Review Article

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Oral cavity lesions in COVID-19 patient- a neglected and morbid clinical entity in current pandemic

Santosh Kumar Swain*

Department of Otorhinolaryngology and Head & Neck Surgery, IMS and SUM hospital, Siksha "O" Anusandhan University, K8, Kalinga Nagar, Bhubaneswar, Odisha, India

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*Correspondence:

Dr. Santosh Kumar Swain,

E-mail: santoshvoltaire@yahoo.co.in

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) is highly contagious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 infections are usually associated with acute respiratory symptoms along with fever, myalgia, fatigue, altered taste and smell sensation. However, some oral cavity manifestations have been found in COVID-19 patients. There is debate whether these oral cavity manifestations are due to SARS-CoV-2 infection or secondary to patient's systemic condition. Currently research shows that SARS-CoV-2 affect the respiratory tract and other organs those have angiotensin converting enzyme 2 (ACE2) receptors. ACE2 receptors are abundantly present in the oral cavity tissues which prone for SARS-CoV-2 infection. The oral cavity lesions in COVID-19 patient ranges from ulcers in the oral cavity to candidiasis, recurrent herpes simplex, geographical tongue, mucositis and petechiae. COVID-19 infection significantly affects the oral cavity and salivary glands. Gustatory dysfunction or dysgeusia is a common oral cavity manifestation of COVID-19 patient. Clinicians should keep in mind about different lesions of the oral cavity and taste disturbances of the COVID-19 patients which will help the early diagnosis, treatment and avoid morbidity of the patient. There is still debate on exact cause for oral manifestations of the COVID-19 infections and its impact. This review article discusses the details of this neglected clinical entity such as oral cavity lesions in COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, Oral cavity, Aphthous ulcer, Candidiasis, Dysgeusia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection is a fatal disease and considered as global public health emergency. COVID-19 infection is associated with wide range of the disease patterns which ranges from mild to life threatening pneumonia. COVID-19 pandemic is currently evolving and associated with more complication with involvement of the oral cavity lesions. In early part of the COVID-19 pandemic, it was thought that absence of the oral cavity involvement is a differentiating point of the COVID-19 exanthema in comparison to the other viral exanthemas. Patients with COVID-19 infection present with wide ranges of symptoms and signs. There are oral cavity lesions found in COVID-19 patients which often neglected

by the treating clinicians. If the oral cavity lesions are neglected, these may result in increase of morbidity among the COVID-19 patients. The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) directly or indirectly affect the oral cavity of the patient The treatment of the COVID-19 infections may result in certain adverse effects in the oral cavity leading to ulcerations, recurrent herpes simplex infections and xerostomia due to reduced salivary flow.³ Currently, SARS-CoV-2 has been found from the saliva of the COVID-19 patients and it has been demonstrated that reverse transcriptase polymerase chain reaction (RT-PCR) from the saliva which is more sensitive test than nasopharyngeal swab test.⁴ The first entry point of the SARS-CoV-2 which infect the respiratory tract is the oral cavity of COVID-19 patient.⁵ There are no robust

epidemiological studies are lacking for oral cavity diseases or lesions in COVID-19 patients, indicating that these medical entities are neglected.

METHODS OF LITERATURE SEARCH

The research articles related to the oral cavity manifestations or oral lesions in COVID-19 patients were searched through multiple approaches. First, we conducted an online search of the PubMed, Scopus, Google Scholar and Medline databases with word oral cavity manifestations, COVID-19 infections, ulcerative lesions of oral cavity, gustatory dysfunction and candidiasis in COVID-19 patients. A search strategy using preferred reporting items for systemic reviews and meta-analysis guidelines was developed. Randomized controlled studies, observational studies, comparative studies, case series and case reports were evaluated for the eligibility. Review articles with no primary research data were also excluded. The abstracts of the published articles were identified by this search method and other articles were identified manually from the citations. This review article focuses only on oral cavity lesions in COVID-19 patients. This review article reviews the epidemiology, etiopathology of the oral lesions by SARS-CoV-2 virus infections, different oral cavity lesions and its management in COVID-19 patients. This review article presents a baseline from where further prospective trials can be designed and help as a spur for further research in this important clinical aspect as oral cavity lesions of the COVID-19 patients where not many studies are done.

