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"Oral Manifestations of COVID-19"

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ABSTRACT: COVID-19 is member of family Coronaviridae, which during 1st wave had different oral manifestations like athous stomatitis, herpes labials, herpes simplex, herpes zoster. These oral manifestations were due to anxiety, stress& continuous fever in COVID patients. But during 2nd wave due to use of steroids, long term hospital stay & contaminated oxygen cylinder use, oral manifestations like oral candidiasis & mucormycosis were mostly reported. This Review is an effort to highlight the important oral manifestations that were during COVID ERA.

KEYWORDS: COVID, ORAL MANIFESTATIONS, MUCORMYCOSIS

Introduction:

SARS-CoV-2, the agent of COVID-19, is a member of the family Coronaviridae. It belongs to the Betacoronavirus subfamily, together with two other highly pathogenic viruses, SARS-CoV and MERS-CoV. It is a positive-sense single-stranded RNA (+ssRNA) virus with envelope-anchored spike protein receptors that facilitate its entry into host cells. Angiotensin-converting enzyme 2 (ACE2) is the main receptor involved in COVID-19 pathogenesis. It is abundantly present on the ciliated cells of the airway epithelium, or alveolar type 2 cells, which are the primary sites attacked by the virus. Direct contact with patients and their respiratory droplets is a well-known mode of transmission.[1]

The most common symptoms reported by patients with COVID-19 are fever; respiratory symptoms, such as a cough or shortness of breath; and general fatigue. Other less common symptoms include headache, taste distortion, anosmia, and sore throat. Moreover, some patients present with gastrointestinal symptoms, such as diarrhoea, nausea, or vomiting. The severity of these symptoms depends on many factors, such as the time of exposure to the virus and the patient's age and gender, as well as the presence of coexisting diseases. Investigators found that patients with autoimmune diseases were more prone to the infection.[2]
66.7% of the prevalence studies reported primary oral manifestations directly due to COVID-19 like taste alterations, xerostomia, and salivary gland diseases. One prevalence study conducted showed an increase in the incidence of Herpes Zoster cases during Covid pandemic times.[1]
While four observational studies (19.04%) showed multiple secondary oral manifestations like sialadenitis, dry mouth, mucocutaneous lesions, aphthous ulcers, enanthem, opportunistic infections like mucormycosis, aspergillosis, oral pseudomembranous candidiasis, geographic tongue, coated tongue. Significantly, in at least two questionnaire-based surveys, Temporomandibular disorders (TMD) were found to be increased, emphasising the psychological impact of COVID-19.[2]
Additionally, oral mucosal lesions were presented only in case reports and case series. These included primary manifestations probably caused directly by SARS-CoV-2 and secondary manifestations caused as a sequelae and treatment of COVID-19 infection. Infection like oral ulcers, angina bullosa hemorrhagica, burning mouth, erythematous macules, plaque-like changes in the tongue, masticatory muscle pain, acute infectious par otitis and secondary manifestations like facial palsy, enanthem resembling petechiae without erythema, Melkersson-Rosenthal syndrome, Bell's palsy, par otitis, Guillain-Barre syndrome, secondary herpetic gingivostomatitis, macroglossia, and trigeminal neuralgia.[1]
However, various oral manifestations of COVID-19 reported till date has different pathogenesis. Dysgeusia (altered taste), hypogeusia (diminished sense of taste) and ageusia (complete loss of taste) were the most commonly reported initial symptoms even before the diagnosis of COVID-19 was confirmed. The most probable pathogenesis of taste disturbances in COVID-19 is due to peripheral neurotropism and direct toxicity to taste buds or olfactory epithelium. Other contributory factors may include inadequate saliva, pro-inflammatory cytokines, angiotensin II accumulation, systemic diseases, hypozincemia, and excessive use of chemicals. Also, published studies state that angiotensin-converting enzyme 2 (ACE 2) cell receptors are expressed in abundance on respiratory epithelium and oral mucosa, mainly dorsal surface of the tongue.[3]
Hyposalivation is one of the most common symptoms present in almost all the patients of COVID-19 and one of the important reasons for candida infection on tongue. Several theories explain this association. The ACE-2 receptor is abundantly expressed on the epithelial cells of the salivary glands, and when infected by SARS-CoV2, these receptors are overexpressed ending in acute and chronic sialadenitis and causing disruption in salivary secretion and xerostomia.[4]

During the COVID-19 pandemic, clinically significant candidiasis has been reported. In India, Candida species was the third common pathogens (4.1%) of secondary bloodstream

infections among patients with COVID-19, following Klebsiella pneumoniae (10.9%) and Acinetobacter baumannii (8.8%). Moreover, another study in central India found that the incidence of secondary infections caused by Candida species (24.3%) was the same as that due to A. baumannii complex. Several risk factors, including lung injury, immunosuppression, the need for oxygen therapy, monoclonal antibodies, and steroid therapy, predispose the cases of COVID-19 to fungal infections. COVID-19 patients showed an impaired immune response, including decreased upregulation of monocyte CD80, and impaired release of interleukin (IL)-6, Tumor necrosis factor (TNF), IL-1α, and IL-1β toward C. albicans infection.[5]

