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Review Article

Oral Cues associated with Coronavirus Disease 2019 Infection – A Systematic Review

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Abstract

Introduction: A global pandemic has been broken out in December 2019 by human-to-human transmission of novel corona virus disease (COVID -19). Since then, it has affected more than million people worldwide and causing numerous death. Most of the cases are mild (80%), while 20% of the infected patients may develop severe disease, and 5% may become critically ill and develop pneumonia or acute respiratory distress syndrome. The general clinical manifestations include fever, chills, cough, fatigue, muscle or body aches, soreness of throat, shortness of breath, headache, nausea, vomiting or diarrhoea. In recent times, few studies have documented several oral manifestations associated with COVID-19. Hence we aim to summarize the oral cues associated with COVID-19.

Methodology: The review was reported as per the PRISMA checklist, and the literature search was conducted in 4 databases and in grey literature as well as a manual search across the reference lists of included studies. Studies published in only English language and those which mentioned oral signs and symptoms in patients with COVID-19 were included.

Conclusion: Taste disorder was the foremost common oral symptoms in patients with COVID-19. Identifying these lesions could help clinicians to treat their patients more efficiently. But several oral manifestations of this disease are underreported due to the lack of oral examination of patients with COVID-19 owing to the lockdown and the carelessness of patients regarding these manifestations that might be less serious compared to the typical COVID-19 manifestations. So, a thorough oral examination should be routinely performed for all suspected COVID-19 cases.

Key words: Coronavirus, COVID-19, Oral manifestations, Review

INTRODUCTION

A global pandemic has been broken out in December 2019 by human-to-human transmission of novel coronavirus disease (COVID-19). Since then, it has affected more than million people worldwide with death of many. Compared to other recent pandemics, COVID-19 shows in general, less severe clinical manifestations but is spreading with great ease. On January 8, 2020, the Chinese Center for Disease Control and Prevention announced officially the identification of a new strain of coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the causative pathogen of the global COVID-19 pandemic.[1] SARS-CoV-2 is a single-chain RNA virus that is the cause of novel COVID known as COVID-19. Most human cases of COVID-19 are mild (80%), while 20% of infected patients may develop severe disease, and 5% may become critically ill and develop pneumonia or acute respiratory distress syndrome, which requires mechanical ventilation and intensive care unit hospitalization.[2] Coronavirus invades human cells through the receptor angiotensin-converting enzyme 2 (ACE2) through single cell RNA sequencing data analyses.[3] The study of Xu *et al.* found that the receptor-binding domain of the 2019-novel coronavirus (nCoV) S-protein supports strong interaction with human ACE2 molecules.[4] Thus ACE 2 expressing cells become the target for viral entry and infection. Type II alveolar cells of lung, absorptive enterocytes from ileum and colon, esophagus upper and stratified epithelial cells, myocardial cells, cholangiocytes, bladder urothelial cells, and kidney proximal tubule cells shows high ACE2 expression.[5] The general clinical manifestations shown by the patient

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infected with SARS-CoV-2 are fever, chills, cough, fatigue, muscle or body aches, soreness of throat, shortness of breath, headache, nausea, vomiting, or diarrhea.[6]

This meta-analysis presents the information available about the oral manifestations in COVID-19 with lesions presented at the mucosal level, salivary glands and alterations in the olfactory system and taste.

METHODOLOGY

Literature Search and Eligibility Criteria

We searched PubMed library, Scopus databases, Web of Science databases, and Google Scholar for published literature using the keywords "coronavirus," "SARS-CoV-2," "SARS-CoV-2," "COVID-19," "nCoV," "nCoV" and "2019-nCoV" from December 2019 to November 2020.

Reference lists of included studies were also screened for retrieving additional articles. Articles published in English language were taken during literature search. Eligible articles reported the epidemiological and clinical features of COVID-19 and the prevalence of oral manifestations in infected patients. The following studies were excluded: Duplicate publications, reviews, editorials, and studies pertaining to other coronavirus related illnesses, such as Middle East respiratory syndrome. A total of 37 articles that met the inclusion criteria were obtained [Table 1].

Data Extraction

The following information was extracted and tabulated [Table 2] with author, age, sex, oral manifestations, site, duration, systemic manifestations, any special investigations performed, and treatment of oral lesions.

