



SARS-COV2 Associated Oral Lesions- A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: COVID-19 disease is caused by SARS-CoV-2 virus and it was declared pandemic by World Health Organization (WHO) on March 11,2020. The coronavirus infection has an affinity for ACE2 receptors and by attaching to them, the virus enters the host cells. Along with many body organs like lungs, kidney, liver, upper respiratory tract, nervous system, skeletal muscles, ACE2 concentration is also found in abundance in epithelial cells of tongue and salivary glands.

Materials and Methods: Recent studies, researches, documents and case reports published in the world medical literature in the year 2020-2021 were searched and documented in our study. The search engines used were PUBMED, google scholar, WEB OF SCIENCE etc.

Results: Dysgeusia, xerostomia, sore throat, aphthous and herpetiform ulcers, candidiasis, enanthema, Kawasaki like lesions were the most common among various oral manifestations. Others includes plaque like changes, gingival inflammation, necrotizing gingivitis, erythema - multiforme, angina-bullosa like lesions, Melkersson-Rosenthal Syndrome, Oral mucormycosis etc. The sites of infection mainly include tongue, gingiva, hard and soft palate, buccal and labial mucosa etc.

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Conclusion: The etiopathogenesis of such lesions cannot be directly correlated with COVID-19 and factors such as stress, immunosuppression, co-infections, secondary lesions, opportunistic infections, systemic diseases, poor oral hygiene etc. must be considered. Management of stress is an important factor. In this review article various oral lesions are discussed in COVID-19 infection states in detail. The importance of earliest diagnosis of oral lesions is to be kept in mind to prevent further complications.

Keywords: COVID-19; SARS-CoV-2 virus; ACE2 receptors; oral lesions; oral manifestations.

1. INTRODUCTION

Coronavirus disease 19(COVID-19) is caused by newly discovered novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2). The WHO declared the disease as global pandemic last year on March 11,2020 [1] and potentially a life-threatening respiratory disease. It was identified in December 2019 after its outbreak in China (Wuhan) [1,2].

It presents as a lot of symptoms among whom fever, sneezing, dry cough, shortness of breath, taste alteration, anosmia, fatigue are characteristic [3,4]. It may worsen to fulminant pneumonia and severe respiratory distress if not treated early in many cases [5]. Mostly present as mild, some are moderate and severe and a little percentage as critically ill, even some are asymptomatic also [4,6]. Surprisingly, the features are different for every other person and the course of the disease depends majorly on the immunity of the patient affected. It can spread from an infected patient via droplets mainly through oral, nasal and eye mucous secretions [2]. It has an incubation period of 1 to 14 days, mostly between (3-7) days [2].

RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) test from oropharynx is considered an effective method for detection of SARS-CoV-2 from human saliva and its sensitivity is higher than nasopharyngeal test [7].

There is a higher incidence of SARS-CoV-2 virus's nucleic acid in oropharyngeal swabs of infected patients [1]. The coronavirus enters the cells of human through receptor angiotensin-converting enzyme 2(ACE2) indicated by single-cell RNA-seq data analysis [1,6]. ACE2 is found in cell membranes of lungs, kidney, liver, upper respiratory tract, nervous system, skeletal muscles etc. It has been found that oral cavity presents ACE2 expression particularly in epithelial cells of tongue and salivary glands, and naturally it becomes prone or becomes the target cells for SARS-CoV-2 infection [1,3,6].

The coronavirus disease results in various oral/oropharyngeal manifestations which may be either a direct effect of the disease or may be secondary to any underlying disease, immune status following COVID-19 infection, or any drugs used for treatment of the same [6].

The most common oropharyngeal features seen are dysgeusia, sore throat and xerostomia [7,8]. Dysgeusia, ageusia and anosmia are inflammation induced symptoms of COVID-19 [9]. Among others, aphthous ulcers, herpetiform ulcers, candidiasis, cheilitis, white plaque, blisters, petechiae, enanthema, geographic tongue, fissured tongue, desquamative gingivitis, vesiculobullous lesions, mucormycosis, angina-bullosa like lesions, erythema-multiforme like lesions, Kawasaki-like lesions (in children with Kawasaki disease) have also been reported [4,6]. Although whether these symptoms are a direct manifestation of SARS-CoV-2 virus or they carry a different etiopathogenesis is yet to be known [4,5].

The most common intraoral sites of infection are the various parts of tongue, gingiva, hard and soft palate, buccal and labial mucosa, oropharynx, tonsillar pillar etc. and each one has different presentation.

Patients suffering from coronavirus disease suffer from stress and therefore oral hygiene maintenance is sometimes neglected. Many bacteria, virus, fungus may be found alongside normal commensals like Streptococci, Fusobacterium, Treponema, Prevotella intermedia, Candida species etc. [10] Therefore, bacterial co-infection, stress, lack of oral hygiene, immunosuppression, co-morbidities must also be considered.

Oral lesion presentation due to the virus is a broad classification and must not be neglected [7]. More clinical evidence and research are needed to establish the co-relation between SARS-CoV-2 and intraoral manifestations [3].

Table 1. Shows description of oral lesions in a broader way with age, gender, site, etiology, treatment, reported diagnosis, histopathology etc. from each of the articles with author/journal name

