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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

Oral manifestations of COVID-19 disease: A review article

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Abstract

Dysgeusia is the first recognized oral symptom of novel coronavirus disease (COVID-19). In this review article, we described oral lesions of COVID-19 patients. We searched PubMed library and Google Scholar for published literature since December 2019 until September 2020. Finally, we selected 35 articles including case reports, case series and letters to editor. Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), and palate (22%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. Oral lesions were symptomatic in 68% of the cases. Oral lesions were nearly equal in both genders (49% female and 51% male). Patients with older age and higher severity of COVID-19 disease had more widespread and sever oral lesions. Lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyper-inflammatory response secondary to COVID-19 are the most important predisposing factors for onset of oral lesions in COVID-19 patients.

KEYWORDS
aphthous, COVID-19, gingivostomatitis, manifestation, oral

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-chain RNA virus that is the cause of novel coronavirus disease known as COVID-19. The most common clinical symptoms are fever, headache, sore throat, dyspnea, dry cough, abdominal pain, vomiting, and diarrhea. Angiotensin converting enzyme 2 (ACE 2) receptor is a known receptor for SARS-CoV-2 that is found in the lung, liver, kidney, gastrointestinal (GI) and even on the epithelial surfaces of sweet glands and on the endothelia of dermal papillary vessels. Todate, various cutaneous manifestations of COVID-19 disease have been described including varicelliform lesions, pseudochilblain, erythema multiforme (EM)-liker lesions, urticaria form, maculopapular, petechiae and purpura, mottling, and livedo reticularis-like lesions.[1,2]

At the beginning of COVID-19 pandemic, it was assumed that lack of oral involvement is a differentiating feature of COVID-19 exanthema relative to other viral exanthemas. Recently, SARS-CoV-2 has been detected from saliva of the patients and it has been demonstrated that reverse transcriptase-polymerase chain reaction (RT-PCR) from saliva can even be a more sensitive test in comparison with nasopharyngeal test. Furthermore, ACE2 has been found in oral mucosa, especially with more density on dorsum of tongue and salivary glands relative to buccal mucosa or palates. To date, there is only one systematic review that described oral manifestations of COVID-19 disease; however, it mostly focused on impairment of taste. Dysgeusia is the first recognized oral symptom of COVID-19 reported in 38% of patients, mostly in North Americans and Europeans, females, and patients with mild-moderate disease severity.[1] In this review article, we described oral lesions of COVID-19 patients.

TABLE 1 Clinical and laboratory characteristics of patients with oral manifestations

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Verdoni[28]	7/5 (2/9-16)Y	M = 7 F = 3	–	MP Acral swelling	NA	–	Lip Oral cavity (80%)	–	Fever Diarrhea Conjunctivitis Meningeal sign lymphadenopathy		20% + (PCR) 80% (IgG) 30% (IgM)	Kawasaki-like	–	–
Jones[29]	6 M	F	–	MP Acral swelling	Cracked lip Prominent papilla in tongue	–	Lip Tongue	–	Fever Conjunctivitis Tachypnea	2	+ (PCR)	Kawasaki-like	IVIG ASA	Increased levels of CRP, ESR Hypoalbuminemia
Pouletty[30]	10 (4/7-12/5)Y	M = 8 F = 8	Over weight Asthma	Rash	Cracked lip (87%)	–	Lip	–	Fever Respiratory & GI symptom Anosmia	–	69% + (PCR)	Kawasaki-like	IVIG CS ANTI IL1, IL6 HCH	Increased levels of cardiac markers Increased levels of CRP, ESR Lymphocytopenia
Singh[19]	44Y	M	DM HTN	Non blanch able erythema Necrosis	Extensive mucosal damage	–	Lip Tongue	–	Malaise Dyspnea	4		Vascular inflammation Ischemic reperfusion injury		
Chiotos[31]	5Y	F	–		Fissured lip	–	Lip	–	Fever Diarrhea Conjunctivitis	–		Kawasaki-like	IVIG	Thrombocytopenia Increased levels of cardiac marker
Chiotos[31]	9Y	F	–	–	Fissured lip Straw berry tongue	–	Lip Tongue	–	Fever Diarrhea Conjunctivitis	–	+ (PCR)	Kawasaki-like	IVIG ASA CS	Increased levels of CRP, ESR
Chiotos[31]	12Y	M	–	–	Fissured lip	–	Lip	–	Fever Abdominal pain Diarrhea	–	(–) (PCR)	Kawasaki like	IVIG Milrinone	Increased levels of Cardiac marker Increased levels of CRP, ESR
Chiu[32]	10Y	M	–	–	Cracked lip Erythema	–	Lip Oropharynx	–	Fever Cough Diarrhea Conjunctivitis	–	+ (PCR)	Kawasaki-like	Dopamine	Leukocytosis Lymphocytopenia Increased levels of CRP, ESR, D-dimer, Procalcitonin Increased levels of Cardiac markers
Mazzotta[26]	9Y	M	–	Urticaria Angioedema Acral edema	Glossitis Cheilitis	Painful	–	–	Fever Cough Diarrhea Conjunctivitis	28-84	+ (Ig G)	Kawasaki-like	CS	–