EPIDEMIOLOGY

Approximately 10% of the COVID-19 patients develop severe acute respiratory syndrome and 1 to 2% of elderly age group die.6 There are certain possible oral cavity symptoms are found in the COVID-19 patients. Ageusia or dysgeusia is the first documented oral cavity symptom in approximately 38% of COVID-19 patients, mostly in North Americans and Europeans, female and patients with mild to moderate disease severity. Approximately 7% of the patients with RT-PCR positive have plaque like changes in the dorsum of the tongue.8 There are no exact documentation regarding the percentage of patients of COVID-19 infection presenting with oral cavity lesions except few case reports. As there is similarity of the oral lesions to the skin lesions, it is thought that their prevalence is almost same. One study documented the prevalence of the skin lesions in patients with COVID-19 infection is 1.8% to 20.4%.10

ETIOPATHOLOGY

The exact etiology for oral cavity lesions in COVID-19 patients is still uncertain. The etiology is thought to be multifactorial. The diseases or lesions at the oral cavity of COVID-19 patients may be related to direct or indirect action of SARS-CoV-2 on the mucosal cells of the oral cavity, hypersensitivity of the medications used in the

treatment of COVID-19 infection or due to lowering of the general condition of the health of the patient by the diseases itself or by prolonged hospitalization.9 Respiratory tract is the main door of entry of SARS-CoV-2 and it is thought that oral cavity mucosal cells are first cells to be affected by the virus. 11 One study showed that high expression of ACE-2 receptors is found in oral mucosal cells, resulting infection of these cells. 11 Reduced general health conditions of the COVID-19 patient predispose to the oral lesions such as opportunist infections like candidiasis and herpes. 12 Prolonged hospitals stay increased the risk for oral diseases, reinforcing the importance of proper oral cavity hygiene during hospitalization. SARS-CoV-2 attacks human cells through ACE-2 receptors as current data indicate that ACE-2 acts as the primary host cell receptors for this virus.¹³ This virus binds to ACE-2 with helps of spike like protein on its surface and this ACE-2 will act as a cellular portal for entry of the virus and results in COVID-19 infection.¹⁴ The organs with high ACE-2 expressions like lower respiratory tract can act as target cells for SARS-CoV-2 infection which leads to inflammatory reactions at the organs such as salivary glands and tongue which result in loss of taste sensation and formation of oral ulceration by destruction of keratinocytes and oral fibroblasts. 15 High viral load in the saliva and nasal secretion can be a etiopathogenic factor for developing the oral cavity changes associated with COVID-19 infection, which shows the direct impact of the virus on the oral tissues. 16 Presence of the SARS-CoV-2 virus in the saliva is reason why the common mode of transmission is the inhalation of droplets from the infected patient. However, all COVID-19 positive patients will not present with oral cavity lesions because of the difference in the expression of ACE-2 in oral cavity tissues.17

Medications for COVID-19 infections may be associated with adverse outcomes concerning oral cavity, resulting in various opportunistic infections such as candidiasis, herpes simplex virus (HSV-1), non-specific oral ulcers, fixed drug eruptions, dysgeusia, dry mouth/xerostomia and gingivitis because of impaired immune system and/or susceptible oral cavity mucosa. 18 In COVID-19 infection, the cytokines storm and unregulated Th17 immune response may be associated with adverse outcomes in the oral cavity. 19 In COVID-19 patient, raised levels of tumor necrosis factor (TNF)- α lead to chemotaxis of neutrophils in the oral mucosa and development of aphthous like lesions. Immunosuppression and stress secondary to COVID-19 infection may be possible causes for development of oral lesions. 20

CLINICAL MANIFESTATIONS

COVID-19 patients often present with the different clinical manifestations such as fever, headache, myalgia, cough, fatigue, dyspnea and gastrointestinal complaints.²¹ COVID-19 patients with oral cavity lesions often complain of sores in the mouth. Patient with oral cavity lesions is usually present with dysphagia or odynophagia.

Important oral related symptoms include hypogeusia, xerostomia or dry mouth and chemosensory alterations.²² On examinations, painful ulcerations are found at buccal mucosa, palate and tongue. Besides ulcerated lesions, multiple reddish macules of different sizes are often scattered over the palate, lips and tongue. Taste disturbance may be considered as the most relevant and early oral cavity manifestation in COVID-19 patients.