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Oral Diseases , 2020	Milagros Díaz Rodríguez ²⁰	43	F	yes	Apthous like lesions ,burning sensation, tongue depapillation	Tongue	Last 2 weeks	Immunosuppression, Stress	Mouthrinse (Triamcinolone acetonide 0.05%)	Apthous-like lesions.	-
Oral Diseases , 2020	Milagros Díaz Rodríguez ²⁰	53	M	yes	Burning sensation ,unilateral commissural fissures, dysgeusia	Lip	After hospital discharge	Immunosuppression, Stress	Ointment (Neomycin, Nystatin, Triamcinolone acetonide)	Commissural Chelitis	-
Oral Diseases , 2020	Milagros Díaz Rodríguez ²⁰	78	F	yes	Intense dry mouth, lesions	Tongue, Hard palate, Soft palate, Lip	Since hospitalization	Immunosuppression, Stress	Solutions and gels, Nystatin rinse, Neomycin, Triamcinolone acetonide	Pseudomembranous Candidiasis and Angular Chelitis	-
Oral Diseases , 2020	Carmen Martín Carreras-Presas	56	M	Suspected	Pain in palate, sore throat Multiple orange coloured lesions with	Palate	After sending home	Emotional distress	Valacyclovir 500mg, topical antiseptics	Herpetic recurrent stomatitis	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Oral Diseases , 2020	Carmen Martín Carreras-Presas ¹⁶	58	M	Suspected	an erythematous halo Pain and multiple small ,pinpoint, yellowish ulcers unilaterally with an erythematous halo	Palate	-	Underlying disease, Emotional distress	Topical antiseptic mouthwash	Herpetic infection?	-
Oral Diseases , 2020	Carmen Martín Carreras-Presas ¹⁶	65	F	Yes	Pain in tongue, blisters(pruritic than painful), bulla, desquamative gingivitis	Tongue, Internal lip mucosa	After 1 month	Underling disease, Emotional distress	Hyaluronic acid, chlorhexidine mouthwash, prednisolone 30mg	Erythema multiforme	-
Journal of Dental Research, 2020	Juliana Amorim dos Santos ⁵	67	M	Yes	White plaque associated with multiple pinpoint yellowish ulcers, Nodule(1cm), atrophic areas surrounded by an elevated	Tongue, Lower lip	24 th day of hospitalization	Secondary lesions due to deterioration of systemic health and treatments due to Covid-19	Fluconazole, oral nystatin, chlorhexidinedigluconate (0.12%), alcohol free mouthrinse,	Herpetic recurrent oral lesions associated with Candidiasis ,Fibroma, Geographic tongue	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Otolaryngology– Head and Neck Surgery, 2020	Ameen Biadse ^{e2}	36.25	-	Yes	yellow-white halo Dysgeusia, xerostomia, sore-throat, plaque like changes, swelling, oral bleeding, facial pain, masticatory muscle pain	Tongue, palate, gingiva	-	-	hydrogen peroxide	-	-
Oral Diseases , 2020	Saygo Tomo ³⁷	37	F	Yes	Dysgeusia, burning mouth sensation, dry mouth. Diffuse erythema with some petechia and discrete depapillation	Borders of the tongue	From beginning	oral mucositis due to a mucosal hypersensitivity to the presence of the SARS-CoV-2 in the epithelium	Hydration , chlorhexidinemouth washes(0.12%)	Oral mucositis	-
Oral Diseases , 2021	Jay Patel ¹¹	35	F	suspected	severe halitosis, generalized erythematous and edematous gingivae, and necrotic	Gingiva, interdental papillae	After 3 days	Bacterial co-infection	Metronidazole 400mg, chlorhexidine mouthwash (0.12%)	Necrotizing gingivitis	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Dermatology Ther	FilizCebeci Kahraman ²¹	51	M	yes	interdental papillae in both the maxillary and mandibular labial sextants, bleeding gums. Bilateral submandibular lymphadenopathy	Oropharynx, hard palate, soft palate	From beginning to after 10 days	Oropharyngeal involvement is probable with Covid-19	Antibiotherapy	Enanthema, Diffuse oropharyngeal erythema, petechia, and pustule formation	-
Journal of	Gianfranco	63(mean value)	M & F	Yes (Modera	Pain, Burning, Bleeding,	Tongue, gingiva	Maximum appeared	Probably pre-	Hyaluronic acid,	Oral lesions in	superficial band-like

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Clinical Medicine, 2021	Favia ⁷			te)	Taste disorders, Difficulty to chewing and swallowing, Geographic tongue, Fissured tongue, Ulcerative lesion, Blisters, Hyperplasia of papillae, Angina bullosa, Candidiasis Ulcero-necrotic gingivitis, Petechiae		within 1 week and before Covid-19 specific therapies	existing conditions, Sars-CoV-2-related & Treatment-related lesions, Lesions related to poor oral hygiene	chlorhexidine mouthwash or gel 2%, Miconazole nitrate, Topical tranexamic acid	half of the cases occurred in early stages of Covid-19. Therefore, the presence of oral lesions could represent an initial sign of peripheral thrombosis	lichenoid appearance of the inflammatory infiltrate with prominent vascular hyperplasia. Thrombosis of sub-epithelial and deeper vessels, etc.
Journal of Clinical Medicine, 2021	Gianfranco Favia ⁷	74(mean value)	M & F	Yes (Severe)	Pain, Burning, Bleeding, Taste disorders, Difficulty to chewing and swallowing, Geographic tongue, Fissured tongue,	Tongue, gingiva, palate	Maximum appeared within 1 week and before Covid-19 specific therapies	Probably pre-existing conditions, Sars-CoV-2-related & Treatment-related lesions, Lesions	Hyaluronic acid, chlorhexidine mouthwash or gel 2%, Miconazole nitrate, Topical tranexamic acid	Oral lesions in half of the cases occurred in early stages of Covid-19. Therefore, the presence	superficial band-like lichenoid appearance of the inflammatory infiltrate with prominent vascular hyperplasia. Thrombosis

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
					Ulcerative lesion, Blisters, Hyperplasia of papillae, Angina bullosa, Candidiasis, Ulceronecrotic gingivitis, Petechiae			related to poor oral hygiene	ic acid	of oral lesions could represent an initial sign of peripheral thrombosis	of sub-epithelial and deeper vessels, etc.
Journal of Clinical Medicine , 2021	Gianfranco Favia ⁷	81(mean value)	M & F	Yes (Critical)	Taste disorders, Ulcerative lesion, Hyperplasia of papillae, Angina bullosa, Candidiasis, Ulceronecrotic gingivitis, Petechiae, Spontaneous oral hemorrhage	Gingiva, tongue, palate	Maximum appeared after 1 week or after therapies	Probably pre-existing conditions, Sars-CoV-2-related & Treatment-related lesions, Lesions related to poor oral hygiene	Hyaluronic acid, chlorhexidine mouthwash or gel 2%, Miconazole nitrate, Topical tranexamic acid	Oral lesions in half of the cases occurred in early stages of Covid-19. Therefore, the presence of oral lesions could represent an initial sign of peripheral thrombosis	superficial band-like lichenoid appearance of the inflammatory infiltrate with prominent vascular hyperplasia. Thrombosis of sub-epithelial and deeper vessels, etc.
Internati	Miguel	43	F	Yes	Aphthous	Right	After 4 days	Cytokine	-	History of	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Journal of Dermatology, 2020	Dominiguez-Santas ¹⁵				ulcer(1 in number)with erythematous peripheral rim	buccal mucosa		storm due to Covid-19		recurrent aphthous stomatitis, Oral aphthous ulcers	
International Journal of Dermatology, 2020	Miguel Dominiguez-Santas ¹⁵	33	M	Yes	Aphthous ulcer(1 in number)	Superior mucogingival junction	After 3 days	Cytokine storm due to Covid-19	-	Oral aphthous ulcers	-
International Journal of Dermatology, 2020	Miguel Dominiguez-Santas ¹⁵	37	M	Yes	Aphthae(7 in number)	Ventral right side of tongue mucosa	After 5 days	Cytokine storm due to Covid-19	-	Oral aphthous ulcers	-
International Journal of Dermatology, 2020	Miguel Dominiguez-Santas ¹⁵	19	M	Yes	Clustered Aphthae(4 in number)	Right side of inferior labial mucosa	From beginning	Cytokine storm due to Covid-19	-	Oral aphthous ulcers	-
Cell Proliferation, 2020	Lili Chen ¹	52(mean age)	M & F	Yes	Amblygeusia, dry mouth, dryness and inflammation of mouth, enlargement of lymph nodes in submandibula	Oral cavity	-	SARS-CoV-2 could cause partial impairment of oral tissues. Change in	-	Oral symptoms may be frequently manifested by COVID-19 patients	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
					r regions			psychological status, poor oral hygiene or microbiota imbalance caused by therapeutic drugs			
The Journal of the American Dental Association, 2021	Steven Halepas ³	7.8(mean age)	M & F	Yes	Swelling, redness, cracking of labial mucosa, Red strawberry tongue appearing as hyperplastic papilla against an erythematous dorsal tongue. White strawberry tongue presenting as hyperplastic papilla against a white coating of the dorsal tongue.	Labial mucosa, Tongue	At the time of admission	Post-viral inflammatory reaction	-	The presence of oral or oropharyngeal changes may be early indicators of Multisystem Inflammatory Syndrome in Children (MIS-C) in the setting of COVID-19 infection.	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Oral Surg Oral Med Oral Pathol Oral Radiol 2021	Monique Abreu Pauli ²³	50	F	Yes	Painful, A deep ulcerated lesion located at the center of the hard palate (over the midline). The bone was exposed, and the lesion measured around 2 cm at the widest diameter. The lesion was surrounded by an erythematous halo, the borders appeared lobulated, and focal areas were swollen	Hard palate	After 8 days	Debilitating condition from poorly controlled diabetes, acute inflammatory immune response due to Covid-19, Covid-19 related oral manifestation	Incisional biopsy, Antibiotics, NSAIDs, Tramadol, antiseptic mouthwashes, Intravenous Amphotericin B with hydrocortisone	Oral Mucormycosis	Heavy mixed acute and chronic inflammatory infiltrate with necrosis and large nonseptate, thin-walled fungal hyphae that branch at a 90° angle. The microorganisms are aggregated around blood vessels
Med Oral Patol Oral Cir Bucal. 2020	CiroDantas Soares ¹⁰	42	M	Yes	Painful ulceration, multiple reddish macules of different sizes	Buccal mucosa, hard palate, tongue, lips	-	Thrombotic vasculopathy due to SARS-COV-2	Biopsy done, 3 weeks follow up	Primary reaction due to SARS-COV-2	Epithelium demonstrating vacuolization and haemorrhage in the