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Indu[13]	NS	M	–	–	Ulcer	Burning Itching Painful	Lip Tongue	10	Fever	–4	+ (PCR)	Zosteriform	–	–
Taşkın[25]	61Y	F	–	Nodules	Minor aphthous ulcer	–	Hard palate Buccal	–	Fever Fatigue Myalgia Arthralgia	–	+ (PCR)	Atypical Sweet syndrome	AZT HCH Oseltamivir Tocilizomab Favipiravir	Increased levels of CRP, ESR, D-dimer Leukocytosis
Taşlıdere[24]	51Y	F	–	–	Swollen lip Fissured tongue	–	Lip Tongue	–	Malaise Unilateral Facial paralysis Facial edema	Coincident	–	MRS	HCH AZT CS	Increased levels of CRP Negative Serology for HSV, CMV,EBV, coxsackie Ground glass opacity in CT scan
Brandão[7]	28Y	M	–	–	Aphthous-like Ageusia	–	Lip Tongue	6	Fever Cough Headache Myalgia Chills Anosmia	8	+ (PCR)	–	Mouthwash	–
Brandão[7]	29Y	M	–	–	Aphthous-like Ageusia	Painful	Tongue	5	Cough Dyspnea Fever Malaise Headache Anosmia	8	+ (PCR)	–	Ipratropium bromide Fenoterol hydrochloride	–
Brandão[7]	35Y	M	–	–	Aphthous-like	–	Tonsil	8	Fever Malaise Sore throat Cough Hyposmia Ageusia Odynophagia	6	+ (PCR)	–	–	–
Brandão[7]	32Y	F	–	–	Aphthous -like	–	Tongue	5	Dysgeusia Fever Cough Headache Anosmia	10	+ (PCR)	–	Dipyrone	–

(Continues)

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Brandão[7]	72Y	M	HTN DM	–	Aphthous-like Necrosis Hemorrhagic ulcer	painful	Lip	7	Fever Dyspnea	5	+ (PCR)	–	P/T AZT Ceftriaxone Acyclovir PBM	Increased levels of CRP Lymphocytopenia Positive PCR for HSV
Brandão[7]	83Y	F	HTN COPD Obesity Parkinson Pancreatitis	–	Aphthous-like Petechiae Necrosis	painful	Tongue Hard palate	5	–	2	+ (PCR)	–	Ceftriaxone PBMT P/T	Negative PCR for HSV Lymphocytopenia
Brandão[7]	71Y	F	HTN DM CRF Obesity	–	Aphthous-like Hemorrhagic necrosis Ulcer	painful	Tongue Lip	15	Fever Cough Dyspnea	4	+ (PCR	–	AZT Ceftriaxone Acyclovir PBMT	Positive PCR for HSV
Brandão[7]	81Y	M	HTN COPD	–	Aphthous-like Necrosis Hemorrhagic ulcer	painful	Lip Tongue	11	Dry Cough Dyspnea Fever Chills Dysgeusia	5	+ (PCR)	–	AZT Ceftriaxone Acyclovir PBMT	Increased levels of CRP Ground glass opacity in CT scan Positive PCR for HSV
Malih[8]	38Y	M	–	MP	Erythema Aphthous-like	Painful	tonsil	–	Fever Fatigue Myalgia Loss of taste and smell	3	+ (PCR)	–	Acetaminophen	–
Labé[22]	3Y	M	–	Exanthema Palmar edema	Cheilitis Glossitis Stomatitis	–	Lip Tongue Oral cavity	–	Fever Asthenia Cervical LAP	–	–	Kawasaki-like	IVIG	Increased levels of CRP Leukocytosis Ground glass opacity in CT scan
Labé[22]	6Y	M	–	Target lesions	Erosion Cheilitis Hemorrhagic crust	painful	Lip Gingiva	21	Loss of appetite	7	+ (PCR)	EM like	–	Negative serology for mycoplasma Negative PCR for HSV
Aghazadeh[9]	9Y	F	–	Papule Plaque	Vesicles Erosions	–	Lip Tongue Buccal	7	Fever Weakness Loss of appetite Abdominal pain Diarrhea	Coincident	+ (PCR)	Herpetiform	Acetaminophen	Bilateral ground glass opacity