Gustatory dysfunction is probably best-known oral cavity manifestation of COVID-19 patient.²³ Dysgeusia is the first recognized oral cavity symptom of the COVID-19 patient in approximately 38% of the patients, mostly in Europeans, American's females and patients with mild to moderate disease severity.²⁴ Loss of taste sensation (ageusia) occurs in the viral infection of the olfactory cranial nerves or because of the rhinitis and nasal block. Ageusia is often associated with loss of smell (anosmia). Anosmia is associated with retro-nasal olfaction which is a sensory process, combining ortho-nasal smell and taste patterns and help to perceive the flavor. This mechanism is usually disturbed temporarily at the time of upper respiratory tract infection because of the mucosal inflammation and blockage of the nasal passage, so directly obstruct flavor and odour molecules from entering the olfactory cleft.²⁵

Patients with COVID-19 infection may present with blisters or ulcers or diffuse reddish lesions which involve keratinized and non-keratinized tissues of the oral cavity. These lesions of the oral cavity are found on the palate, lips, buccal mucosa and tongue. ²⁶ Presence of oral cavity lesions are simultaneously found with loss of taste and smell in patients. Severe form of oral cavity manifestations may be reported in elderly aged patients and in severe and disseminated types of oral cavity lesions. ²⁷

The oral cavity diseases/lesions in COVID-19 patients have no special predilection to any genders and more found in age group. The clinical presentations are quite heterogenous with variations in the nature and locations of the lesions.²⁶ Aphthous like lesions is most prevalent in the oral cavity of COVID-19 infection. Erythema is a T-cell mediated immune condition which is associated with a young to middle aged person. Erythema is predominantly found in boys.²⁸ Aphthous like lesions in the oral cavity are seen as multiple shallow ulcers (Figure 1) with erythematous halos and yellowish to whitish pseudo membranes on the both non-keratinized and keratinized mucosa of the oral cavity. Aphthous like lesions without necrosis are found in patients with mild infection while aphthous like lesions with necrosis and hemorrhagic crusts are found more commonly in elderly age group with immunosuppression and severe infections. These lesions are usually healed by 5 to 15 days.²⁹

Whitish and reddish patches or plaques may be seen on the dorsum of the tongue, gingiva and palate of COVID-19 patients. These whitish patches are usually due to candidiasis which often occur due to long term antibiotic

therapy, poor general health status and reduced oral hygiene.³⁰ COVID-19 patients may present with lip swelling, fissured tongue and facial nerve paralysis, which is called Melkersson-Rosenthal syndrome. This patient is usually cured completely after treatment of COVID-19 infection.³¹ In COVID-19 patients, petechiae may be found on the palate, lower lip and oropharynx. The latency period for patients of petechiae is shorter in comparison to the patients with both petechiae and macular lesions. Thrombocytopenia in COVID-19 infection or certain drugs prescribed are the cause for petechiae.³²



Figure 1: COVID-19 patient showing multiple aphthous ulcers in the oral cavity.

COVID-19 patient may present with halitosis, submandibular gland lymphadenopathy and oral lesions. The oral cavity lesions may include diffuse erythematous lesions, painful oedematous gingiva and necrosis of interpapillary areas.³² The clinical diagnosis of necrotizing periodontal disease may occur by bacterial infection along with COVID-19 infection. These oral lesions recovered usually after 5 to 7 days.³² There may be nonspecific lesions found in the oral cavity of COVID-19 patient and the lesions may include diffuse erythematous lesions (Figure 2), papules, patches and plaques on the lip mucosa, tongue, hard palate and oropharynx. Immunosuppression and stress are often associated with COVID-19 infection which result in appearance of the secondary type of herpetic gingivostomatitis.33 In some cases, COVID-19 positive patients present with blisters in the lip mucosa, desquamative gingivitis and skin rashes.



Figure 2: COVID-19 patient showing diffuse erythematous lesions on palate.

ORAL CAVITY LESIONS AND ITS EXAMINATIONS

Clinical examinations of the oral cavity may show several painful ulcers with irregular margins with varying sizes with red and non-hemorrhagic background. These ulcerative lesions are usually seen on anterior two-third part of the tongue. Sometimes, the ulcers almost involve the palate and floor of the oral cavity. Sometimes along with oral cavity lesions, COVID-19 patients may present with skin manifestations. Ulcerative or erosive lesions with irregular borders are found on the palate, tongue, buccal mucosa and lips (Figure 3). Drug eruption, vasculitis or thrombotic vasculopathy secondary to COVID-19 infections are thought to be the cause for development of erosive or ulcerative lesions in the oral cavity.³⁴



Figure 3: COVID-19 patient presenting with ulcerations on lips.