RESULTS

Oral manifestations were swelling, cracked lip, extensive mucosal damage, ulcer, erosion, bulla, vesicle, pustule, fissured or geographic tongue, prominent papilla or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, purpura, erythema, spontaneous bleeding, dysgeusia or hypogeusia, herpetiform stomatitis, edematous gingiva, angular cheilitis or burning sensation, and dry mouth. The most common sites involved in descending order were lips (46%), tongue (38%), hard palate (37%), buccal mucosa (14%), gingiva (13%), labial mucosa (6%), oropharynx (6%), tonsil (6%), and soft palate (4%). Provisional diagnoses of the lesions were angular cheilitis, aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Erythema Multiforme (EM) like, mucositis, drug eruption, necrotizing periodontal disease (NPD), angina bullosa-like, atypical Sweet syndrome, Kawasaki-like Vascular inflammation Ischemic reperfusion injury, Zosteriform, Thrombocytopenia and enanthema due to COVID-19, and Melkerson Rosenthal syndrome. The results of literature are summarized in Table 2.[7-41]

Oral lesions in 68% of the cases were symptomatic including burning sensation, pain, or pruritus. Oral lesions were slightly higher in males (69% males and 57% females). The age of incidence ranged between 3 and 78 years. Oral lesions were more prevalent as age increases. Systemic manifestations included fever, cough, chills, vomiting, diarrhea, conjunctivitis, meningeal sign, lymphadenopathy, tachypnea, respiratory and gastrointestinal (GI) symptoms, anosmia, malaise, dyspnea, headache, sorethroat, pneumonia, asthenia, fatigue, respiratory distress, nasal congestion, dysgeusia, arthralgia, facial edema, loss of apetite, and weakness. Latency time period between appearance of systemic symptoms and oral lesions was 4 days up to 12 weeks after onset of systemic symptoms. The longest latency period was noticed in Kawasaki-like lesions. Oral lesions healed within 2–4 weeks after appearance. Medications prescribed for oral lesions depend on the etiology. Treatment done was chlorhexidine and metronidazole mouthwash, Nystatin, non-steroidal anti-inflammatory drugs (NSAIDs), Vitamins C and D,

Table 1: Literature search methodology

Identification	Screening	Eligibility	Included
• Pubmed-364 • Scopus-560 • Web of science-270 • Embace-480 • Records identified through first database searching (*n*=1700) • Records after duplicates removed (*n*=1300)	• Grey literature • Google scholar (*n*=50) • Full text article assessed in phase 2 (*n*=80)	• Reviews, letters, conference abstracts, personal opinion, book chapters (*n*=4) • Non-confirmed COVID-19 (*n*=2) • Case reports for taste disorders (*n*=7) • Population selection criteria based on another main disease (*n*=3) • Studies containing data included in other studies or other • studies in which it is not possible to state if they contain duplicate data (*n*=2) • Taste disorder as criteria for population inclusion (*n*=19)	• Studies included in systematic review (*n*=37)

