ORIGINAL RESEARCH

Oral Manifestations in Hospitalized COVID Patients

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Abstract

Aim: Evaluation of oral lesions in COVID-hospitalized patients, analyzing the potential etiopathogenetic mechanisms.

Materials and methods: We evaluated a total of 58 hospitalized COVID patients in the time span from April 2021 to May 2021. The group analyzed consists of 38 male patients (66%) and 20 female patients (34%), aged between 22 and 92, with a preponderance of 60–80 years. All patients underwent an oral evaluation in order to detect the various oral manifestations; moreover, the onset time of these lesions has been correlated with the time of manifestation of the general symptoms of COVID infection.

Results: Xerostomia has been the most frequent oral manifestation detected (30 patients, 51.7% of the sample), followed by ageusia (16 patients, 27.6%), and white tongue (13 patients, 22.4%).

Other oral manifestations observed were aphthous lesions, fissured tongue, metallic taste, tingling in the lip and chin, and burning mouth syndrome.

Conclusion: Our findings show a significant correlation between the oral manifestations and the burst of viral replication phase in COVID patients.

Clinical significance: Awareness of the possible oral manifestations of COVID infection is important to conduct a correct diagnosis in oral pathology.

Keywords: Ageusia, COVID-19, Oral manifestations, White tongue, Xerostomia.

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Introduction

Coronaviruses are a large cluster of viruses that infect upper respiratory tract in humans and cause common infections like cold and flu; their name originates from the presence of "club-shaped" surface projections of glycoprotein (Spikes) that confer a crown-like aspect to the virus particles.[1]

The three highly virulent pathogenic lineages (SARS-CoV, MERS-CoV, and SARS-CoV-2) cause severe respiratory distress syndrome leading to pulmonary insufficiency and serious systemic impairment.[2]

CoV virus reported firstly at Wuhan has been described as a new virus belonging to the β-CoV group and then named as new coronavirus (2019-nCOV) by Chinese researchers[3]; on 11th February 2020 this virus has been renamed by the World Health Organization as SARS-CoV-2 and the related illness has been indicated as COVID-19.

SARS-CoV-2 is a single stranded nonsegmented RNA virus and structurally has a spherical or pleomorphic shell.[4–6]

SARS-CoV-2 action occurs as a result of the interaction between surface glycoprotein Spike S and angiotensin converting enzyme (ACE)—2,[7] a membrane carboxypeptidase that is widespread in human tissues.

Spike S affinity for ACE-2 is far higher (10–20 times) than similar protein of SARS-CoV-1 affinity to ACE-2; moreover, ACE-2 expression depends on age, sex, and genetic factors, explaining the low case fatality rate (CFR) in pediatric patients compared to the patients older than 80 years (CFR 0 if less than 8 years and CFR 21.9% if more than 80 years). Unfortunately, ACE-2 expression also increases with comorbidities such as obesity, diabetes, chronic cardiopulmonary disease, cancer, and the use of immunosuppressant drugs: these patients, in fact, are inclined to develop serious diseases.[8]

Clinical presentations of COVID-19 range from asymptomatic and mildly-symptomatic forms to acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome.

Approximately 17.9–33.3% of COVID patients remain asymptomatic[9] while symptomatic patients report fever, cough, gasping and less frequently sore throat, anosmia, dysgeusia, anorexia, nausea, discomfort, myalgia, and diarrhea. Symptoms may appear after an incubation period ranging from 1 to 14 days, commonly between 4 and 7 days.[10]

Patients with severe COVID-19 illness can manifest ARDS commonly with an onset of 1 week after the initial symptoms. Spike protein interaction with ACE-2 activates the renin-angiotensin system provoking pulmonary damage with vasoconstriction, edema, leukocyte infiltration, apoptosis, and pulmonary interstitial fibrosis.[11]

Some patients with COVID-19 report gastrointestinal disorders such as nausea, vomiting, and diarrhea as the first symptoms. The gastrointestinal symptoms can be explained because ACE-2 is detectable in the epithelial cells of tongue, oral cavity, esophagus, ileum, and colon.[12]

Up to 12% of COVID patients undergo cardiac problems presenting as abnormal levels of cardiac enzymes, acute myocardial

