	18 (4.7%)	2 (1.3%)	0 (0.0%)	8 (4.8%)	8 (19.0%)
Other findings	8 (2.1%)	5 (3.1%)	0 (0.0%)	2 (1.2%)	1 (2.4%)

CT = Computed tomography; PCR = Polymerase Chain Reaction.

test was positive in 210 (54.8%) patients and 13 patients whose PCR tests were negative had COVID-19 pneumonia on thoracic CT. One hundred and seventy-seven patients whose PCR tested positive and 8 patients whose PCR tested negative but had pneumonia compatible with COVID-19 had oral mucosal manifestations (175 (78.4%) out of 223 COVID-19 patients). The distribution of oral mucosal examinations of patients according to PCR and CT results was presented in Table 1.

Examination findings and complaints according to PCR results of patients without pneumonia were evaluated in Table 2. The PCR test was positive in 71 of 139 patients without pneumonia. There was no difference between the two groups (PCR test positive and negative patients without pneumonia) in terms of age, gender, and duration of complaints. Dry mouth sensation (xerostomia) was significantly higher in patients with positive PCR tests (P = 0.001). Normal oral mucosa findings were more common in patients with negative PCR tests compared to those with positive PCR tests (P < 0.001). It was noteworthy that the frequency of microvesicles on the tonsils or pharynx and petechiae in the oropharynx were significantly higher in those with positive PCR tests (both with P < 0.001). In addition, there was a significant difference between the patients with positive PCR tests and with negative PCR tests in terms of the presence of primary/secondary herpes infection, oral aphthae, and erythema of tonsils and pharynx (P = 0.036, P = 0.040, P = 0.022, respectively).

Assessment of examination findings and complaints according to CT results of patients with a definitive diagnosis of COVID-19 are as Table 3. No difference was observed between the PCR-positive patients with and without pneumonia in terms of complaints and findings.

Parameters with P <0.1 in Table 2 were subjected to logistic regression analysis. Tables 4 and 5 show the results of univariate and multivariate analyzes of parameters potentially related to PCR positivity, respectively. It was found that microvesicles on tonsils or pharynx were most associated with PCR positivity in patients without lung involvement according to both univariate and multivariate analysis (OR = 14.11, 95% CI: [4.04-.49.32], P < 0.001, OR = 15.64, 95% CI: [3.38-.73.45], P < 0.001, respectively). Additionally, both analyses revealed that dry mouth sensation (xerostomia), erythema of the tonsils and pharynx, and petechiae in the oropharynx were more related to PCR positivity in patients without lung involvement (P < 0.05). Univariate analysis showed that oral aphthae were also associated with PCR positivity (OR = 2.55, 95% CI: [1.03-6.34], P = 0.044). While it was not found that there was no relationship between primary/secondary herpes infection and PCR positivity according to univariate analysis,

Table 2. Evaluation of examination findings according to PCR results and complaints of patients without pneumonia.

Parameters		No evidence of pneumonia on the CT		P
		PCR negative (N = 68)	PCR positive (N = 71)	
Age (year); median (IQR)		40 (22.0)	39 (23)	0.813
Sex, N (%)	Woman	30 (44.1%)	40 (56.3%)	0.150
	Man	38 (55.9%)	31 (43.7%)	
Complaint duration (day); median (IQR)		4 (2.0)	4 (2.0)	0.796
Current complaints, N (%)				
Throat ache		27 (39.7%)	27 (38.0%)	0.839
Headache		29 (42.6%)	28 (39.4%)	0.700
Loss of taste and smell		2 (2.9%)	6 (8.6%)	0.275
Back or chest pain		31 (45.6%)	43 (60.6%)	0.077
Dry mouth sensation (Xerostomia)		2 (3.0%)	15 (21.1%)	0.001
Other symptoms (typical-atypical)		64 (94.1%)	69 (97.2%)	0.435
Oral mucosa examination, N (%)				
Normal oral mucosa findings		37 (54.4%)	9 (12.7%)	<0.001
Erythema of tonsils and pharynx		28 (41.2%)	43 (60.6%)	0.022
Micro vesicles on tonsils or pharynx		3 (4.4%)	28 (39.4%)	<0.001
Cryptic tonsillitis		1 (1.5%)	6 (8.5%)	0.116
Oral candidiasis (Suspected)		13 (19.1%)	20 (28.2%)	0.210
Tonsillar hypertrophy		8 (11.8%)	11 (15.5%)	0.522
Petechiae in the oropharynx		10 (14.7%)	30 (42.3%)	<0.001
Leukoplakia		0 (0.0%)	0 (0.0%)	N/A
Geographic tongue		1 (1.5%)	1 (1.4%)	1.000
Scrotal tongue		7 (10.3%)	5 (7.0%)	0.495
Primary/secondary herpes infection		2 (3.0%)	9 (12.7%)	0.036
Oral aphthae		8 (11.8%)	18 (25.4%)	0.040
Cheilitis or angular cheilitis		1 (1.5%)	4 (5.6%)	0.366
Other findings		3 (4.5%)	2 (2.8%)	0.674