Table 2: Detailed characteristics of included studies

Sl. No.	Author	Age/Sex	Oral Lesions	Site	Duration	Systemic Manifestations	Covid-19 Diagnostic Tests	Treatment Done
1	Verdoni *et al*.[7]	7/5 9-16	Mild swelling	Lip Oral cavity (80%)		Fever Diarrhea Conjunctivitis Meningeal sign lymphadenopathy	PCR-20% IgG-80% IgM 30%	------
2	Jones *et al*.[8]	6M	Cracked lip Prominent papilla in tongue	Lip tongue	------	Fever Conjunctivitis Tachypnea	PCR	
3	Pouletty *et al*.[9]	10(M=8, F=8)	Cracked lip	lip	-------	Fever Respiratory and GI symptom Anosmia	PCR-+69 %	IVIG CS ANTI IL1, IL6 HCH
4	Singh *et al*.[10]	44/F	Extensive mucosal damage	Lip Tongue	----	Malaise Dyspnea		
5	Chiotoset al.[11]	5/F	Fissured lip					
6	Chiotos *et al*.[11]	9/F	Fissured lip	lip		Fever Diarrhea		
7	Chiotos *et al*.[11]	12/M	Fissured lip	lip		Fever Diarrhea conjunctivitis		
8	Chiu *et al*.[12]	10/M	Cracked lip Erythema	Lip oropharynx		Fever Cough diarrhea	PCR	
9	Mazzotta *et al*.[13]	58/M	Unilateral multiple small ulcers	Palate	7	----		Mouthwash
10	Carreras-Presas *et al*[14]	56/M	Dysgeusia Herpetiform stomatitis	Hard palate	10	Fever Asthenia LAP	2	
11	Carreras-Presas *et al*[14]	60/M	Macule Petechiae	Palate	---	----	19	AZT HCH L/R
12	Jimenez-Cauhe *et al*.[15]	60/M	Macule Petechiae	Palate	---	----		L/R HCH AZT T CS L/R HCH AZT Toclizomab CS
13	Jimenez-Cauhe *et al*.[15]	40/M	Purpura	Palate	---	---		
14	Jimenez-Cauhe[15]	60/M	Macule Petechiae	Palate	---	---	PCR	L/R HCH AZT
15	Jimenez-Cauhe[15]	40/M	Purpura EM like	Palate		Enanthema due to covid 19		L/R HCH
14	Patel and Woolley[16]	35/F	Bleeding Halitosis Generalized edematous gingiva Necrosis	Gingiva		Fever LAP submandibular		Metronidazole mouthwash
15	Chaux-Bodard *et al*.[17]	45/F	Patch	Tongue	10	Asthenia	PCR	Vasculitis
16	Dominguez-Santas *et al*.[18]	19/M	Minor aphthous	Lip	---	Fever Headache Anosmia Malaise Dyspnea	PCR	----

(Contd...)

Table 2: *(Continued)*

Sl. No.	Author	Age/Sex	Oral Lesions	Site	Duration	Systemic Manifestations	Covid-19 Diagnostic Tests	Treatment Done
17	Dominguez-Santas *et al*.[18]	37/M	Minor aphthous	Tongue	----	-----	PCR	---
18	Dominguez-Santas *et al*.[18]	33/M	Minor aphthous	Mucogingival junction	-----	Pneumonia Fever Malaise	PCR	---
19	Dominguez-Santas *et al*.[18]	43/F	Minor aphthous	Buccal	----	Bilateral pneumonia Fever Malaise	PCR	
20	Putra *et al*.[19]	29/M	Papule Aphthous stomatitis		---	Fever Myalgia Sore throat Dry cough	PCR	Paracetamol AZT HCH Oseltamivir Vitamin C Vitamin D
21	Carreras-Presas *et al*.[14]	65/F	Rash Desquamative gingivitis	Tongue Gingiva		Fever Diarrhea	-----	Antibiotics CS HCH HA L/R
22	Kämmerer *et al*.[20]	46/M	Multiple ulceration covered by yellow gray membrane	Oral cavity Gingiva	---	Fever Fatigue Dry cough Respiratory distress LAP submandibular	PCR	AZT Meropenam Acyclovir
23	Tapia *et al*.[21]	42/M	Burning	Hard palate	7	Fever Malaise Dysgeusia Headache	PCR	Acetaminophen Mouthwash CS
24	Tapia *et al*.[21]	55/F	Tongue enlargement Purple blister	Tongue	5	Fever Headache Nasal congestion	PCR	Acetaminophen
25	Tapia *et al*.[21]	51/F	Vascular like purple macule Non bleeding Purple plaque	Palate	--	Fever Malaise Dysgeusia Arthralgia	PCR	Acetaminophen
26	Tapia *et al*.[22]	41/F	Erythematous blister	Hard palate	----	Fever Malaise Dysgeusia Hyposmia	PCR	Acetaminophen Fexofenadine
27	Rodríguez *et al*.[22]	78/F	Dry mouth Atrophy of surface of tongue White and red patches Fissured tongue	Tongue Hard palate Soft palate Lip	----	---	PCR	Artificial saliva Nystatin Neomycin CS
28	Rodríguez *et al*.[22]	43/M	Angular chelitis with burning sensation	Lip	10	Dysguisea Anosmia Diarrhea Pneumonia	PCR	Mouthwash CS
29	Chérif *et al*.[23]	35/F	Chapped lips Ulcer Hypogeusia	Tongue Lip	10	Fever Myalgia Dyspnea Dry cough Vomiting Diarrhea	PCR	AZT Mouthwash
30	Ansari *et al*.[24]	75/M	Painful Irregular ulcer in erythematous background	Hard palate	7	Hypoxia	PCR	AZT Mouthwash

(Contd...)