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Spec Care Dentist. 2020	Robert Onner Cruz Tapia ¹²	41	F	Yes	Erythematous bulla of 6 mm of soft consistency nonbleeding bulla	Hard palate	During quarantine time	Associated with COVID-19	-	Angina bullosa hemorrhagic-like lesion	superficial portion of the lamina propria, with hyperaemic vessels. Lymphocytic infiltration in the connective tissue and different-sized thrombi
Spec Care Dentist. 2020	Robert Onner Cruz Tapia ¹²	51	F	Yes	Diffuse vascular-like purple macule on the left palatal mucosa of 12 mm size and papule-plaque of 8 mm on the right palatal mucosa, and	Palatal mucosa	-	Associated with COVID-19	-	Vascular disorder	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Spec Care Dentist. 2020	Robert Onner Cruz Tapia ¹²	55	F	Yes	the lesions were non-bleeding and asymptomatic purple bulla of 8 mm diameter and soft consistency on the right side of tongue	Tongue	During quarantine time	Associated with COVID-19	-	Angina bullosa hemorrhagic-like lesion	-
Spec Care Dentist. 2020	Robert Onner Cruz Tapia ¹²	42	M	Yes	Burning sensation, multiple and irregular reddish macules of 3-4mm in diameter with indurated consistency	Hard palate	From beginning	Associated with COVID-19	Topical Mometasone 0.1% in solution after oral hygiene, chlorhexidine 0.12% mouthwash, Incisional Biopsy	Mucosal non-specific localized vasculitis and thrombosis	Squamous parakeratinized stratified epithelium with paranuclear and cytoplasmic vacuolization in the spinous layer, marked hemorrhage and vascular congestion with focal thrombi formation in the stroma

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
International Journal of Infectious Diseases, 2020	Jairo Corchuelo ⁹	40	F	Yes	Petechiae on the lower lip, canker sores on the lateral edge of the tongue and attached gingiva of tooth 34, whitish spots on the dorsum of the tongue with greater concentration in the posterior ventral area, melanin pigmentation in the gingiva bonded to previous teeth,	Tongue, Lip, Gingiva	-	Result of inflammatory processes, frequent use of antibiotics or alterations in the immune response	Ibuprofen, Vitamin D, Azithromycin, Mouthwash, Nystatin	Mild Oral Candidiasis, thrombocytopenia due to ibuprofen, postinflammatory hyperpigmentation	with prominent erythrocyte extravasation and chronic inflammatory cells -

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Oral Diseases , 2020	Reza Ansari ¹⁴	56	F	Yes	lymphadenopathy at the neck level Painful ulcers with irregular margins and varying sizes in red and non-hemorrhagic background.	Entire hard palate	After 5 days	Stress, mucosal ulcer due to COVID-19	Incisional Biopsy, topical medication (mixture of diphenhydramine, dexamethasone, tetracycline, and lidocaine)	Oral stress and aphthous ulcers	Tissue diffuse edema with mucosal desquamation, along with granulation and ulceration under the mucosa with invasion of mononuclear cells with large and glassy nuclei. Neutrophilic cell invasion was also seen following secondary bacterial infection.
Oral Diseases , 2020	Reza Ansari ¹⁴	75	M	Yes	Dysphagia, Several painful small ulcers, with	Anterior of the tongue	1 week after hospitalization	Stress, mucosal ulcer due to COVID-	Incisional Biopsy, topical medication	Oral stress and aphthous ulcers	Tissue diffuse edema with mucosal

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
					irregular margins, in red and non-hemorrhagic background			19	n (mixture of diphenhydramine, dexamethasone, tetracycline, and lidocaine)		desquamation, along with granulation and ulceration under the mucosa with invasion of mononuclear cells with large and glassy nuclei. Neutrophilic cell invasion was also seen following secondary bacterial infection.
Journal of Oral and Maxillofacial Pathology, 2020	Sudip Indu ¹⁷	-	M	Yes	Painful, burning, itching sensation, Irregular, shallow, round to oval in shape ulcer(0.5mm×0.5mm) with erythematous	Unilateral, Lower left labial mucosa, left antero-ventral surface of tongue	Before 2 days	Could be an initial manifestation of the coronavirus disease process	Betadine gargling, warm water drinking, ascorbic acid, zinc supplements	Herpes zoster infection	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
JAMA Dermatol ogy, 2020	Juan Jimenez-Cauhe ²	40-69	M=2 F= 4	Yes	halo,Well-circumscribed ulcer Macule, petechiae	Palate	Before 2 days - After (2-24) days	Enanthema due to COVID-19	Azithromycin, corticosteroids, hydroxychloroquine, lopinavir, ritonavir, tocilizumab	Enanthema	-
Clinical and Experimental Dermatology, 2020	Juan Jimenez-Cauhe ⁴ ₁	66.75 (58-77)	F=4	Yes	Macule, petechiae	Palate	19.5	Erythema - multiforme like	Azithromycin, ceftriaxone, corticosteroids, hydroxychloroquine, ritonavir/lopinavir	Erythema - multiforme like	a normal basket-weave stratum corneum, and mild to moderate spongiosis in epidermis, dermis-dilated vessels filled with neutrophils, extravasation of red blood cells, lymphocytic perivascular