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Kämmerer[10]	46Y	M	HLP CAD	–	Multiple ulceration covered by yellow gray membrane	Painful	Oral cavity Gingiva	–	Fever Fatigue Dry cough Respiratory distress LAP submandibular	5 days after intubation	+ (PCR)	Secondary herpetic Gingivostomatitis	AZT Meropenem Acyclovir	Increased levels of CRP, IL6, Eosinopenia Positive PCR for HSV Positive serology for HSV(IgM) Bilateral ground glass opacity in CT scan
Cruz Tapia[23]	42Y	M	_	_	Macules	Burning	Hard palate	7	Fever Malaise Dysgeusia Headache	14	+ (PCR)	Mucositis due to vasculitis and thrombosis	Acetaminophen Mouthwash CS	_
Cruz Tapia[23]	55Y	F	–	–	Tongue enlargement Purple blister	–	Tongue	5	Fever Headache Nasal congestion	2	+ (PCR)	Angina bullosa-like	Acetaminophen	–
Cruz Tapia[23]	51Y	F	HTN	_	Vascular-like purple macule nonbleeding Purple plaque	–	Palate	–	Fever Malaise Dysgeusia Arthralgia	–	+ (PCR)	Vascular disorder	CS AZT NSAID	–
Cruz Tapia[23]	41Y	F	_	_	Erythematous blister	–	Hard palate	–	Fever Malaise *Dysgeusia* Hyposmia	–	+ (PCR)	Angina-bullosa-like	Acetaminophen Fexofenadine	–
Díaz Rodríguez[6]	78Y	F	–	–	Dry mouth Atrophy of surface of tongue White & red patches Fissured tongue		Tongue Hard Palate Soft palate Lip	15	–	–	+ (PCR)	Pseudomembranous candidiasis Angular cheilitis due to Stress Immunosuppression	Artificial saliva Nystatin Neomycin CS	–
Díaz Rodríguez[6]	53Y	M	–	–	Angular cheilitis	Burning	Lip	10	Dysgeusia Anosmia	Few days after discharge	+ (PCR)	Cheilitis due to stress and immunosuppression	Nystatin CS Neomycin, Mouthwash	–
Díaz Rodríguez[6]	43Y	F	–	–	Multiple ulcer covered by yellow-gray membrane Lingual depapillation	Burning	Tongue	10	Fever Malaise Dysgeusia Anosmia Diarrhea Pneumonia	14	+ (PCR)	Aphthous-like due to stress and immunosuppression	Mouthwash CS	–

(Continues)