Table 2: *(Continued)*

Sl. No.	Author	Age/Sex	Oral Lesions	Site	Duration	Systemic Manifestations	Covid-19 Diagnostic Tests	Treatment Done
31	Ansari *et al*.[24]	56/F	Painful Irregular ulcer in erythematous background	Hard palate	7	Fever Dyspnea	PCR	Remisidivir AZT
32	Biadsee *et al*.[25]	36.25/F	Plaque bleeding swelling Xerostomia Dysgeusia	Tongue Palate Gingiva	--	Fever Cough Myalgia Sore throat Anosmia GI symptoms	PCR	
33	Olisova *et al*.[26]	12/F	Swollen irritated Pronounced lingual papilla	Tongue	3	Fever Fatigue Headache	PCR	Paracetamol
34	Tomo *et al*.[27]	37/F	Erythematous Depapillation of tongue	Tongue	14	Fever Asthenia Dysgeusia Anosmia	PCR	CS Dipyrone Mouthwash
35	Ciccarese *et al*[28]	19/F	Erosion Ulcer Hemorrhagic crust Petechial	Lip Palate Gingival Oropharynx	5	Fever Fatigue Hyposmia Sore throat	PCR	IVIG CS
36	Sakaida *et al*[29]	52/F	Erosion	Lip Buccal	---	Fever Dyspnea Drycough	PCR	
37	Brandiao *et al*.[30]	72/M	Painful Aphthous like necrosis Hemorrhagic ulcer	Lip	7	Fever Dyspnea	PCR	Increased levels of CRP Lymphocytopenia Positive PCR for HSV
38	Brandiao *et al*.[30]	81/M	Aphthous like necrosis Hemorrhagic ulcer	Lip Tongue	11	Dry cough Dyspnea Fever Chills Dysgeusia	PCR	AZT Cefriaxone Acyclovir PBMT
39	Malih *et al*.[31]	38/M	Erythema Aphthous like	Tonsil	---	Fever Asthenia Cervical LAP	PCR	Acetaminophen
40	Labé[32]	3/M	Cheilitis Glossitis Stomatitis	Lip Tongue Oral cavity	---	Loss of appetite	PCR	---
41	Aghazadeh *et al*.[33]	9/F	Vesicles Erosion	Lip Tongue Buccal	7	Fever Weakness Loss of appetite Abdominal pain	PCR	AcetaminophenI
42	Indu[34]	NS/M	Burning ulcer	Lip tongue	10	Fever	PCR	---
43	Taskin *et al*.[35]	61/F	Minor aphthous ulcer	Hard palate Buccal	---	Fever Fatigue Myalgia Arthralgia	PCR	AZT HCH Oseetamivir Toclizomab Favipiravir
44	Taşlıdere *et al*.[36]	51/F	Swollen lip Fissured tongue	Lip Tongue	---	Malaise Unilareral facial paralysis Facial edema	---	HCH AZT CS
45	Brandiao *et al*.[30]	29/M	Painful Aphthous like aguesia	Lip Tongue	6	Fever Cough Headache Myalgia Chills Anosmia	PCR	Mouthwash

(Contd...)