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injury, and cardiac shock resulting from arrhythmia: in fact, ACE-2 is largely expressed in the cardiac cells also.[13]

Renal manifestations can manifest due to SARS-CoV-2 direct invasion of podocytes and tubular proximal cells; these patients tend to have a higher mortality.[14]

Recalcati in a study based on 88 COVID patients observed that approximately 20.4% of patients had dermatological manifestations.[15]

Moreover, around 14.8% of COVID patients had myalgia or arthralgia, mostly at the beginning of the disease.[16]

Another clinical condition that exacerbates COVID symptoms is diabetes, leading to higher probability to develop a severe COVID disease.[17]

The possible expression of ACE-2 enzyme in the oral cavity was evaluated and, thanks to particular immunohistochemical studies, it was possible to identify the presence of this receptor at the level of the squamous epithelium of the tongue, the taste buds, the gingival squamous epithelium, the submandibular and parotid glands, and in saliva. This could explain the presence of alterations at the level of the oral cavity.[18]

The aim of our study was to evaluate the presence of pathological alteration in the oral cavity in a cluster of hospitalized COVID patients, investigating the possible etiopathogenic mechanisms and differentiating these symptoms from the usual oral pathologies or dysfunctions that are not COVID related.[19–24] This argument represents an important field of search in oral pathology because the widespread of COVID infection could arise a large number of lesions in patients previously exempt from oral alterations; thus, the identification of a possible association between COVID infection and oral lesion represents the basis for a correct diagnosis and consequently a correct treatment plan.

Materials and Methods

In our observational study we examined a total of 58 hospitalized patients, admitted to the Infectious Diseases Department of San Gerardo Hospital (Monza, Italy) during the period from April 2021 to May 2021; our sample size was restricted only to hospitalized patients in order to obtain a significant evaluation of the possible oral manifestation during a severe COVID disease.

Inclusion criteria were positivity to COVID-19 verified with nasopharyngeal swab analyzed with polymerase chain reaction (PCR)-real time method and the consent to be examined for the purpose of our investigation.

Exclusion criteria were patients not able to answer our queries because of being sedated or patients referred to the departments for non-COVID related reasons.

Our study was conducted in accordance with the World Medical Association Declaration of Helsinki and all patients signed an informed written consent that allowed us to record the oral manifestations detected.

Each patient in this study underwent the same evaluation protocol, consisting of a data collection phase and a dental visit. The evaluation was characterized by:

- An initial phase in which the patients' demographic data and health histories were collected, in particular information regarding recent and past health status and habits, such as smoking. Subsequently, information regarding hospitalization for COVID-19 was collected, considering, in particular, laboratory tests and the type of treatment needed.
- A dental evaluation, in which, at first, the symptoms reported by the patients pertaining to the oral cavity were collected, correlating with the moment of onset with respect to the appearance of the general manifestations of COVID-19. Subsequently, a complete evaluation of the soft and hard tissues of the oral cavity was carried out, through the use of appropriate instruments. In case of presence of visible alterations, such as aphthous lesions, grooves, or white lesions on the tongue, a collection of photographic documentation was carried out, after procuring an adequate informed consent.

The dental visits were carried out in accordance with the protocols established in the COVID-19 departments, using the appropriate protective equipment for operator and patients.

Our sample consisted patients of different level of disease severity but all the patients were evaluated at the beginning of their hospitalization that coincided with the worsening of symptoms and thus the need for serious hospital therapies.

Once a diagnosis of oral lesion was established, the duration of those symptoms was recorded.

Moreover, we conducted a statistical analysis using Student's *t*-test, Chi-square test, or a Fisher's test, with a level of significance of $p < 0.05$.

Results

Patients who underwent our evaluations voluntarily took part in the study and were informed about the purposes of this survey. A total of 58 hospitalized COVID-19 patients were evaluated at the Infectious Diseases Department of the San Gerardo Hospital (Monza, Italy). In the group analyzed, 38 patients (66%) were male while 20 (34%) were female.

Patients were aged between 22 and 92 years and the age-group most analyzed was between 60 and 80 years (Fig. 1).

Figure 2 collects the main alterations in the oral cavity found in COVID-19 positive patients undergoing dental evaluation.