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Chérif[27]	35Y	F	–	Macule	Chapped lips Ulcer *Hypogeusia*	–	Tongue Lip	10	Fever Myalgia Dyspnea Dry cough Vomiting Diarrhea	–	+ (PCR)	Kawasaki-like	HCH AZT Cefuroxime	Thrombocytopenia Anemia Neutrophilia Lymphopenia Increased levels of liver and cardiac markers Increased levels of CRP,LDH, ferritin
Ansari[18]	75Y	M	HTN	–	Irregular ulcer in erythematous background	Painful	Tongue (anterior)	7	Hypoxia	7	+ (PCR)	Mucosal ulcer due to COVID-19	AZT, Mouthwash	Negative Serology for HSV 1-2
Ansari[18]	56Y	F	DM	–	Irregular ulcer in erythematous background	Painful	Hard palate	7	Fever Dyspnea	4	+ (PCR)	Mucosal ulcer due to COVID-19	Remidisivir AZT	Negative Serology for HSV 1–2
Biadsee[3]	36.25Y	NS	HTN DM Hypothyroidism Asthma	–	Plaque bleeding Swelling Xerostomia Dysgeusia	–	Tongue Palate Gingiva		Fever Cough Myalgia Sore throat Anosmia GI symptoms	–	+ (PCR)	–	–	–
Olisova[11]	12Y	F	–	Purpura Macule	Swollen, Irritated Pronounced lingual papilla	–	Tongue	3	Fever Fatigue Headache	3	+ (PCR)	–	Paracetamol	Increased levels of ESR CRP
Tomo[36]	37Y	F	–	–	Erythema Depapillation of tongue	Painful	Tongue (border)	14	Fever Asthenia Dysgeusia Anosmia	9	+ (PCR)	Mucositis due to hypersensitivity to SARS-CoV-2	CS Dipyrone Mouthwash	–
Ciccarese[17]	19Y	F	–	Macules Papules Petechiae	Erosion Ulcer Hemorrhagic crust Petechial	–	Lip Palatal Gingival Oropharynx	5	Fever Fatigue Hyposmia Sore throat	7	+ (PCR)	Thrombocytopenia due to COVIDS-19 and cefixime	IVIG CS	Thrombocytopenia Leukocytosis Increased levels of liver markers and LDH
Sakaida[16]	52Y	F	–	MP Petechiae	Erosion	–	Lip Buccal	–	Fever Dyspnea Dry cough	–3	+ (PCR)	Drug eruption	NSAID Clarithromycin SAM Levofloxacin Cs	Leukocytosis Lymphopenia Neutrophilia Increased level of CRP

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Dominguez-Santas[37]	19Y	M	–	–	Minor aphthous	–	Lip	–	Fever Headach Anosmia Malaise dyspnea	0	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Dominguez-Santas[37]	37Y	M	–	–	Minor aphthous	–	Tongue	–	–	5	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Dominguez-Santas[37]	33Y	M	–	–	Minor aphthous	–	Mucogingivl junction	–	Pneumonia Fever Malaise	3	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Dominguez-Santas[37]	43Y	F	–	–	Minor aphthous	–	Buccal	–	Bilateral pneumonia Fever Malaise	4	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Putra[5]	29Y	M	_	Papule	Aphthous Stomatitis	–	–	–	Fever Myalgia sore throat Dry cough	6	+ (PCR)	Enanthema due to COVID-19	Paracetamol AZT HCH Oseltamivir Vitamin C Vitamin D	Increase level of CRP
Martín Carreras-Presas[12]	65Y	F	HTN Obesity	Rash	Desquamative gingivitis	Painful	Tongue Gingiva	28	Fever Diarrhea	25	+ (serology)	EM-like	Antibiotic CS HCH HA L/R	–

(Continues)

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Martín Carreras-Presas[12]	58Y	M	DM HTN	–	Unilateral multiple small ulcers	Painful	Palate	7	–	–	–	Herpetiform	Mouthwash	–
Martín Carreras-Presas[12]	56Y	M	–	–	Dysgeusia, Herpetiform Stomatitis	Painful	Hard Palate	10	Fever Asthenia LAP	2	NP	Herpetiform	Val acyclovir Mouthwash HA	–
Jimenez-Cauhe[21]	60Y	M = 2 F = 4	–	EM-like	Macule Petechiae	–	Palate	–	–	19		Enanthema due to COVID-19	AZT HCH L/R	
Jimenez-Cauhe[21]	40Y			Purpura EM-like	Petechiae Macule Petechiae	–	Palate Palate	–	–	2 24	–	Enanthema due to COVID-19 Enanthema due to COVID-19	L/R HCH AZT T CS L/R HCH AZT Tocilizomab CS	Thrombocytopenia High D-dimer High D-dimer
Jimenez-Cauhe[21]	50Y													
Jimenez-Cauhe[21]	60Y		–	EM-like	Macule Petechiae	–	Palate	–	–	19	+ (PCR)	Enanthema due to COVID-19	L/R HCH AZT	High D-dimer
Jimenez-Cauhe[21]	60Y		–	Papule Vesicle	Petechiae	–	Palate	–	–	–2	+ (PCR)	Enanthema due to COVID-19	L/R HCH AZT	High D-dimer
Jimenez-Cauhe[21]	40Y		–	purpura	Macule	–	Palate	–	–	12	+ (PCR)	Enanthema due to COVID-19	L/R HCH	Thrombocytopenia High D-dimer
Patel[33]	35Y	F	_	_	Bleeding Halitosis Generalized edematous erythematous gingiva Necrosis	Painful	Gingiva	5	Fever LAP submandibular	3	NP	Bacterial co-infection	Metronidazole Mouthwash	_
Chaux-Bodard[14]	45 Y	F	-	Patch	Ulcer	Painful	Tongue (dorsal)	10	Asthenia	–	+ (PCR)	Vasculitis	–	–