Table 2: *(Continued)*

Sl. No.	Author	Age/Sex	Oral Lesions	Site	Duration	Systemic Manifestations	Covid-19 Diagnostic Tests	Treatment Done
46	Brandiao *et al*.[30]	35/M	Aphthous like	Tonsil	8	Fever Malaise Sore throat Cough Hyposmia Ageusia Odynophagia	PCR	---
47	Brandiao *et al*.[30]	32/F	Aphthous like	Tongue	5	Dysgeusia Fever Cough Headache Anosmia	PCR	Dipyrone
48	Soares *et al*.[37]	42/M	Ulcer Blister Vesicle	Buccal mucosa Tongue Lip Hard palate	21	Fever Cough Dyspnea	PCR	CS Dipyrone
49	Dos Santos *et al*.[38]	67/M	White plaque multiple yellowish ulcer Geographic tongue Erythema Hypogeusia	Tongue Palate Tonsil	14	Fever Diarrhea Dyspnea	PCR	Mouthwash Fluconazole Nystatin AZT Cefriaxone HCH Meropenem T/S
50	Corchuelo and Ulloa[39]	40/F	Petechiae Whitish area Brown pigmentation	Tongue Lip gingiva	20	LAP of neck	IgG	Ibuprofen Vitamin D AZT Mouthwash Nystatin
51	Jimenez-Cauhe *et al*.[40]	66/F	Petechiae Macule	Palate	14-21	EM like	---	AZT Cefriaxone Cs HCH L/R
52	Kahraman and Çaskurlu[41]	51/M	Large erythematous petechiae Pustules	Hard palate Oropharynx Soft palate Ageusia	A few days	Fever Fatigue Dry cough Sore throat Anosmia	IgM	clarithromycin

PCR: Polymerase chain reaction, Ig: Immunoglobulin, EM: Erythema Multiforme, CRP: C-reactive protein, HSV: Herpes simplex virus, GI: Gastrointestinal

oral Fluconazole, topical or systemic corticosteroids, systemic antibiotics, systemic Acyclovir, artificial saliva, and photobiomodulation therapy.[7-41]

DISCUSSION

An increasing number of studies have reported the involvement of the oral lesions in patients with COVID-19. The occurrence of oral lesions is due to

1. Presence of ACE2 receptors in the oral cavity which leads to direct inoculation of the virus
2. Decreased host immunity
3. The effect of high dose steroids administered to the patient for managing general symptoms of COVID-19 infection.

ACE2 Expression in the Oral Cavity

The ACE2 receptor, which the SARS-CoV-2 binds to infect the host cells, is highly expressed in the epithelial cells of the tongue.[5] The interaction of SARS-CoV-2 with gustatory components and ACE2 receptors supports a direct effect in COVID-19 – related taste disorders.[42] A study was conducted to investigate the potential routes of 2019-nCov infection on the mucosa of oral cavity by Xu *et al*. and was found that ACE2 could be expressed in the oral cavity.[4] Among the different oral sites, ACE2 expression was higher in tongue than buccal and gingival tissues. These findings indicated that the mucosa of oral cavity may be a potentially high risk route of 2019-nCov infection.[43] The expression of ACE2 in minor salivary glands was found higher than that in lungs.[44] Thus, salivary glands could be potential target for

COVID-19 and the salivary gland could be a major source of the virus in saliva. In addition, before lung lesions appear SARS-CoV RNA can be detected in saliva. This suggests that COVID-19 transmitted by asymptomatic infection may originate from infected saliva.[45]

We aimed to investigate the pooled prevalence of oral manifestations in patients with COVID-19. This study presented several cases of SARS-Cov-2 infection, with oral manifestations developing during the infectious period of the disease. The loss of taste and smell also appeared concomitant with oral manifestations. The oral lesions were more severe and widespread in older patients with more severe COVID-19 infection. The common oral manifestations were as follows:

Taste Disorders

Taste disorders were the foremost common oral symptoms in patients with COVID-19. Chemosensory disorders are defined as diseases related to the sense of smell and/or taste. Taste disorders are classified as quantitative or qualitative disorders, of which hypogeusia may be a decreased sense of taste, ageusia is that the absence of a way of taste, and dysgeusia could be a qualitative distortion of gustatory sensation. It was the higher prevalence in Europe and North America than in Asia and a significant association with COVID-19– positive diagnosis, mild/moderate COVID-19 severity, and female patients.[46] In this meta-analysis, patients with COVID-19 presented a prevalence of 20% for overall taste disorders, 14% for dysgeusia, 4% for hypogeusia, and 2% for ageusia. These results confirm that taste disorders may be a significant and specific symptom of mild/moderate COVID-19 cases.