The most common alterations were xerostomia (51.7%) followed by ageusia (27.6%) and the presence of a white tongue (22.4%). Other manifestations identified include the presence of aphthous lesions (10.3%), tingling in the chin and lip (8.6%), the presence of grooves on the tongue (8.6%), the metallic taste of water and food (8.6%), and the burning mouth syndrome of the oral cavity (6.9%).

In addition, the period of onset of those manifestations in the oral cavity has been evaluated with respect to the appearance of general symptoms of COVID-19 (Fig. 3).

Alterations such as ageusia, aphthous lesions, burning of the oral cavity (or burning mouth syndrome), tingling of the lip and chin, and metallic taste, were reported by the patients in conjunction with the onset of the general symptoms of COVID and before being hospitalized. In particular, 11 patients (19%) said they had developed a dry oral cavity in conjunction with the general symptoms, in the same way only three patients (5.2%) and two patients (3.4%) reported, respectively, the appearance of a white tongue and grooves on the tongue in the initial days of infection.

The duration of symptoms was also evaluated: aphthous lesions disappeared within 7 days while white tongue presented the longer duration until 19 days; the duration of symptoms are reported in Figure 4.

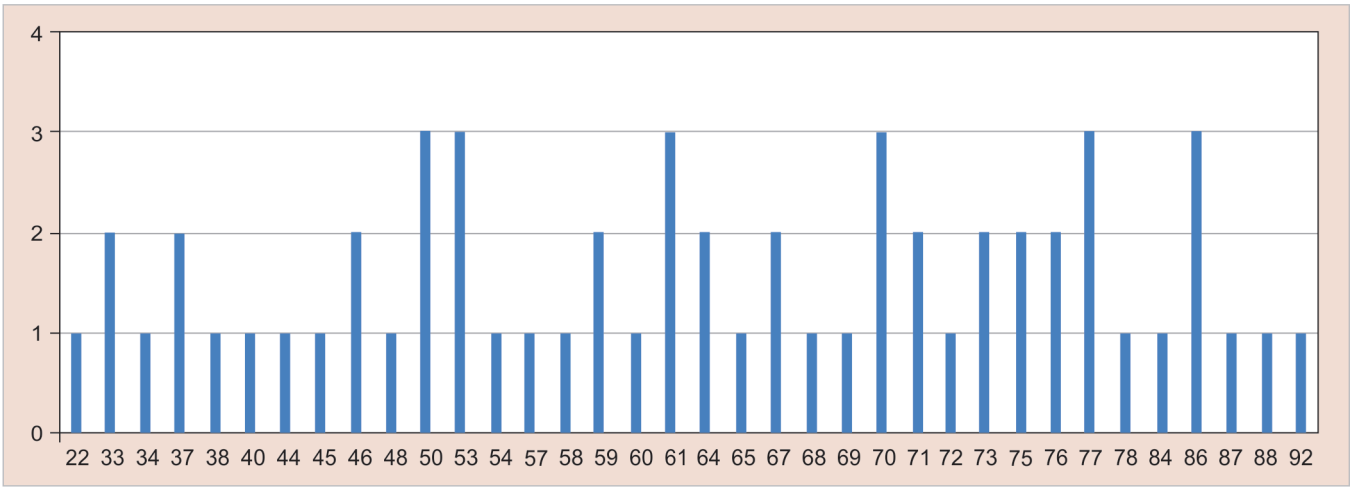

Fig. 1: Sample size distribution by age