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Soares[15]	42Y	M	DM HTN	Petechiae Vesicle Blister	Ulcer Macules	Painful	Buccal Tongue Lip Hard Palate	21	Fever Cough Dyspnea	–	+ (PCR)	Thrombotic vasculopathy due to SARS –CoV-2	CS Dipyrone	IHC: negative for other viral and trepnema palladium
dos Santos[4]	67Y	M	CAD HTN PCK RT	–	White plaque Multiple yellowish ulcer Geographic tongue Erythema Hypogeusia	–	Tongue Palate Tonsil	14	Fever Diarrhea Dyspnea	24	+ (PCR)	Herpetiform lesions secondary to determination of systemic health and treatment	Mouthwash Fluconazole Nystatin AZT Ceftriaxone HCH Meropenem T/S	Positive Culture for *+Saccharomyces cerevisiae*
Corchuelo[20]	40Y	F	–	–	Petechiae Whitish area Brown pigmentation	Painful	Tongue Lip Gingiva	20	LAP of neck	–	+ (IgG)	Candidiasis Thrombocytopenia due to ibuprofen PIH	Ibuprofen Vitamin D AZT Mouthwash Nystatin	–
Jimenez-Cauhe[35]	66.7(58-77)Y	F = 3	_	EM-like	Petechiae Macule	–	Palate	14-21	_	19.5 (16-24)	_	EM-Like	AZT Ceftriaxone Cs HCH L/R	Increase levels of CRP High D-dimer Lymphocytopenia Negative serology for syphilis, M. Pneumonia and other viral
Cebeci Kahraman[34]	51Y	M	_	_	Large erythematous Petechiae Pustules	Painful	Hard palate Oropharynx Soft palate Ageusia	A few days	Fever Fatigue Dry cough Sore throat Anosmia	10	+ (IgM)	Enanthema due to COVID-19	Clarithromycin	–

Abbreviations: AZT, azithromycin; CAD, chronic arterial disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM, diabetes mellitus; HCH, hydroxychloroquine; HLP, hyperlipidemia; HTN, hypertension; L/EX, lower extremity; M, month; MP, maculopapular; MRS, Melkersson-Rosenthal syndrome; P/T, piperacillin/tazobactam; PCK, poly cystic kidney; PIH, postinflammatory hyperpigmentation; RT, renal transplantation; SAM, ampicillin sulbactam; T/S, trimethoprim/sulfamethoxazole; Y, year.

2 | METHODS

We searched PubMed library and Google Scholar for published literature using keywords "COVID-19" or "SARS-CoV-2" or "coronavirus disease 2019" AND "oral" OR "buccal mucosa" in the abstract or title since December 2019 until September 2020. We also searched related articles in the reference lists of the found articles. Finally, we selected 35 articles after deletion of non-English literature and opinion articles.

3 | RESULTS

Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. Oral lesions were symptomatic (painful, burning sensation, or pruritus) in 68% of the cases. Oral lesions were nearly equal in both genders (49% female, 51% male). Latency time between appearance of systemic symptoms and oral lesions was between 4 days before up to 12 weeks after onset of systemic symptoms. In three cases, oral lesions preceded systemic symptoms and in four cases oral and systemic symptoms appeared simultaneously. The longest latency period belonged to Kawasaki-like lesions. Oral lesions healed between 3 and 28 days after appearance. Different types of therapies including chlorhexine mouthwash, nystatin, oral fluconazole, topical or systemic corticosteroids, systemic antibiotics, systemic acyclovir, artificial saliva, and photobiomodulation therapy (PBMT) were prescribed for oral lesions depends on the etiology[3-37]. The results of literature are summarized in Table 1.