Aphthous-like Lesions

Aphthous-like lesions appeared as multiple shallow ulcers with erythematous halos and yellow-white pseudomembranous on the both keratinized and nonkeratinized mucosa. Oral lesions appeared concomitant with systemic symptoms. Latency time period was between 2 and 10 days. Lesions healed within 5–15 days. Regression of oral lesions was seen with improvement of systemic disease. One patient had positive history of recurrent aphthous stomatitis. The lesions were of two types, one resembling aphthous-like ulcers in young patients with mild cases of COVID-19 and another with more widespread patterns resembling herpes simplex virus (HSV)-1 necrotic ulcers and hemorrhagic crust in the more severe and immunosuppressed older individuals. An overall prevalence was 20% of aphthous like lesions with 10% of patients had painful lesions. There was necrosis observed in 10% of cases and there was no necrosis in 40% of cases.[30,22] 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.[30] Furthermore, the increased level of tumor necrosis factor (TNF)-α in COVID-19 patients can lead to chemotaxis of neutrophils to oral mucosa and development of aphthous like lesions. Stress and immunosuppression secondary to COVID-19 infection could be other possible reasons for appearance of such lesions in COVID-19 patients.[47]

Necrotizing periodontal disease (NPDs)

A 35-year-old female presented with fever, submandibular lymphadenopathy, halitosis, and oral lesions. Oral manifestation included necrosis of inter-papillary areas. Gingiva was painful, diffuse erythematous, and edematous. Provisional diagnosis was NPD due to bacterial coinfections (especially *Prevotella intermedia*) along with COVID 19. The lesions were healed after 1 week. The major etiological bacterial species for several acute periodontal lesions is considered as *P. intermedia* along with Fusobacterium and Treponema species. This constitutes a major proportion of the microbiota present in NPDs lesions. SARS-CoV-2 infection may predispose individuals to NPDs through bacterial co-infection caused by P. intermedia.[16]

Enanthema

Enanthema occurs in various types of viral diseases including dengue fever disease, Ebola virus disease, herpangina, human herpes virus infections, measles, and roseola infantum. Approximately 88% of enanthema are caused by infectious diseases, especially of viral etiology.[2] Petechiae, macules, papules, or vesicles may present with enanthema in the mouth. Erythematous-vesicular and petechial patterns were also present in association with viral infections. It is more frequent in adults.[40] This is consistent with the present study, in which 7 patients (13%) had petechiae as a main component of the enanthema. It occurred 2 days after the onset of COVID-19 symptoms, making association with the drug intake unlikely. The presence of enanthema is a strong clue that suggests a viral etiology rather than a drug reaction, especially when a petechial pattern is observed.[15,19] Different types of enanthema such as aphthous-like ulcers, Koplik's spots, Nagayama's spot, petechiae, papulovesicular, or maculopapular lesions, white or red patches, gingival and lip swelling have been reported with various viral infections. Both keratinized (hard palate, gingiva, and dorsum of tongue) and nonkeratinized (labial and buccal) mucosae can be involved.[2]

Ulcer and Erosion

Ulcerative or erosive lesions were one of the most commonly reported oral manifestations of COVID-19. These lesions appeared as painful lesions with irregular borders. These are mainly seen on the tongue, hard palate, and labial mucosa. Latency time period of lesions was 4–7 days. But in one case, lesions appeared 3 days before the onset of systemic

symptoms. Two studies performed laboratory investigations such as polymerase chain reaction (PCR) for HSV-1 and HSV-2 and showed negative herpes antibodies.[24] Lesions healed after 5–21 days. Different factors including drug eruption (to NSAID in one case), vasculitis, or thrombotic vasculopathy secondary to COVID-19 were suggested as etiology for development of ulcerative and erosive lesions.[48]

Vesiculobullous Lesions

Eight studies reported oral vesiculobullous lesions in patients with COVID-19. The clinical presentations varied greatly, ranging from blisters, to erythematous lesions, to petechial, and erythema multiform-like lesions.[48] Oral lesions were present on the tongue and buccal mucosa as vesicular eruptions and erosions. Prodromal symptoms were also present. Lesions regressed after 1 week.