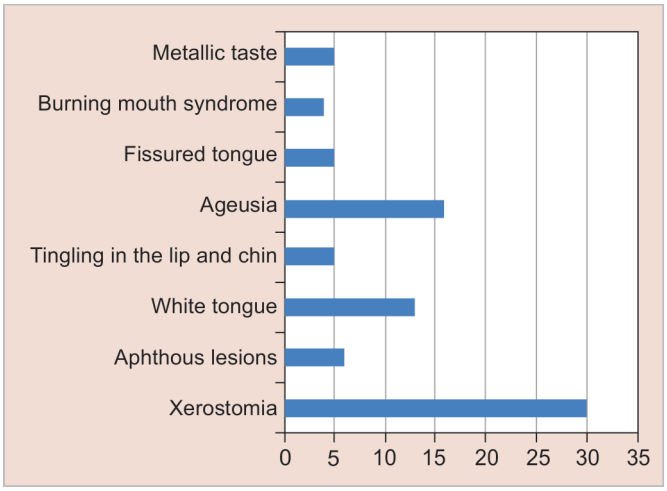

Fig. 2: Distribution of oral changes

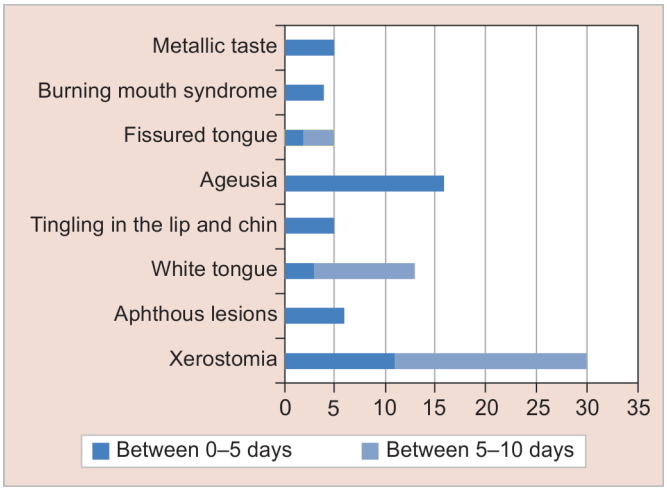

Fig. 3: Period of onset of oral changes

Moreover, we conducted a statistical analysis and the results are reported in Table 1; we noticed a statistical significant correlation between oral manifestations and arterial hypertension for $p < 0.05$.

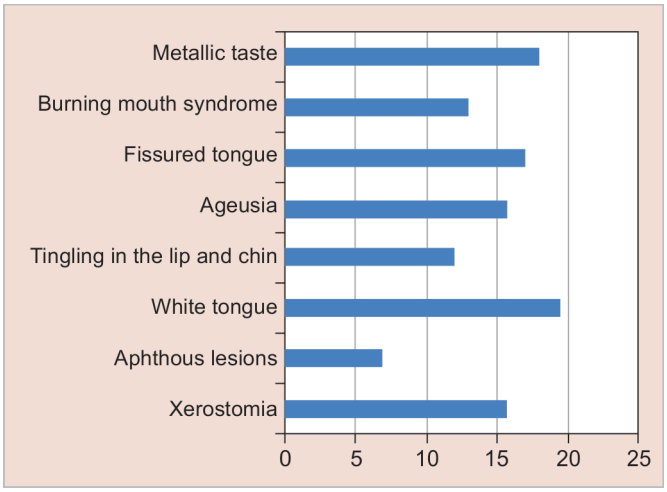

Fig. 4: Average duration of oral alterations

Discussion

COVID-19 disease is a viral infection with multi-organ manifestations characterized by complications of different severity. The first to report oral alterations and manifestations associated with COVID-19 were Chaux-Bodard et al.,[25] documenting a case report concerning an irregular lingual ulcer on the back of the tongue; since then, several articles on this subject have been published.

Ageusia, or loss of taste, is considered one of the characteristic symptoms of SARS-CoV-2 infection. In literature there are three systematic reviews that are focused in particular on gustatory dysfunction. In a first review by Aziz et al.,[26] the prevalence of ageusia/dysgeusia was estimated in 49.8%, while Amorim dos Santos et al.[27] found that the prevalence of dysgeusia, hypogeusia, and ageusia was 38%, 35%, and 24%, respectively; Cirillo et al.[28] indicated that the overall prevalence of gustatory dysfunction shows geographical differences ranging from 5.6 to 96%.