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Clinical and Experimental Dermatology, 2020	T. Kamm erer ¹⁸	46	M	Yes	Painful ulceration in the mouth, multiple sharply circumscribed ulcerations of the oral mucosa covered by yellow–grey membranes ,sub-mandibular lymphadenitis , medical history of recurrent herpes labialis infection	Right side of buccal mucosa	3 days after extubation	Covid-19 infection ,prolonged inpatient care, stress, immunosuppression	Azithromycin, meropenem, acyclovir	Secondary herpetic gingivostomatitis	and interstitial infiltrate etc. multiple nuclei with herpes simplex virus 1/2 antibodies after immunohistochemical staining.
Hospital Pediatrics, 2020	Veena G. Jones ²⁵	6	F	Yes	Cracked lip, prominent papilla in tongue	Lip, tongue	After 2 days	Kawasaki-like	Intravenous immunoglobulin, acetylsalicylic acid	Kawasaki disease with concurrent COVID-19 infection	-
Eur. J. Pediat.	Mazzotta F ²⁶	9	M	IgG(+)	Chelitis, glossitis,	Lip, tongue	After 3 weeks	Due to COVID-19	Corticosteroids	Kawasaki-like	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Dermatol . 2020					painful						
S. Karger AG, Basel 2020	Narges Malih ³⁸	38	M	Yes	Erythema, aphthous ulcer, painful, loss of taste	Left Tonsil	After 3 days	-	Acetaminophen	Covid-19 disease with cutaneous presentation	-
Ann Rheum Dis 2020	Poulett ^{y27}	10(mean age)	M=8 F=8	69% (+)	Cracked lip	Lip	-	Associated with COVID-19	Intravenous immunoglobulin, corticosteroids etc.	Kawasaki disease	-
Pediatric Cardiology, 2020	Joanne S. Chi ^{u28}	10	M	Yes	Cracked lip, erythema	Lip, oropharynx	-	-	Dopamine	Kawasaki-disease and myocarditis	-
International Journal of Dermatology, 2020	Nessa Aghazadeh ¹⁹	9	F	Yes	Vesicles, erosions	Lip, anterior tongue, buccal mucosa	Coincident	Cutaneous manifestation of COVID-19 disease, COVID-19 related dermatosis	Acetaminophen	Herpetiform	Skin lesions show vascular microthrombi and lymphocytic vasculitis.
J Eur Acad Dermatol Venereol . 2020	P. Labé ²⁴	3	M	-	Chelitis, glossitis, stomatitis	Lip, tongue, oral cavity	-	COVID-19 associated	Intravenous immunoglobulin	Kawasaki-like	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
J EurAcad Dermatol Venereol . 2020	P. Labé ²⁴	6	M	Yes	Erosion, chelitis, hemorrhagic crust, painful	Lip, gingiva	After 7 days	COVID-19 associated	-	Erythema-multiforme like	-
J EurAcad Dermatol Venereol . 2020	Banu Taşkın ³⁹	61	F	Yes	Minor aphthous ulcer	Hard palate, buccal mucosa	-	Exaggerated neutrophilic response due to COVID-19	hydroxyc hloroquin e, azithromycin, and oseltamivir, toclizumab, favipiravir	Erythema nodosum like Sweet Syndrome	Predominant cells in inflammatory infiltration-neutrophils
Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Thais Bianca Brandão ⁶	81	M	Yes	Dysgeusia, Clustered ulcers 1 to 1.5 cm in diameter covered with crusts. They are covered with a mucopurulent membrane and the so-called aphthous-like pattern Ulcerative painful lesions	Lower lip(vermilion), anterior dorsal tongue	Last few days of hospital admission	Severe case of COVID-19, immunosuppression	Azithromycin, ceftriaxone , acyclovir, photomodulation therapy	Herpetiform ulcers	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Thais Bianca Brandão ⁶	71	F	Yes	with superficial necrosis Small hemorrhagic ulcerations, focal areas of shallow necrosis	Upper and lower lip, anterior dorsal tongue	At time of hospital admission	Severe case of COVID-19, immunosuppression	Azithromycin, ceftriaxone, acyclovir, photobiomodulation therapy	Herpetiform ulcers	-
Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Thais Bianca Brandão ⁶	83	F	Yes	Painful ulcer, Focal erythema/petechia and a shallow necrotic area	Right lateral border of the tongue, anterior hard palate	Simultaneous to hospital admission	Severe case of COVID-19, immunosuppression	Piperacillin/tazobactam, ceftriaxone, photobiomodulation therapy	-	-
Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Thais Bianca Brandão ⁶	72	M	Yes	Hemorrhagic ulcerations. Painful “aphthous-like” necrotic ulceration	Upper and lower lip vermilion, right lower lip mucosa	Few days after hospital admission	Severe case of COVID-19, immunosuppression	Piperacillin/tazobactam, azithromycin, and ceftriaxone, acyclovir photobiomodulation therapy	Herpetiform ulcers	-
Oral	Thais	32	F	Yes	Multiple	Apex	After 10 days	Mild case	Dypirone	Aphthous	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Surg Oral Med Oral Pathol Oral Radiol. 2020	Bianca Branda ^{o6}				shallow ulcers and circular with a whitish center and surrounded by an erythematous halo, ranging from 3 to 4 mm	and anterior lateral border of tongue		of COVID-19		like ulcers	
Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Thais Bianca Branda ^{o6}	35	M	Yes	Isolated peritonsillar major aphthous-like ulcer, shallow, circular, covered by a fibrinopurulent membrane and surrounded by an erythematous halo, measuring 0.5 cm	Tonsillar pillar	After 6 days	Mild case of COVID-19	-	Aphthous like ulcers	-
Oral Surg Oral Med Oral Pathol Oral	Thais Bianca Branda ^{o6}	29	M	Yes	Ageusia, Painful ulcer, shallow, 1 cm, with a whitish pseudomembrane	Ventral portion of tongue	After 6 days	Mild case of COVID-19	lpratromium bromide, fenoterol hydrochloride	Aphthous - like ulcers	-

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Radiol. 2020					surrounded by an erythematous halo						
Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Thais Bianca Brandão ⁶	28	M	Yes	Ageusia, aphthous like ulcers, another ulcer	Upper and lower labial mucosa, right lateral border of tongue	After 8 days	Mild case of COVID-19	0.12% non-alcoholic chlorhexidine mouthwash	Aphthous like ulcers	-
Lancet 2020	Lucio Verdoni ²⁹	7.5	M=7 F=3	Yes	-	Lip, oral cavity	-	Associated with COVID-19	-	Kawasaki-like disease	-
Journal of the Pediatric Infectious Diseases Society, 2020	Kathleen Chiotos ³⁰	5	F	-	Fissured lip	Lip	-	Potentially driven by a disordered immunological response following SARS-CoV-2 infection	Intravenous immunoglobulin	Kawasaki-like	
Journal of the Pediatric Infectious Diseases Society, 2020	Kathleen Chiotos ³⁰	9	F	Yes	Fissured lip, strawberry tongue	Lip, tongue	-	Potentially driven by a disordered immunological response	Intravenous immunoglobulin, acetyl	Kawasaki-like	