4 | DISCUSSION

Enanthema can develop in various types of viral diseases including dengue fever disease, Ebola virus disease, herpangina, human herpes virus (HHV) infections, measles, and roseola infantum. Infectious diseases, especially of viral etiology, constitute approximately 88% of causes of enanthema. 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.[38] Biadsee and colleagues demonstrated that 7% of the patients with RT-PCR positive test had plaque-like changes on the dorsum of tongue. Also, swelling of oral cavity (including palatal, lingual, and gum) was reported by 8% of the patients. Furthermore, appearance of oral lesions was simultaneously found with loss of taste and smell in the patients and more severe and disseminated oral lesions were reported in older patients and in severe COVID-19.[3] In another study, enanthema was reported in 29% of cases with confirmed COVID-19 and cutaneous exanthema.[35]

4.1 | Aphthous-like lesions

Aphthous-like lesions appeared as multiple shallow ulcers with erythematous halos and yellow-white pseudomemberanes on the both keratinized and nonkeratinized mucosae. In one patient, oral lesions appeared simultaneously with systemic symptoms and in other patients, latency time was between 2 and 10 days. One patient had positive history of recurrent aphthous stomatitis (RAS) and two patients had positive PCR for herpes simplex virus (HSV).[4-8,37] Aphthous-like lesions without necrosis were observed in younger patients with mild infection, whilst aphthous-like lesions with necrosis and hemorrhagic crusts were observed more frequently in older patients with immunosuppression and severe infection. Lesions healed after 5 to 15 days.[7] Regression of oral lesions was in parallel association with improvement of systemic disease. 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.[4]

4.2 | Herpetiform/zosteriform lesions

Herpetiform lesions presented as multiple painful, unilateral, round yellowish-gray ulcers with an erythematous rim on the both keratinized and nonkeratinized mucosae. Manifestations of these lesions preceded, coincided with, or followed systemic symptoms. In one case, geographic tongue appeared after recovery of herpetiform lesions. Stress and immunosuppression associated with COVID-19 was the suggested cause for appearance of secondary herpetic gingivostomatitis.[4,9,10,12,13]

4.3 | Ulcer and erosion

Ulcerative or erosive lesions appeared as painful lesions with irregular borders on the tongue, hard palate, and labial mucosa. Lesions appeared after a latency time of 4 to 7 days and in one case, lesions appeared 3 days before the onset of systemic symptoms and recovered after 5 to 21 days. In two cases, PCR for HSV-1 and HSV-2 was performed and was negative. Different factors including drug eruption (to NSAID in one case), vasculitis, or thrombotic vasculopathy secondary to COVID-19 were suggested as causes for development of ulcerative and erosive lesions.[14-19]

4.4 | White/red plaques

White and red patches or plaques were reported on dorsum of tongue, gingiva, and palate of patients with confirmed or suspected COVID-19. Candidiasis due to long-term antibiotic therapy, deterioration of general status, and decline in oral hygiene can be the cause of white or red patches or plaques.[4,6,20]

4.5 | EM-like lesions

EM-like lesions appeared as blisters, desquamative gingivitis, erythematous macules, erosions, and painful cheilitis with hemorrhagic crust in patients with cutaneous target lesions in the extremities. Lesions appeared between 7 and 24 days after the onset of systemic symptoms and recovered after 2 to 4 weeks.[12,21,22]

4.6 | Angina bullosa-like lesions

Angina bullosa-like lesions presented as asymptomatic erythematous-purple blisters without spontaneous bleeding on the tongue and hard palate in two confirmed cases of COVID-19.[23]

4.7 | Melkerson-Rosenthal syndrome

There was a report of a 51-year-old woman presenting with complaint of malaise and unilateral lip swelling, fissured tongue and right facial paralysis. She had past history of Melkersson-Rosenthal syndrome since 4 years ago that was spontaneously cured with no relapse. Laboratory data demonstrated an increased level of CRP and computed tomography (CT) scan showed ground-glass opacities in both lungs. The patient cured completely after treatment of COVID-19 disease.[24]