In our study, 16 patients reported a loss of taste and 27.6% reported ageusia as one of the first symptoms of infection. Ageusia has been reported more frequently than anosmia (25.9%). In addition, three patients (5.1%) said they perceived a loss of taste without a loss of smell, confirming that ageusia and anosmia are not necessarily related. The possible mechanisms of onset of loss of taste due to infection by SARS-CoV-2 are different: the

Table 1: Statistical analysis

	Overall	*With oral symptoms*	*Without oral symptoms*	
Variable	*N = 58*	*n = 42*	*n = 16*	*p-value*
Age	62 (55.8–66.2)	63.3 (58.9–67.7)	58.5 (48.2–68.8)	0.32
Gender				
Male	38 (65.5)	28 (66.7)	10 (62.5)	0.77
Female	20 (34.5)	14 (33.3)	6 (37.5)	
Comorbidity				
Diabetes	10 (17.2)	9 (21.4)	1 (6.3)	0.17
Arterial hypertension	19 (32.8)	17 (40.5)	2 (12.5)	0.04
Coronary artery disease	18 (31.0)	14 (33.3)	4 (25)	0.53
Chronic bronchopulmonary disease	11 (18.9)	10 (23.8)	1 (6.3)	0.12
Chronic kidney disease	4 (6.9)	3 (7.1)	1 (6.3)	0.90
Neoplasia	9 (15.5)	7 (16.7)	2 (12.5)	0.69
Smoking	15 (25.9)	10 (23.8)	5 (31.3)	0.56
Obesity	10 (17.2)	9 (21.4)	1 (6.3)	0.17

p value using Student's *t*-test (age) and the remaining variables using either Chi-square test or a Fisher's test.

epithelial cells of the mucous membrane of the oral cavity express ACE-2 receptors for SARS-CoV-2, in particular they were found mainly at the level of the back of the tongue and at the level of the gum tissues.[29] ACE-2 is responsible for the entrance of the virus in the cell and is expressed in the taste cells of the foliate and fungiform papillae of the tongue.[30] SARS-CoV-2 could directly damage the ACE-2 expressing cells of the taste buds during the virus entry process, resulting in taste dysfunction. Since the human salivary glands express ACE-2,[31] infection of the salivary glands with SARS-CoV-2 would affect the secretion of saliva, thereby altering the ability to perceive taste. In our study, eight patients reported dryness of the oral cavity together with loss of taste. However, only three of these patients reported to have developed xerostomia as one of the first symptoms of SARS-CoV-2 infection: it is possible, therefore, that the loss of taste is linked to damage of the papillae due to a reduced production of saliva.

The study on the effects of inflammation induced at the level of epithelial cells of the taste buds lead to the understanding that inflammation attenuates cell proliferation and interferes with the renewal of taste cells, suggesting that inflammation may be related to taste disorders associated with infectious diseases. It has therefore been hypothesized that SARS-CoV-2 infection may cause ageusia through virus-induced inflammation and release of proinflammatory cytokines.[32]

Neurological manifestations of COVID-19 are attributed to peripheral nervous system (PNS) and/or central nervous system (CNS) disorders.[33] Since SARS-CoV-2 can affect the nerves of the PNS, it is assumed that damage at the level of any of the cranial nerves involved (facial nerve and glossopharyngeal nerve) in the transmission of the gustatory stimulus induces gustatory dysfunction.

Several studies have highlighted the onset of xerostomia in COVID-19 positive patients. Among them, Fathi et al.[34] evaluated a total of 10 COVID-19 patients with signs of xerostomia. Surprisingly xerostomia, in about 60% of patients, appeared 1–4 days before hospitalization and administration of medications for management of COVID-19 symptoms. Also, Freni et al.[35] reported signs of xerostomia in 32% of COVID-19 patients in their survey. These researchers showed that in most cases xerostomia occurred before other symptoms of the disease, and the severity of the disorder decreased after 15 days.

Fantozzi et al.[36] reported xerostomia in 45.9% of patients as one of the first symptoms in 19.6% of patients with SARS-CoV-2 infection with a median onset time of 7 days (range: 4–7.8) before diagnosis of COVID-19.

In our study, xerostomia was the most frequent symptom in the oral cavity, affecting a total of 30 patients (51.7%).

The causes for which patients hospitalized for COVID-19 may develop a dryness of the oral cavity are different: it is known that certain medications induce the onset of xerostomia (lopinavir, ritonavir, and interferons).[37] It is also possible that the prolonged use of oxygen therapy may favor the onset of a feeling of dryness in the oral cavity. Moreover, anxiety and concerns related to being affected by the disease and hospitalization could be considered underlying factors for xerostomia in patients.[34]

In our study, 11 patients (19%) reported that the feeling of dryness in the oral cavity manifested itself as one of the first symptoms of the infection, before the beginning of specific drug therapies and before hospitalization. This fact leads to hypothesize a different etiology for xerostomia, directly linked to SARS-CoV-2 infection.