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
Diseases Society, 2020								gical response following SARS-CoV-2 infection	salicylic acid, corticosteroids		
Journal of the Pediatric Infectious Diseases Society, 2020	Kathleen Chiotos ³⁰	12	M	No	Fissured lip	Lip	-	Potentially driven by a disordered immunological response following SARS-CoV-2 infection	Intravenous immunoglobulin, milrinone	Kawasaki-like	
American Journal of Emergency Medicine, 2020	Bahadır Taşlıdere ³¹	51	F	Yes	Medical history of Melkersson-Rosenthal syndrome. Hyperemic, firm oedema extending towards the jaw, peripheral facial paralysis(right side), right nasolabial	Right lower lip, tongue	Coincident	Co-existence between Melkersson-Rosenthal syndrome and COVID-19 and it may be a cause for recurrence of the syndrome.	Hydroxychloroquine, azithromycin, steroid therapy	Melkersson-Rosenthal syndrome	Areas of inflammation involving lymphocytes, plasma cells, mast cells

Journal Name & Year	First Author Name	Patient Age (year)	Gender	Covid (+)	Oral Lesions	Site	Appearance Of Symptoms	Etiology	Treatment	Reported Diagnosis	Histopathological Findings
J Wound Ostomy Continen ce Nurs. 2020	Charlene Singh ⁴⁰	44	M	Yes	sulcus obliterated and asymmetrical to the right of the mouth corner, fissure line Extensive mucosal damage	Lip, tongue	After 4 days	Vascular inflammation, ischemic reperfusion injury	Azithromycin, prednisolone	Skin and mucosal damage, deep tissue injury, mucosal injury, pressure injury	-

Table 2. Shows number of total cases observed, types of cases, how many cases occurred in male and female, site, predisposing conditions for each published article with author/journal name in a more concise form

Journal Name & Year	First Author Name	Number Of Total Cases Observed	Types of cases	Male	Female	Site of the oral lesion	Any predisposing conditions
Oral Diseases, 2020	Milagros Díaz Rodríguez ²⁰	3	1.Apthous like lesions 2.Commissural Chelitis 3. Candidiasis & Angular Chelitis	1	2	2- tongue 2- lip 1-hard palate/soft palate	-
Oral Diseases, 2020	Carmen Martín Carreras-Presas ¹⁶	3	1.Herpetic recurrent stomatitis(2) 2.Erythema multiforme(1)	2	1	2-palate 1-tongue, internal lip mucosa	Diabetis/hypertension(1), hypertension/obesity (1)

Journal Name & Year	First Author Name	Number Of Total Cases Observed	Types of cases	Male	Female	Site of the oral lesion	Any predisposing conditions
Journal of Dental Research, 2020	Juliana Amorim dos Santos ⁵	1	Herpetic recurrent oral lesions associated with Candidiasis, Fibroma, Geographic tongue	1	-	Tongue, lower lip	Coronary disease, hypertension, polycystic kidney disease, kidney transplant, pulmonary venous thromboembolism
Otolaryngology–Head and Neck Surgery, 2020	Ameen Biadsee ²	128	Dysgeusia(67), xerostomia(72), sore-throat(34), plaque like changes(9), swelling(10), oral bleeding(6), facial pain(18), masticatory muscle pain(15)	58	70 (maximum symptoms found in women)	Tongue, palate, gingiva	Hypertension, diabetes mellitus, hypothyroidism, asthma, smoking
Oral Diseases, 2020	Saygo Tomo ³⁷	1	Oral mucositis	-	1	Borders of the tongue	-
Oral Diseases, 2021	Jay Patel ¹¹	1	Necrotizing gingivitis	-	1	Gingiva, interdental papillae	-
Dermatology Ther	FilizCebeci Kahraman ²¹	1	Enanthema, Diffuse oropharyngeal erythema, petechia, and pustule formation	1	-	Oropharynx, hard palate, soft palate	-
Journal of Clinical Medicine, 2021	Gianfranco Favia ⁷	123	Dysgeusia(79), Geographic tongue(7), Fissured tongue(5), Ulcerative lesion(65), Blisters(19), Hyperplasia of papillae(46), Angina bullosa(11), Candidiasis(28) Ulceronecrotic gingivitis(7), Petechiae(14),	70	53	Tongue, gingiva, palate	Probably pre-existing conditions, Sars-CoV-2-related & Treatment-related lesions, Lesions related to poor oral hygiene

Journal Name & Year	First Author Name	Number Of Total Cases Observed	Types of cases	Male	Female	Site of the oral lesion	Any predisposing conditions
International Journal of Dermatology, 2020 Cell Proliferation, 2020	Miguel Dominguez-Santas ¹⁵	4	spontaneous oral hemorrhage(1) Apthous ulcer	3	1	Buccal mucosa, mucogingival junction, tongue, labial mucosa	-
	Lili Chen ¹	108	Amblygeustia(51) (F>M) , dry mouth(50)(M=F), dryness and inflammation of mouth(12)(M>F), enlargement of submandibular lymph nodes(1)(F=1)	52	56	Oral cavity	-
The Journal of the American Dental Association, 2021	Steven Halepas ³	47	Swelling, redness, cracking of labial mucosa(23) Red strawberry tongue, white strawberry tongue(5)	51.1%	48.9%	Labial mucosa, Tongue	Multisystem Inflammatory Syndrome in Children(MIS-C)
Oral Surg Oral Med Oral Pathol Oral Radiol 2021	Monique Abreu Pauli ²³	1	Oral Mucormycosis	-	1	Hard palate	Diabetis, wearing a Removable partial denture
Med Oral Patol Oral Cir Bucal. 2020	CiroDantas Soares ¹⁰	1	Painful ulceration, multiple reddish macules of different sizes	1	-	Buccal mucosa, hard palate, tongue, lips	Diabetis mellitus, hypertension
Spec Care Dentist. 2020	Roberto Onner Cruz Tapia ¹²	4	Angina-bullosahemorrhagic like lesion(2), Mucosalnonspecific localized vasculitis and thrombosis(1), Vascular disorder(1)	1	3	Hard palate, palatal mucosa, tongue	Hypertension(1)
International	Jairo	1	Mild Oral Candidiasis	-	1	Tongue, lip, gingiva	-

Journal Name & Year	First Author Name	Number Of Total Cases Observed	Types of cases	Male	Female	Site of the oral lesion	Any predisposing conditions
Journal of Infectious Diseases, 2020	Corchuelo ⁹						
Oral Diseases, 2020	Reza Ansari ¹⁴	2	Oral stress and aphthous ulcers	1	1	Hard palate, anterior of the tongue	Diabetis(1), Hypertension(1)
Journal of Oral and Maxillofacial Pathology, 2020	Sudip Indu ¹⁷	1	Herpes zoster infection	1	-	Unilateral, Lower left labial mucosa, left antero-ventral surface of tongue	-
JAMA Dermatology, 2020	Juan Jimenez-Cauhe ²²	6	Enanthema (macule, petechiae)	2	4	Hard and soft palate	-
Clinical and Experimental Dermatology, 2020	Juan Jimenez-Cauhe ⁴¹	4	Erythema multiforme like (Macule, petechiae)	-	4	Palate	-
Clinical and Experimental Dermatology, 2020	T. Kammerer ¹⁸	1	Secondary herpetic gingivostomatitis	1	-	Right side of buccal mucosa	Hypercholesterinaemia and coronary heart disease
Hospital Pediatrics, 2020	Veena G. Jones ²⁵	1	Cracked lip, prominent papilla in tongue (Kawasaki-like)	-	1	Lip, tongue	Kawasaki disease
Eur. J. Pediat. Dermatol. 2020	Mazzotta F ²⁶	1	Chelitis, glossitis, painful	1	-	Lip, tongue	Kawasaki disease
S. Karger AG, Basel 2020	Narges Malih ³⁸	1	Erythema, aphthous ulcer, painful, loss of taste	1	-	Left tonsil	-
Ann Rheum Dis 2020	Pouletty ²⁷	16	Cracked lip (Kawasaki like)	8	8	Lip	Kawasaki disease, overweight, asthma
Pediatric Cardiology, 2020	Joanne S. Chiu ²⁸	1	Cracked lip, erythema (Kawasaki-like)	1	-	Lip, oropharynx	Kawasaki disease