4.8 | Atypical sweet syndrome

There was a report of 61-year-old female who presented complaining 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. RT-PCR for COVID-19 was positive. Skin biopsy showed diffuse neutrophilic infiltration in the upper dermis with granulomatous infiltration in the lower dermis and subcutaneous area that was compatible with erythema nodosum-like Sweet syndrome.[25]

4.9 | Kawasaki-like disease

Oral lesions including cheilitis, glossitis, and erythematous and swollen tongue (red strawberry tongue) appeared in COVID-19 patients with Kawasaki-like disease (Kawa-COVID). The long duration of latency between appearance of systemic symptoms (respiratory or gastrointestinal) and onset of oral or cutaneous symptoms 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.[22,26-32]

4.10 | Necrotizing periodontal disease

There was a report of a 35-year-old female suspicious for COVID-19 who presented with fever, submandibular lymphadenopathy, halitosis, and oral lesions. Oral lesions included a painful, diffuse erythematous and edematous gingiva with necrosis of inter-papillary areas. The suggested diagnosis was necrotizing periodontal disease due to bacterial coinfections (especially prevotella intermedia) along with COVID-19. The lesions recovered after 5 days.[33]

4.11 | Vesicles and pustules

We found a report of a 9-year-old female presenting with fever, weakness, abdominal pain, and diarrhea that coincided with oral and acral erythematous papular exanthema. Oral lesions included vesicular eruptions and erosions on the tongue and buccal mucosa. PCR test for COVID-19 was positive. Lesions cured after 1 week.[9]

There was also another report on a 51-year-old male presented with fever, fatigue, dry cough, dysgeusia, anosmia, and a positive serology for COVID-19. After 10 days, widespread erythema appeared on hard palate and oropharynx with petechiae and pustules on soft palate border. The suggested diagnosis was enanthema due to COVID-19 and the lesions cured after a few days.[34]

4.12 | Petechiae

In a few studies, Petechiae were reported on the lower lip, palate, and oropharynx mucosa. Latency time for patients with petechiae was shorter compared to the patients with both petechiae and macular lesions. Thrombocytopenia due to COVID-19 infection or the prescribed drug were suggested as possible causes of petechiae.[20,21,34,35]

4.13 | Nonspecific lesions (mucositis)

Erythematous-violaceous macules, patches, papules and plaques on the tongue, lip mucosa, hard palate, and oropharynx were reported in several studies. Thrombotic vasculopathy, vasculitis, hypersensitivity associated to COVID-19 could be the causes of mucositis in patients with COVID-19. Mucosal hypersensitivity secondary to COVID-19, thrombotic vasculopathy, and vasculitis might be the possible causes of mucositis in COVID-19.[8,15,21,23,34-36]

4.14 | Postinflammatory pigmentation

There was one report of pigmentation in the attached and interpapillary gingiva in a 40-year-old female. Increased levels of inflammatory cytokines (including interleukin-1 [IL-1], tumor necrosis factor [TNF]-α) and arachidonic acid metabolites (prostaglandins) secondary to production of stem cell factor (SCF) and basic-fibroblast growth factor (bFGF) from keratinocytes of basal layer lead to postinflammatory pigmentations.[20]

5 | CONCLUSION

Aphthous-like lesions, herpetiform lesions, candidiasis, and oral lesions of Kawasaki-like disease are the most common oral manifestations of COVID-19 disease. An older age and severity of COVID-19 disease seem to be the most common factors that predict severity of oral lesions in these patients. Lack of oral hygiene, opportunistic infections, stress, underling diseases (diabetes mellitus, immunosuppression), trauma (secondary to intubation), vascular compromise, and hyper-inflammatory response secondary to COVID-19 might be are the most important predisposing factors for the development of oral lesions in COVID-19 patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Behzad Iranmanesh, Maryam Khalili, Rezvan Amiri, and Mahin Aflatoonian contributed to the study conception and design. Material preparation, data collection, were performed by Behzad Iranmanesh, Maryam Khalili, Rezvan Amiri, Hamed Zartab, and Mahin Aflatoonian The first draft of the manuscript was written by Behzad Iranmanesh and Mahin Aflatoonian and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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