Proper examination of the oral cavity is often challenging for clinicians in COVD-19 patients. The examination of the oral cavity of COVID-19 patients require use of personal protective equipment (PPE).³⁵ PPE includes hand hygiene, gown, face mask, face shield and hand gloves. There are different levels of the PPE such as standard, contact, droplet and airborne precautions. The guidelines for standard precautions by centre for disease control and prevention (CDC) include hand hygiene, respiratory hygiene with cough etiquette, proper placement of the patient, cleaning of the equipment, devices, environment and laundry as well as safety procedures.³⁶ The contact precautions are usually used when the transmission of infection through direct contact with infected person or with contaminated items or body fluids. Contamination of the mucous membranes is the most important method for transmission of the infection.³⁷ So, respirators and goggles are essential to provide a tight seal and minimize the chance of direct aerosol transmission and also prevent accidental self-contamination by touching the mucosal surfaces. Full face or hood powered air purifying respirators (PAPRs) are specially made to provide even higher protection to the health care workers against hazardous particles and minimize the risk of the potential face seal leakage, particularly in those who cannot be successfully fit tested with help of respirators.

DIAGNOSIS

Biopsy can be done from the ulcerative lesions of the oral cavity with hematoxylin & eosin (H&E) staining. The histopathology often shows tissue diffuse edema with mucosal desquamation along with ulcerations and granulations under the mucosal lining with invasion of the mononuclear cells with large and glassy nuclei. There may be invasion of the neutrophils in case secondary bacterial infection. The serological tests can be done for herpes simplex virus type 1 and type 2 antibodies. Reverse transcriptase polymerase chain reaction (RT-PCR) is helpful for confirmation of SARS-CoV-2 infection. 38 Nasopharyngeal samples are usually collected for RT-PCR. Chest X-ray or computed tomography (CT) scan is done to find out the pulmonary pathology in COVID-19 patient. ³⁸ Serum samples can be sent for antibody testing. Viral cultures are not recommended test.

TREATMENT

Topical medications like mixture of dexamethasone, diphenhydramine, tetracycline and lidocaine are used to cure the oral symptoms. The ulcerative lesions are healed usually after one week of the treatment without any evidence of scarring.³⁹ Along with treatment for oral lesions, COVID-19 positive patients should be treated with remdesivir or azithromycin, corticosteroids and other supportive treatment. Local antiseptics like hydrogen peroxide-based suspension are important choice to reduce the viral burden.⁴⁰ The clinicians like dentist or otolaryngologists should follow strict precautionary such as wear personal protective equipment during examining the oral cavity of COVID-19 patients. The hypersensitivity reaction in the oral cavity or vaccination for COVID-19 infection may be the cause for oral cavity lesions, which should be carefully taken into consideration for managing such lesions. The drug which causes oral cavity manifestation in COVID-19 patients should be stopped. The adverse effects by vaccine for COVID-19 particularly in the oral cavity should be treated immediately. As stress is an important factor for triggering the oral ulcers or aphthous ulcer (stress ulcer), the psychological counselling is helpful for healing of these types of ulcers in the oral cavity.⁴¹ There is a large gap in the understanding of the etiopathogenesis, epidemiology, clinical manifestations and treatment of the COVID-19 infections and oral cavity lesions. There should be continuous monitoring and physical examination of the oral cavity in COVID-19 patients and early management.

CONCLUSION

COVID-19 infection can cause different oral lesions. These patients must require examination of oral cavity. Lack of oral hygiene, stress, opportunistic infection underlying diseases like diabetes mellitus for manifesting oral lesions in COVID-19 patients. Clinicians should keep these oral cavity lesions in mind during examination of the COVID-19 patients. Appropriate treatment of the COVID-

19 infections and maintaining oral hygiene will help to improve the oral cavity lesions. The comorbidities of the COVID-19 patients such as old age, diabetes mellitus, hypertension and stress are strongly associated with poor prognosis which trigger the lesions in the oral cavity. The oral cavity of the COVID-19 patients should be evaluated in case of prolonged hospitalization or immunosuppressive status which may help to patient's recovery.

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