Journal Name & Year	First Author Name	Number Of Total Cases Observed	Types of cases	Male	Female	Site of the oral lesion	Any predisposing conditions
International Journal of Dermatology, 2020 J EurAcadDermato IVenereol. 2020	Nessa Aghazadeh ¹⁹	1	Herpetiform	-	F	Lip, anterior tongue, buccal mucosa	-
	P. Labé ²⁴	2	Chelitis, glossitis, stomatitis (Kawasaki-like); Erosion, hemorrhagic crust, chelitis, painful(Erythema multiforme like)	2	-	Lip, tongue, oral cavity, gingiva	Kawasaki disease(1)
J EurAcadDermato IVenereol. 2020 Oral Surg Oral Med Oral Pathol Oral Radiol. 2020	Banu Taşkın ³⁹	1	Minor aphthous ulcer (Erythema nodosum like Sweet Syndrome)	-	1	Hard palate, buccal mucosa	-
	Thais Bianca Brandao ⁶	8	Herpetiform ulcers(3); Aphthous-like ulcers(4)	5	3	Lower lip(vermilion)-3, upper lip-2, anterior dorsal tongue-2, lateral border of the tongue-3, anterior hard palate-1, lower lip mucosa-2, Apex of tongue-1, tonsillar pillar-1, Ventral portion of tongue-1, upper labial mucosa-1	Hypertension, Diabetes mellitus(1); Hypertension, obesity, Chronic Obstructive Pulmonary Disease(COPD), Parkinson's, Pancreatitis(1); Hypertension, obesity, Chronic Renal Failure, Diabetes mellitus(1); Hypertension, COPD(1)
Lancet 2020	Lucio Verdoni ²⁹	10	-(Kawasaki-like)	7	3	Lip, oral cavity	Kawasaki disease

Journal Name & Year	First Author Name	Number Of Total Cases Observed	Types of cases	Male	Female	Site of the oral lesion	Any predisposing conditions
Journal of the Pediatric Infectious Diseases Society, 2020 American Journal of Emergency Medicine, 2020 J Wound Ostomy Contenance Nurs. 2020	Kathleen Chiotos ³⁰	3	Fissured lip-3; Strawberry tongue-1, Kawasaki-like	1	2	Lip- 3 Tongue-1	Kawasaki disease
	Bahadır Taşlıdere ³¹	1	Orofacial oedema, facial paralysis, fissured tongue (MRS)	-	F	Lower lip, tongue	Melkersson-Rosenthal Syndrome(MRS)
	Charleen Singh ⁴⁰	1	Extensive mucosal damage	1	-	Lip, tongue	Diabetes mellitus, hypertension

Table 3. Shows total cases, type of lesions, number of cases of each lesion from all articles searched

Total cases	Type of lesions	Number of cases
488	Oral ulcers	87
	Chelitis	3
	Glossitis	1
	Candidiasis	31
	Erythema multiforme	6
	Fibroma	1
	Geographic tongue	8
	Dysgeusia	147
	Xerostomia	134
	Sore throat	34
	Plaque-like changes	9
	Swelling	45
	Oral bleeding	6
	Facial pain/masticatory muscle pain	33
	Submandibular lymph node enlargement	1

Total cases	Type of lesions	Number of cases
	Oral mucositis	1
	Necrotizing gingivitis	8
	Enanthema	41
	Fissured tongue	5
	Hyperplasia of papilla	46
	Angina-bullosa like lesions	13
	Amblygeusia	51
	Strawberry tongue	5
	Cracked lip	23
	Oral mucormycosis	1
	Mucosal non-specific localised vasculitis and thrombosis	2
	Kawasaki-like lesions	33
	Melkersson-Rosenthal Syndrome like lesions	1
	Extensive mucosal damage	1

The aim of this study is a review of maximum of the oral lesion presentation associated with COVID-19 previously described and explained by many authors and a collection and overview of the same for better understanding and knowledge in depth.

We have searched recent studies published from previous year and this year (2020,2021) in search engines like PubMed, Google Scholar etc. We have typed the keywords like oral lesions, COVID-19, SARS-CoV-2, oral mucosa, manifestations. (Table1,2,3)

2. COVID 19 AND ALLIED ORAL LESIONS

Angiotensin Converting Enzyme 2(ACE2) receptor is a membranous protein presented by oral epithelium specially the salivary gland and the tongue [11]. It is found in abundance in oral tissues [12]. The virus SARS-CoV-2 has an invasive ability and special affinity for receptors for ACE2. Naturally the oral epithelium becomes the host cells or the target organ for infection and an easy route for entry for the virus, causing inflammatory response in salivary gland and tongue mucosa epithelium [12,6]. Studies have also indicated that salivary glands carry the most RNA linked to protein than tongue mucosa, buccal mucosa, palate, tonsils for the attack of the virus. ACE2 receptor and an enzyme called TMPRSS (transmembrane protease, serine 2) are included under them. They help the virus in fusing its membrane with cells of the host and thus gains entry [12]. Therefore, saliva is a major reservoir for SARS-CoV-2 infection as per reports [1]. SARS-CoV-2 interaction with ACE2 can also result in dysgeusia by impairment of taste buds [6]. Due to this pathogenesis, the oral signs and symptoms related to this virus may be taken into account and studied further.

2.1 Description of the Commonly Presented Oral Lesions

2.2.1 Dysgeusia

The most important feature among all may be the altered taste or dysgeusia associated with loss of smell that is noticed in patients infected with COVID-19. Thus, they are one of the earliest indicators. The cranial nerves 1,7, 9,10 may be affected by SARS-CoV-2 and also the cells supporting their transmission. Again, ACE2 receptors are present in huge numbers in tongue mucosa which helps the virus to infect and attack the cells because of their affinity for ACE2

receptors [12] through dopamine and serotonin synthesis pathway coregulation [6].

SARS-CoV-2 can bind with sialic acid (essential salivary mucin component) thus altering gustatory sensation. Also, ACE inhibitors and ACE2 blockers used in COVID-19 treatment causes taste disorders by G protein-coupled and sodium channel inactivation. After recovery from COVID-19 and their discontinuation taste sensation becomes normal [6].