CT = Computed tomography; IQR = Inter-quartile range; N/A = not applicable; PCR = Polymerase Chain Reaction.

they were related in multivariate analysis (OR = 11.15, 95% CI: [1.57-97.53], P = 0.029, Table 5). Moreover, PCR positivity is nearly 8 times higher in patients with any oral mucosa findings (OR = 8.22, 95% CI: [3.5319.17], P < 0.001). Lung involvement in patients with PCR positivity is related to only cheilitis or angular cheilitis (OR = 3.94, 95% CI: [1.11-14.02], P = 0.034, Table 4).

Conclusions

Enanthema and various oral lesions are among the typical symptoms of many viral diseases [5]. In a large series of patients with atypical exanthems, erythematous-vesicular and petechial patterns were found most commonly associated with viral infections [11]. Up to date, numerous oral mucosal lesions associated with COVID-19 infection have been reported [5-9,12-15]. However, it remains unclear whether oral manifestations develop directly from the SARS-CoV-2 infection or due to systemic consequences of COVID-19, given the possibility of co-infection and impaired immune response or drug side effects [9].

The prevalence of oral cavity signs of COVID-19 is not known, but it was reported that oral manifestations were present in 25.65% of 666 patients in a large study [16]. Mild severity of the disease was assumed to be associated with no or minor symptoms [16]. In the present study, there were normal oral mucosa findings in 21.5 % of 223 patients with confirmed COVID-19.

According to our study results, the most common oral manifestations associated with COVID-19 were erythema of

Table 3. Evaluation of examination findings according to CT results and complaints of patients with a definitive diagnosis of COVID-19.

Parameters		Patients with PCR positive		P
		CT: Normal (N = 71)	CT: Pneumonia (N = 42)	
Age (year); median (IQR)		39 (23)	49(21)	0.058
Sex, N (%)	Woman	40 (56.3%)	21 (50.0%)	0.514
	Man	31 (43.7%)	21 (50.0%)	
Complaint duration (day); median (IQR)		4 (2)	5 (4)	0.074
Current complaints, N (%)				
Throat ache		27 (38.0%)	9 (21.4%)	0.067
Headache		28 (39.4%)	16 (38.1%)	0.888
Loss of taste and smell		6 (8.6%)	6 (14.3%)	0.361
Back or chest pain		43 (60.6%)	26 (61.9%)	0.988
Other symptoms (typical-atypical)		69 (97.2%)	40 (95.2%)	0.627
Dry mouth sensation (Xerostomia)		15 (21.1%)	5 (11.9%)	0.122
Oral mucosa examination, N (%)				
Normal oral mucosa findings		9 (12.7%)	8 (19.0%)	0.360
Erythema of tonsils and pharynx		43 (60.6%)	22 (52.4%)	0.395
Micro vesicles on tonsils or pharynx		28 (39.4%)	12 (28.6%)	0.243
Cryptic tonsillitis		6 (8.5%)	5 (12.2%)	0.527*
Oral candidiasis (Suspected)		20 (28.2%)	8 (19.0%)	0.278
Tonsillar hypertrophy		11 (15.5%)	10 (23.8%)	0.272
Petechiae in the oropharynx		30 (42.3%)	18 (42.9%)	0.950
Leukoplakia		0 (0.0%)	0 (0.0%)	N/A
Geographic tongue		1 (1.4%)	0 (0.0%)	1.000
Scrotal tongue		5 (7.0%)	7 (16.7%)	0.125
Primary/secondary herpes infection		9 (12.7%)	4 (9.5%)	0.764
Oral aphthae		18 (25.4%)	13 (31.0%)	0.519
Cheilitis or angular cheilitis		4 (5.6%)	8 (19.0%)	0.054
Other findings		2 (2.8%)	1 (2.4%)	1.000