The entry of the virus inside the glandular epithelial cells involves the establishment of a series of mechanisms that lead to oxidative stress and apoptosis, resulting in damage to the salivary glands themselves with interference in the secretory function and resulting in xerostomia or reduced saliva flow.[31] SARS-CoV-2 could, in fact, cause acute sialadenitis by binding to ACE-2 receptors in the epithelium of the salivary glands and subsequently lysing the cells. However, the evaluation of patients affected by xerostomia did not reveal the characteristic manifestations of sialadenitis, such as swelling, redness of the skin, or expression of purulence from the excretory duct. It can therefore be assumed, in these cases, that inflammation of the salivary glands was not the cause of the reduced secretion of saliva.

The development of aphthous lesions at the level of the oral cavity has been reported several times in the literature. A study

conducted by Favia et al.,[38] in particular, observed aphthous lesions in 15.4% of patients, mainly on the tongue and palate. It was also observed that in most cases the onset of these oral lesions occurred within the first week after the onset of symptoms. In addition, Nuno-Gonzalez et al.[39] evaluated the prevalence of mucocutaneous lesions in 666 hospitalized patients, showing that the appearance of aphthous lesions in the oral cavity was present in 6.9% of cases.

In our study, six patients (10.3%) reported that they had been affected by aphthous lesions at the level of the tongue and buccal mucosa. In all observed cases the appearance of such lesions occurred in conjunction with the appearance of general symptoms of COVID within a duration of 5–10 days. Among the possible causes of the onset of aphthous lesions in COVID-19 patients we can identify the drugs administered to patients, poor oral hygiene during hospitalization, the stress related to hospitalization, and the decline of general health with suppression of the immune system and the consequent development of aphthous and ulcerative lesions. However, as previously highlighted, the patients evaluated in this study developed aphthous lesions before being hospitalized and starting drug therapies and in conjunction with general symptoms, consequently we can also hypothesize a possible direct damage caused by the virus itself.

It is believed that COVID-19 can induce the appearance of aphthous lesions thanks to the cytokine storm triggered by the virus itself characterized by an increase in several molecules including interleukin (IL)—2, IL-7, granulocyte colony stimulating factor, interferon-γ-inducible protein 10 (CXCL10), chemoattractiveness protein of monocytes (MCP1), macrophage inflammatory protein-1α (CCL-3), and, in particular, tumor necrosis factor-α (TNF-α). Studies of ACE-2 expression have found higher levels of expression in the surfaces of keratinized epithelial cells of the oral cavity, such as the back of the tongue and the hard palate, rather than in buccal or gingival tissues; this fact determines alterations at the level of the epithelial cells with a consequent increase in the permeability of the outer membrane and consequent apoptosis, leading, therefore, to the formation of aphthous or ulcerative lesions.[40]

Taste alteration is considered an early and temporary symptom of COVID-19.[41] However, many studies have overlooked or misunderstood the appearance of qualitative dysgeusia in COVID-19 positive patients. Parma et al. reported that about 7% of COVID patients developed some kind of taste distortion.[42]

In our study, the appearance of qualitative alterations in taste, described as metallic taste of water or food, affected five patients (8.6%). Similar to ageusia it is possible that qualitative dysgeusia is linked to a loss of smell, since patients with anosmia may report an altered perception of taste. However, only two patients experienced a loss of smell in conjunction with qualitative dysgeusia.

Usually, qualitative dysgeusia could develop as a result of using certain drugs; in particular the perception of a metallic taste is often associated with antibiotics. However, all patients that reported an appearance of taste alteration experienced it in conjunction with general symptoms, before starting a specific therapy. We can therefore exclude that drugs were responsible for the onset of this symptom, suggesting a mechanism induced by the virus itself.