2.1.2 Xerostomia

Xerostomia is the 2nd most common characteristic oral sign associated with COVID-19 infection. Due to the presence of ACE2 receptor in salivary glands as stated above, the virus gets entry into the salivary gland's epithelial cells and the quality and quantity of saliva produced is interrupted. Another cause can be the mouth breathing due to continual use of mask which results in dryness of mouth if not hydrated frequently. Xerostomia can affect oral cavity in caries prevalence and fungal infections due to Candida [12].

2.1.3 Sore throat

Sore throat is also a common finding in many patients with COVID-19 infection. It has been suggested by many authors [2].

2.1.4 Oral ulcers

Oral ulcers are considered to be the most common among all oral lesions characterized in COVID-19 infection. We can divide them into Aphthous-like and Herpetiform-like oral ulcers.

2.1.4.1 Aphthous ulcers

According to many studies, they presented as multiple shallow ulcers and circular with a whitish center and surrounded by an erythematous halo, ranging from 3 to 4 mm, or, (0.5-1)cm may be covered by a fibrinopurulent membrane or with a whitish pseudomembrane. Some present as several painful small ulcers, with irregular margins, in red and non-hemorrhagic background. They may occur in clusters or single [4,13,14].

Increased level of tumour necrosis factor (TNF)- α in COVID -19 patients may result in chemotaxis of neutrophils to oral mucosa and and develop these lesions [6]. They can also develop by

cytokine storm due to COVID-19, stress, immunosuppression. Maximum of them present in tongue, others seen in gingiva, palate, buccal mucosa, labial mucosa, mucogingival junction, tonsillar pillar [4,13,14].

2.1.4.2 Herpetiform ulcers

They present as painful multiple small, pinpoint, yellowish or orange ulcers unilaterally with an erythematous halo, some with burning, itching sensation, irregular, shallow, round to oval in shape ulcer(0.5mm×0.5mm, well-circumscribed. Some are covered with mucopurulent membrane, some with hemorrhagic ulcerations with necrosis. They are most prevalent in tongue, labial mucosa followed by buccal mucosa and palate [4,15,3,16,17,18].

Immunosuppression, emotional distress, secondary lesions associated with COVID-19, extended inpatient care, underlying diseases, COVID-19 related cutaneous manifestation/dermatosis may be the causative factor for these lesions [3,4,15,16,17,18].

2.1.4.3 Ulcer and erosion

They appeared as painful lesions, some as multiple reddish macules of different sizes. Location as per studies can be buccal mucosa, hard palate, tongue, lip and in gingiva also [5,8]. They can be seen in moderate cases of COVID-19 in maximum number [8,5].

Early and late ulcerative lesions are due to SARS-COV-2 related lesions and treatment related lesions respectively. Lesions related to poor oral hygiene leads to ulcero-necrotic gingivitis [5]. Thrombotic vasculopathy secondary to COVID-19 may be another cause [8].

3. CANDIDIASIS

Candidiasis is seen in some cases and manifested mainly in tongue, and also in lip, palate, gingiva. Pain and burning symptoms were seen. Lesions presented as white plaque/whitish areas. Red forms mainly located in tongue with median rhomboid glossitis like appearance, while in palate white forms were more frequent, the first type(white forms) present more in moderate form of COVID-19 and second type(red forms) in intubated patients (severe and critically-ill). Pseudomembranous and mild oral candidiasis were noted, in 1 case it was associated with herpetic recurrent oral lesions [3,5,19,9].

Immunosuppression, stress, secondary lesions, COVID-19 treatment related lesions, lack of oral hygiene can be the probable cause [3,5,19,9].

3.1 Gingival Inflammation/Swelling

One of the important signs reported are bleeding and gingival inflammation in COVID-19 infection. Generalized increase in inflammation due to increased cytokine and interleukin level by SARS-CoV-2 virus can be a major cause. Immune imbalance can also be considered vital factor in this disease, resulting in cytokine storm specially by interleukin-6, which worsens in presence of periodontal disease [12].

3.2 Enanthema

Enanthema is mainly reported by 2 authors. Typical presentations were on hard and soft palate and oropharynx. The signs were inability to taste, sore throat, largely erythematous surface, a few petechiae in the midline and numerous pustular enanthema, more prominent on the left side, 1-3 mm in diameter. Also in another case macule, petechiae were noticed.

Probable reason described by the authors were infection by SARS-CoV-2 virus in oral cavity due to COVID-19 [20,21].

3.3 Necrotizing Gingivitis

Covid-19 infection is also associated with necrotizing periodontal disease. Signs and symptoms included severe halitosis, with generalized erythematous and edematous gingivae. Necrotic interdental papillae and bleeding gums were noted. Bilateral submandibular lymphadenopathy was associated. They are also seen mostly in severe and critical cases of COVID-19 [5,10].

Bacterial co-infections (especially *Prevotella intermedia*), poor oral hygiene and COVID-19 was attributed to such oral lesions [5,10].

3.4 Hyperplasia of Papilla

It was always seen in patients with dysgeusia and characterized by red enlargement of papilla on dorsum and sides of tongue. Moderate form of COVID-19 cases showed a high number of hyperplasia of papilla. They may have an association with COVID-19[5].

3.5 Oral Mucormycosis

It was described by one author in the context of COVID-19 and seen in current year i.e. 2021. It was presented by a female patient (50 yrs), having a painful, deep ulcerated lesion located at the center of the hard palate. The lesion measured around 2 cm with exposed bone and was surrounded by an erythematous halo and had lobulated borders and swollen focal areas. Incisional biopsy was done and medications were advised.

Among the reasons, immunosuppression by diabetes, acute inflammatory immune response due to COVID-19 or, COVID-19 associated oral lesion were considered [22].

3.6 Erythema Multiforme-Like Lesions

This type of lesions were reported by some authors. They characterized by macule, petechiae, some had pain in tongue, pruritic blisters, bulla, desquamative gingivitis, others had erosion, cheilitis, hemorrhagic crust. They were mostly present in tongue, lip, palate or gingiva [15,23,24].

Findings suggested the lesions appeared as a result of underlying disease, emotional distress or COVID-19 associated [15,23,24].

3.7 Geographic and Fissured Tongue

They were found in 2 studies. In 1 study, the lesions were asymptomatic and were pre-existing conditions [5]. In another study, presented as atrophic areas surrounded by elevated yellow-white halo which was associated with fissured tongue. This severe geographic tongue was classified as moderate after recovery from COVID-19. They were thought to be due to secondary lesions as a result of degradation of systemic health or treatments for COVID-19 infection [3].

3.8 Strawberry Tongue and Cracking of Lips

These lesions presented as swelling, redness, cracking of labial mucosa. Red strawberry tongue appeared as hyperplastic papilla against an erythematous dorsal tongue. White strawberry tongue presented as hyperplastic papilla against a white coating of the dorsal tongue [25].

The authors concluded that lesions were due to post-viral inflammatory reaction and these oral changes presented were early indicators of Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19 infection [25].