CT = Computed tomography; IQR = Inter-quartile range; N/A = not applicable; PCR = Polymerase Chain Reaction.

tonsils and pharynx (56.0%), petechiae in the oropharynx (36.3%), microvesicles on tonsils or pharynx (31.8%), oral aphthae (22.8%), oral candidiasis (suspected) (22.4%), and dry mouth sensation (xerostomia) (15.6%), primary/secondary herpes infection (8.5%). Oral lesions described in patients with COVID-19 in the literature were highly heterogeneous. In a few studies, oral vesiculobullous lesions and erosions on the tongue and buccal mucosa, widespread erythema appeared on the hard palate and oropharynx, and petechiae on the lower lip, palate, and oropharynx, herpes simplex lesion in the lip semi mucosa were reported [7,17-19]. Jimenez-Cauhe et al presented 5 patients with COVID-19 who had petechiae on tonsils [20]. Egido-Moreno et al stated that the most prevalent lesions were ulcers, aphthous-like lesions, or erosions, followed by macules and petechiae, plaques bullae, gingival abnormalities, and finally blisters and pustules in their study [12]. Martín Carreras-Presas et al reported different types of oral mucosal lesions (ulcer, vesicle, bulla, and desquamative gingivitis) in patients with COVID-19 [21]. Tuter et al showed that dry mouth is the most common and oral ulcers and tongue lesions are the second common oral manifestation in COVID-19 patients [13]. Cuevas-Gonzalez et al stated that the most common main oral manifestations related to SARS-CoV-2 were dysgeusia, dry mouth, burning mouth, ulcerative lesions, and Candida Albicans infections in their systematic review including a total of 18 studies [6]. A review article revealed that aphthous-like lesions, herpetiform lesions, candidiasis, and oral lesions of Kawasaki-like disease are the most common oral manifestations of COVID-19 [22]. Our findings were partially compatible with the literature.

Table 4. Evaluation of examination findings related to PCR result and lung involvement with univariate logistic regression analysis

Univariate logistic regression analysis	βi	Odds ratio	95% CI		Wald value	P	R^2
			Lower	Upper			
PCR positivity in patients without lung involvement (N = 71/139)							
Back or chest pain	0.61	1.83	0.93	3.60	3.11	0.078	0.02
Dry mouth sensation (xerostomia)	2.16	8.71	1.91	39.72	7.81	0.005	0.08
Any oral mucosa findings	2.11	8.22	3.53	19.17	23.80	<0.001	0.19
Erythema of tonsils and pharynx	0.79	2.19	1.11	4.32	5.16	0.023	0.04
Micro vesicles on tonsils or pharynx	2.65	14.11	4.04	49.32	17.18	<0.001	0.18
Petechiae in the oropharynx	1.45	4.24	1.87	9.63	11.94	0.001	0.09
Primary/secondary herpes infection	1.55	4.72	0.98	22.70	3.75	0.053	0.03
Oral aphthae	0.94	2.55	1.03	6.34	4.05	0.044	0.03
Lung involvement in patients with PCR positivity (N = 42/113)							
Age (year)	0.30	1.03	0.99	1.06	3.48	0.062	0.03
Complaint duration (day)	0.16	1.17	0.99	1.38	3.42	0.064	0.03
Cheilitis or angular cheilitis	1.37	3.94	1.11	14.02	4.49	0.034	0.04

PCR= Polymerase Chain Reaction.

Table 5. Evaluation of examination findings related to PCR result with multivariate logistic regression analysis.