Covid patients already have compromised immunity and presence of comorbidities, stress, and anxiety lead to further immune suppression resulting in reactivation of Herpes Simplex Virus 1 or Herpes Zoster virus. Herpes Labialis typically presents as multiple vesicles in clusters on lips which rupture after 3 days and convert into irregular ulcers.[6]

Putra (2020) reported presence of aphthous stomatitis in Covid patients. In study by Goel et al (2022) aphthous stomatitis was seen in 14.2% of Covid patients. All patients had minor aphthae appearing as shallow, round, well defined ulcers measuring less than 1 cm in diameter having characteristic erythematous halo. These ulcers were present mainly on buccal mucosa or tongue. Development of anxiety and stress associated with this pandemic disease triggers formation of aphthous stomatitis especially in patients with strong autoimmune component. Interestingly, Aphthous ulcers associated with COVID-19 tend to occur in younger patients with mild symptoms concurrent or slightly preceding systemic manifestations.[7]

Immune dysregulation and cytokine storms remain the hallmarks of the recent COVID-19 pandemic caused by spread of SARS-CoV-2. It is suggested to be alike autoimmune diseases in terms of its pathogenesis, manifestations and immune responses. This led to initial identification of ‘immune mediated inflammatory diseases’ patients as a high risk group for contraction of SARS-CoV-2. Nevertheless, the debilitating attack on the immune system by SA Since immune dysregulation is common to OLP and COVID-19, it increases possibility of oral lichen planus as a part of the spectrum of post-COVID conditions. SARS-CoV-2 can render the patients susceptible to various co-infections and superinfections.[8]

The excessive production of reactive oxygen species (ROS) in the mucosal tissues of severely ill COVID-19 patients may explain the significant direct association between severity of COVID-19 and mucositis duration and pain intensity. Secondary infections and drug reactions cannot be ruled out entirely, especially with severely ill patients due to immune dysregulation. In addition, oral mucosal changes were consistently observed in children with pediatric multisystem inflammatory syndrome temporally associated with SARS- COV-2 (PIMS-TS), which is suggested to be linked to IgG antibody-mediated enhancement.[9]

Erythema multiforme (EM) is a skin disease characterized by the appearance, usually on the extremities but often also occurring in other skin areas, of reddish, annular macules, which later become papules, sometimes coalescing to plaques. Drug-induced EM in COVID-19 patients has been related to hydroxychloroquine and has been reported to appear 3 to 10 days after starting the treatment. Drug discontinuation and systemic corticosteroid led to resolving the symptoms. A case also reported the possible link between EM appearance and

azithromycin. The association between the mRNA-1273 (Moderna) COVID-19 vaccine and bullous drug eruption resembling EM has been described. Hydroxychloroquine may also induce a generalized, pustular, and figurate rash, thus clinically resembling EM. Angina bullosa hemorrhagica (ABH) is an uncommon disorder appearing as hematic blisters in the oral and oropharyngeal region. The etiopathogenesis of this lesion is yet unknown and considered multifactorial. However, local trauma of the oral mucosa is the most commonly cited etiology in literature. Most common site of this lesion is the palate; however, it is also seen on labial mucosa, buccal mucosa, and tongue. ABH occurring in patients with diabetes mellitus and hypertension has already been described in literature.[10,11]

Literature suggests that immune-inflammatory processes have been associated with hyperpigmentation of melanin from oral mucosa. Different factors produced during inflammation such as prostaglandins, leukotrienes, cytokines, and inflammatory mediators, may play a role in this response and increased melanogenesis in Covid patients.[9]

Cases have been observed and published where facial palsy was the first symptom observed in SARS-CoV-2 patients and it was suggested that peripheral facial palsy should be added to the spectrum of neurological manifestations associated with COVID-19.[13]

Paroxysmal lancinating pain was found in the right VI region that lasted a few seconds and was triggered by a light touch of the skin at a specific point on the scalp in a 65-year old patient, suggesting SARS-CoV-2 as a possible aetiology of secondary trigeminal neuralgia. However, more studies are needed to establish the neuropathology of this viral infection.[14]

In a 51-year old hospitalised female patient, the right lower lip was hyperaemic and showed firm oedema extending towards the jaw, right facial paralysis and fissured tongue, suggestive of Melkersson-Rosenthal syndrome. It was concluded that activated mast cells may play a significant role in the pathogenesis of COVID-19 infection, as they release cytokines in the lungs and may be a probable etiological factor for this presentation.[16]

Mucormycosis has emerged as a rapidly occurring fungal infection with high mortality. It is caused by a group of filamentous melds within the order Mucorales. Rhizopus is the most common genus associated with mucormycosis among all Mucorales class, followed by Mucor and Lichtheimia. These fungi come into contact via inhalation or ingestion of sporangiospores, and they also enter the human body through puncture wounds and trauma. Healthy individuals have sound defines systems with intact mononuclear and polymorphonuclear cells that kill these fungi. Patients with neutropenia or defective phagocytic activity are prone to mucormycosis.[15]