EM-like lesions presented as cutaneous target lesions in the extremities. There were blisters, desquamative gingivitis, erythematous macules, erosions, and painful cheilitis with hemorrhagic crust in patients with EM like lesions. These lesions are observed in 4% of cases Lesions appeared within 7–24 days after the onset of systemic symptoms. These are healed after 2–4 week.[15]

Melkerson-Rosenthal Syndrome

A 51-year-old female patient presented with complaint of unilateral lip swelling, fissured tongue and right facial paralysis. She had past history of Melkersson-Rosenthal syndrome since 4 years that spontaneously cured with no relapse. Laboratory data demonstrated an increased level of C-reactive protein (CRP). Ground-glass opacities in both lungs was observed in computed tomography scan. The patient cured completely after treatment of COVID-19 disease.[36]

Melkersson–Rosenthal syndrome is characterized by orofacial edema, facial paralysis and fissured tongue. Orofacial edema is the most common component of the triad and the upper lip is usually involved. Peripheral facial paralysis is often unilateral. It is thought to develop due to granulomatous infiltration and edema of the nerve tissue.[49] In this case, orofacial edema was unilateral and located in the lower lip. Peripheral facial paralysis was present on the right side, and the classic triad of the syndrome was completed by the fissured tongue.[36]

Kawasaki-like Disease

Kawasaki-like disease in COVID-19 patients (Kawa-COVID) presented oral lesions including cheilitis, glossitis and erythematous and swollen tongue (red strawberry tongue). The latency period between appearance of systemic symptoms (respiratory or GI) and onset of oral or cutaneous symptoms was long. This could be due to a delayed hyperactivation response of the immune system and secondary release of acute inflammatory cytokines rather than direct effects of virus on the skin and oral mucosa.[7-9]

Post-inflammatory Pigmentation

A 40-year-old female reported with pigmentation in the attached and interpapillary gingiva. Increased levels of inflammatory cytokines (including interleukin-1 [IL-1] and TNF-α) and arachidonic acid metabolites (prostaglandins) secondary to production of stem cell factor and basic-fibroblast growth factor from keratinocytes of basal layer led to post-inflammatory pigmentations.[39]

Herpetiform Lesions

Herpetiform lesions presented as multiple painful, unilateral, round yellowish-gray ulcers with an erythematous rim on the both keratinized and nonkeratinized mucosae. These lesions preceded, coincided with, or followed systemic symptoms. Laboratory test showed increased level of CRP, IL-6, eosinopenia, positive PCR and serology for HSV. Stress and immunosuppression associated with COVID-19 were also suggested as etiology for secondary herpetic gingivostomatitis.[14,20,38]

Zosteriform Lesions

Zosteriform lesions appear as ulcers with symptoms such as painful, burning, and itching occurred mainly on lip and tongue. The lesion healed after 10 days.[34]

Atypical Sweet Syndrome

A 61-year-old female presented with chief complaint of fever, fatigue, arthralgia, myalgia, several erythematous nodules on the scalp, trunk and extremities, and minor aphthous ulcers on the hard palate and buccal mucosa. Reverse transcription PCR for COVID-19 was positive. Diffuse neutrophilic infiltration in the upper dermis and granulomatous infiltration in the lower dermis and subcutaneous area were present in skin biopsy. This was compatible with erythema nodosum-like Sweet syndrome.[35]

Red and White Lesions

Red and white lesions were observed on dorsum of tongue, gingiva, and palate of patients with confirmed or suspected COVID-19. Long-term antibiotic therapy, deterioration of general health, and decline in oral hygiene can be the cause of white or red patches or plaques. Stress and immunosuppression also can be the etiology.[38,39]

Limitations

The limitations of the present study are as follows:

i. No clarity is given about the severity of COVID disease
ii. Majority published data are only case reports and many were published as letter to the editor which led to incomplete reported outcomes.

CONCLUSION

Oral manifestations are common in patients with COVID-19 that may help clinicians identify suspected cases. However, many oral manifestations of this disease are underreported due to the lack of oral examination of patients with COVID-19 due to the lockdown and the carelessness of patients regarding these manifestations that might be less serious compared to the typical COVID-19 manifestations.[48] Hence, a thorough oral examination should be routinely performed for all suspected COVID-19 cases. Dental follow-up must be provided after the patient is dismissed from the hospital. Dentists should also be familiar with all potential orofacial manifestations of COVID-19. Further studies are recommended to document all COVID-19-associated orofacial manifestations using large cohorts of patients. Future studies will help to verify this hypothesis by correlating the symptomatic condition to the viral loads from the swabs or saliva.

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