Multivariate logistic regression analysis	βi	Odds ratio	95% CI		Wald value	P	R^2
			Lower	Upper			
PCR positivity in patients without lung involvement; Step 4 (N = 71/139)							
Dry mouth sensation (xerostomia)	2.14	8.48	1.67	43.11	6.65	0.010	0.32
Micro vesicles on tonsils or pharynx	2.75	15.64	3.38	72.45	12.36	<0.001	
Petechiae in the oropharynx	1.05	2.86	1.10	7.44	4.63	0.032	
Primary/secondary herpes infection	2.41	11.15	1.27	97.53	4.75	0.029	

Multivariate analysis was performed using the "Backward: Wald" method. It was carried out with examination findings such as "Back or chest pain, dry mouth sensation, erythema of tonsils and pharynx, microvesicles on tonsils or pharynx, petechiae in the oropharynx, primary/secondary herpes infection, oral aphthae" with a significance level of p<0.01.
PCR = Polymerase Chain Reaction.

To date, reports generally provide information about the signs and symptoms of the oral mucosa in patients with COVID-19; however, the relationship between PCR positivity and pneumonia and the oral signs and symptoms has not yet been studied. In the present study, it was found that microvesicles on the tonsils or pharynx were most associated with PCR positivity in patients without lung involvement (P < 0.001).

Petechiae in the oropharynx, dry mouth sensation (xerostomia), erythema of tonsils and pharynx, oral aphthae, and primary/secondary herpes infection were also related to PCR positivity (P < 0.05). Cheilitis or angular cheilitis were the only oral signs associated with lung involvement in patients with PCR positivity (P = 0.034). The patients with negative PCR tests had more common normal oral mucosa (P < 0.001). Various hypotheses have been recommended for the etiology of oral lesions. According to some authors, the lesions arise directly from the disease. The expression of ACE2 and transmembrane serine protease (TMRPSS2) are confirmed in oral mucosal epithelia and salivary glands, approving evidence of SARS-CoV-2 direct infection [23]. In addition, since the oral mucosa was the first to be infected with SARS-CoV-2, it was suggested that oral lesions could be the first symptom of COVID-19 [24]. A study has revealed that viruses affect epithelial cells and damage tissue integrity by causing inflammatory reactions [25]. It was suggested that SARS-CoV-2 infects salivary glands, resulting in hyposalivation, taste disorders, xerostomia, and halitosis [23]. According to our study results, we can make the following comment: For COVID-19, a PCR swab is obtained from the tonsillar-pharynx and nasopharynx [8]. Thus, tonsillar-pharynx lesions such as microvesicles on the tonsils or pharynx, petechiae in the oropharynx, erythema of tonsils and pharynx, oral aphthae (only on the tonsillar-pharynx) which were related to PCR

positivity according to our study could suggest the direct effect of SARS-CoV-2. However, dry mouth probably occurs secondary to involvement of the salivary glands and herpes infections may be an opportunistic coinfection. Nevertheless, as these lesions were associated with PCR positivity, the presence of these findings may indicate the presence of the virus in the tonsillar-pharynx. Some studies have suggested that some manifestations such as herpes infections and angular cheilitis are opportunistic coinfection [26,27]. In the present study, angular cheilitis was more frequent in patients with pneumonia, suggesting opportunistic coinfection.

This study has some limitations. Firstly, we only included symptomatic patients with mild-to-moderate disease in the study. Thus, our data cannot support oral lesions in asymptomatic patients or with severe COVID-19. Secondly, as all patients were adults, the study does not provide information on the relationship between oral findings and PCR positivity in children.

Oral aphthae and herpes lesions on the entire oral mucosa were evaluated. Thus, direct virus infection on the tonsillar pharynx could not be differentiated. Another limitation was that oral examination of patients and clinical imaging of lesions were difficult due to the high risk of contamination at the beginning of the pandemic. Nonetheless, we made an effort to evaluate patients correctly and our study provides valuable observations of a large number of cases.

Our study showed that especially microvesicles, petechiae, erythema on the tonsils or pharynx, and some other oral lesions such as dry mouth, oral aphthae, and primary/secondary herpes infection are associated with PCR positivity and can guide us in terms of definite disease. However, the pathophysiological mechanism and relationship of these oral manifestations in COVID-19 should be further investigated.

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