The global prevalence of mucormycosis varies from 0.005 to 1.7 per million populations, while the prevalence is around 80 times higher, with 0.14 per 1000, in India compared to high-income countries, as of 2020. Notably, India has documented the highest number of mucormycosis cases in the world. However, as the second-largest population in the world with high diabetes mellitus (DM) cases, in addition to being the DM capital of the world, the risk for developing the fungal disease is Multifood. Mucormycosis is an invasive opportunistic fungal infection mainly affecting the vasculature of the host organism by hyphae. Different predisposing factors such as hematologic malignancy, neutropenia, systemic corticosteroid use, uncontrolled diabetes, chronic renal failure, stem cell

transplantation, and immunocompromised state, play a vital role as the risk factors in the development of the disease.[16]

Mucormycosis presents with different clinical manifestations like rhino-cerebral manifestation, respiratory manifestation, cutaneous manifestation, gastrointestinal manifestation, disseminated disease, and other manifestations like endocarditis and central nervous system invasion. Mehta and Pandey, in their study, reported that COVID-19 is a culprit of secondary infections due to immune dysregulation because of the widespread use of monoclonal antibodies, broad-spectrum antibiotics, corticosteroid, poor ventilation, and reduced number of T- lymphocytes.[16]

In India's second wave of the COVID-19 pandemic, there is a surge in mucormycosis with clinical manifestations like vision loss, brain abscess, and stroke, increasing the mortality rate in patients with COVID-19. In India, 8848 cases of mucormycosis are documented. 52 deaths were recorded among 1500 cases of mucormycosis in Maharashtra state only.[1,16]

This typical infection affects immunocompromised and diabetic patients most of the time and the symptoms of this deadly infectious condition depend on the site of origin, but generally facial structures (nose, sinuses, eye, and brain) are most involved. The symptoms associated with rhino-orbital-cerebral mucormycosis (ROCM) are of varying degree (runny nose, unilateral or bilateral facial swelling, orofacial pain, low to high grade fever, headache, blurred vision due to proptosis and involvement of orbital contents, loosening of teeth, destruction of periodontal tissue and appearance of black necrotic eschar or dead bone in the palate, buccal vestibule or the maxillary alveolus along with formation of oro-nasal/oro-antral communication).[1]

Although mucormycosis is reported rarely in the localized forms, more recently, several publications have described the clinical management and outcome of mucormycosis infection in the maxillofacial region, for example, the tongue, palate, mandible, maxilla and orbitomaxillary/infra-orbital region. Therefore, mucormycosis should be considered as a possible diagnosis in case of any spontaneous soft tissue necrotic lesions of orofacial area. In head and neck sites, mucormycosis begins by involving maxillary bone or nose and later directly extends to paranasal sinus and from there, spreads to retro-orbital tissues and can disseminate to eye, brain, lungs and to other body organs. Therefore, it is crucially important to understand the etiology to make an early diagnosis to provide an optimum treatment of the underlying predisposing factors and appropriate medical and surgical interventions.[15]

The successful treatment of mucormycosis is always challenging and is based on various approaches, including early diagnosis, discontinuation or reversal of underlying predisposing factors, early and optimal dosage of an active antifungal, and debridement of all the infected tissues. In diabetes mellitus and suspected mucormycosis patients, early and rapid correction of diabetic ketoacidosis is mandatory with judicious use of fluids, sodium bicarbonate, and insulin. Immunosuppressant drugs and Corticosteroids should be tapered abruptly to the lowest possible dose. Additionally, surgical debridement is recommended at earlier stages to remove necrotic and healthy infected tissue. Other modalities such as hyperbaric oxygen to provide oxygen-enriched medium and cytokines are administered along with antifungal therapy.[1]

Awareness of the various oral lesions in COVID-19 is important as these may be the only sign in asymptomatic patients. Oral manifestations of COVID-19 are common in female patients and are linked to specific general COVID-19 symptoms. Taste distortion, xerostomia, candidiasis and oral ulcerations are the most reported oral manifestations. Dentists and other health practitioners should be careful during dental examinations because oral manifestations of COVID-19 may emerge before the onset of general symptoms of COVID-19. Dental professionals may also promote awareness of the common oral manifestations of COVID-19, which may persist for long durations, and provide the proper management and medical attention for them[16].

CONCLUSION

Though, increasing number of patients are reporting oral manifestations in COVID-19, but, it still remains ambiguous whether they are directly due to the deadly infection or are merely seen as secondary presentation during the treatment or due to vaccination. In the current scenario of rapidly changing and new mutated strains of COVID-19 virus, more high-quality prevalence studies are required to be conducted to find a causal relationship between oral symptoms and this highly contagious virus.[16]

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