3.9 Angina-Bullosa Like Lesions

They generally presented in the hard and soft palate, tongue or buccal mucosa as brown-black single multiple bullae with associated petechiae. They were mainly treatment related lesions (patients on anticoagulant medications) and seen mostly in moderate cases of COVID-19. In another study, these angina-bullosa like lesions presented as non-bleeding, asymptomatic lesions and appeared as purple, erythematous bullae (6-8) mm of soft consistency. These lesions were associated with COVID-19 infection [11,5].

3.10 Kawasaki-Like Lesions

They appeared as cracked lip, fissured lip, prominent papilla in tongue, strawberry tongue, erythema, cheilitis, glossitis, stomatitis, may be painful and also affecting oropharynx, oral cavity affecting the children [7,23,26,27,28,29,30,31].

The authors stated that these oral lesions were due to Kawasaki disease with concurrent COVID-19 infection or may be due to disordered immunological response following infection by SARS-CoV-2 virus. These oral lesions characterized may not be having direct effect by the virus [7,23,26,27,28,29,30,31].

3.11 Melkersson-Rosenthal Syndrome

One case was reported of a 51 yrs old women having a medical history of Melkersson-Rosenthal Syndrome with a positive report of COVID-19. She presented with unilateral lip swelling, malaise, orofacial oedema, facial paralysis, fissured tongue, affecting her right side of face. The signs were coincident with COVID-19 infection.

There may be co-existence between COVID-19 and Melkersson-Rosenthal Syndrome and that may have caused its recurrence [32].

4. STRESS AS AN IMPORTANT FACTOR IN DEVELOPMENT OF ORAL LESIONS

Due to highly contagious and sudden outbreak of COVID-19 as a pandemic, anxiety, depression and other stress related reactions among people are inevitable [32]. As a result of halt in the daily activities and social interactions because of lockdown for unknown period of time, people develop depressions and may lose confidence in life which affect their mental health [33]. This kind of panic of the public in psychology is called PSYCHOLOGICAL STRESS. Here COVID-19 become the stressor of public panic. The uncertainty and lack of knowledge of COVID-19, its fast transmission speed and infectious nature and its outcomes in human lives, SARS-CoV-2 virus is responsible for making public nervous and highly stressful [33]. According to WHO, the current death rate due to COVID-19 worldwide is 36.9 lakhs. Many people have negative thoughts in their minds and some may lose their hopes after watching and reading news channels, newspapers and seeing the death rates or number of infected rates, hospitalization news, shortage of beds and treatment in proper time, and it becomes a continuous hammer to their brain. One author reported that females are more prone than males to develop these anxiety, stress and nervousness and that 40yrs or below aged people faces these problems more than those of above 40yrs [33].

Stress response activates autonomic nervous system, mainly sympathetic, via hypothalamic–pituitary–adrenal (HPA) axis, which secretes corticotropin-releasing factor (CRF) and arginine–vasopressin (AVP). Adrenocorticotrophic hormone (ACTH), enkephalins, and endorphins are released as a result of this. Thus, the stress-response function acts by a positive, bidirectional feedback loop. Various other factors released in response to stress are angiotensin II, various cytokines, and lipid mediators of inflammation. They act on different components of HPA axis and intensifies the action [34].

COVID-19 is also seen more in people having comorbidities such as obesity, hypertension, diabetes and cardiovascular disease and periodontitis [35]. Smoking or tobacco consumption in any form for deleting effect of stress imposes an additional risk by contributing to poor oral health status. COVID-19 infection induces oxidative stress, activates unregulated

cytokine offering (cytokine storm) and inflammation. The receptor of SARS-CoV-2 is Angiotensin-converting enzyme 2(ACE2) regulates vascular function by modulating nitric oxide (NO) release and oxidative stress [35].

Psychosomatic reasons with oral diseases are there from long ago and they impose a threat for the development and progression of oral lesions [36]. Various oral manifestations include xerostomia, dysgeusia, aphthous ulcers, herpetiform ulcers, candidiasis, necrotizing periodontitis, erythema multiforme etc. which have a very close relation with stress [34]. A possible mechanism of ACE-2 and reactive oxygen species (ROS) activation by COVID-19 and the repressing of NRF2(nuclear factor erythroid 2-related factor-2) manifests oral symptoms and Acute Respiratory Distress Syndrome (ARDS) in lungs, inflammations and oxidative stress in multiple organs [35].

Reactive oxygen species (ROS) and free radicals are physiologically produced during cellular metabolism. When their balance is disrupted in favour of ROS, a condition called oxidative stress occurs. Uric acid is the main antioxidant in saliva and has role in managing oxidative stress. Inflammatory infections of oral cavity by bacteria in gingiva is initiated which triggers the activation of host defence systems. Thus, production of ROS is increased to disturb pathogenic microorganisms. ROS does not distinguish between pathogenic bacteria (having antioxidant defences) and host structures and destroys the tissue of the organism that has produced them as a 'defence weapon'. ROS action is highly increased in patients with periodontal disease having weak antioxidant defence system. Recurrent aphthous stomatitis (RAS) causes include local trauma, systematic, genetic, immunological, microbial factors, use of immunosuppressive drugs etc. Oxidant-antioxidant equilibrium is thus disturbed and increases production of free radicals. There is compromise of immune system by oxidative stress situation. Cell damage occurs after getting trigger from an increase in free radicals. The enzymatic antioxidant defence system is damaged in RAS having active lesion and has an important role in its pathogenesis [37].

People as a general basis must stay away from the media as far as possible, discuss about positive news, can do free hand exercise or jogging, practice meditation or breathing exercises, indulge themselves in any type of

productive works or can have music therapy to keep their mind fresh and stress-free. Vaccination against COVID-19 among all age groups must be encouraged as fast as possible. This also ensures people to fight the pandemic and hoping for better days to come.

5. CONCLUSION

COVID-19 disease started in Wuhan, China, gradually affected all other countries including India and soon it became a global crisis and became a pandemic. The respiratory system is the target of SARS-CoV-2 virus and alongside it also impairs other body organs. It directly or indirectly affects the oral mucosa mainly due to the presence ACE2 receptor, to which the virus attaches and finds its entry.

Dysgeusia, xerostomia, sore throat, oral ulcers including aphthous and herpetiform, candidiasis, swelling of gingiva, enanthema, oral lesions of Kawasaki-like disease are the most common oral lesions manifested. We have also found 1 case of oral mucormycosis related to COVID-19 disease. We cannot fully correlate the etiopathogenesis of such lesions with COVID-19 or justify its exclusiveness. Several other factors which seem to be worth mentioning includes stress, immunosuppression, underlying systemic disorder, co-infections, secondary lesions, opportunistic infections, older age, slight female predilection, poor oral hygiene, severity of COVID-19 infection, vascular compromise, treatment related lesions, hyper inflammatory response secondary to COVID-19. Hence, we can conclude that there are some lesions having direct association with SARS-CoV-2 virus and in some it has a great contributory effect with other etiopathogenesis keeping in mind.

Stress or emotional distress playing a major part in development of oral lesions must not be neglected in the era of COVID-19. So, its high time for all the generations to keep their mind free from any negative thoughts, have healthy food and music therapy, have social contact, meditation and exercising, and discussing positive news.

Oral health management is also necessary and regular follow up and a visit to the dentist can help decrease most of these oral lesion's progress by early detection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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