It has been observed that serum zinc concentrations of COVID-19 patients, at the time of admission, were significantly lower than in healthy controls and it has been described in some studies that zinc deficiency can induce alterations in sweet, salty, and bitter taste. This is consistent with the qualitative taste dysfunction of COVID-19 patients.[31]

The development of a tongue characterized by a white coating has been included among the possible oral manifestations of COVID-19. Pang et al.[43] reported the frequency of white tongue in positive patients, dividing them according to the severity of the clinical picture (mild, moderate, and severe). The results showed a presence of white coating in 63.6% of mild patients, 54.9% of moderate patients, and 44.9% of severe patients.

In our study, white tongue was found in 13 patients (22.4% of cases). The causes are poor oral hygiene, especially for bed-bound patients or who are unable to practice proper correct oral hygiene operations, and xerostomia. In fact, eight patients reported a concomitant sense of dryness of the oral cavity together with the presence of a white tongue.

Direct damage induced by the virus due to the presence of ACE-2 receptors at the level of the epithelial cells of the taste buds can lead to the onset of inflammatory processes.[18]

Oral candidiasis has been recorded in numerous COVID-19 patients, and most of the reported cases had oral pseudomembranous candidiasis described as white plaque that extends mainly on the back of the tongue and oral mucosa, probably due to the weakening of immune defenses associated with the virus and the use of broad-spectrum antibiotics, corticosteroids, hydroxychloroquine sulfate, and vitamin D.[44] *Candida* infection, in our study, was found in one patient, in which the infection also extended to the esophagus.

Tingling in the lower lip and chin is a symptom of COVID-19 without clear evidence in literature. Gherlone et al.[45] highlighted the incidence of facial tingling in a reduced percentage of patients infected with SARS-CoV-2, identifying this symptom in 3% of the analyzed sample.

In our study, five patients (8.6%) reported the onset of tingling in the lip and/or chin. The appearance of this symptom occurred in all cases in conjunction with the general symptoms.

The burning sensation of the tongue or whole oral cavity, also called burning mouth syndrome, has been related to COVID-19. Sinjari et al.[46] reported 15% of patients with burning sensation in the mouth and Nuno-Gonzalez et al.[39] observed burning mouth in 5.3% of patients.

In our study, four patients (6.9%) reported the appearance of a burning sensation of the oral cavity that in all cases manifested together with the appearance of general symptoms. One of the possible reasons of burning mouth syndrome onset is dryness of the oral cavity[47]; however, none of the patients evaluated reported the appearance of xerostomia simultaneously with the onset of burning sensation of the oral cavity. It is therefore possible that the onset of this syndrome is linked to alterations caused directly by the SARS-CoV-2 virus.

Fissured tongue is a benign condition characterized by the appearance of cracks, grooves, or cuts on the back and/or sides of the tongue that has been detected in some COVID-19 positive patients. According to the literature, the presence of cracks in the tongue occurs in about 31.7% of cases.[42]

In our study, the presence of a fissured tongue was detected in five patients (8.6%). It is believed that the fissured tongue is a congenital anomaly; however, all patients who had this type of alteration reported its appearance following the onset of general symptoms and declared that they never had it before. The possible causes that could lead to the onset of cracks on the tongue could be either Candida infection or xerostomia. Three patients reported a concomitant dryness of the oral cavity and, in these cases, xerostomia may be the reason for the appearance of cracks on the tongue.

The identification of a possible correlation of oral lesions with COVID infection is very important to achieve a correct diagnosis; for example, a xerostomia related to COVID allows us to exclude other possible causes such as Sjögren's syndrome or other systemic diseases or drugs that could be related, thus reflecting on a different and appropriate treatment plan.

Aphthous lesions, white tongue, and other generic symptoms do not require different treatment modality respect to the same lesions non-COVID related, but the finding of a correlation with COVID infection could in any case avoid further investigations that would be unnecessary.

Burning mouth sensations represent a very difficult oral pathology that implicate long and uncertain treatments, often with strenuous tolerance by the patients; the identification of a possible correlation with COVID infection could represent a chance for these patients because we can suppose that once the infection is over also the burning mouth sensation will permanently stop.

Conclusion

This study therefore seems to demonstrate a possible correlation between the alterations found in patients hospitalized for COVID-19 and the infection itself by the virus. From the analysis of the data collected, the symptoms most frequently found at the level of the oral cavity in patients positive for COVID-19 are xerostomia (51.7%), ageusia (27.6%), and white tongue (22.4%). On the basis of this analysis, the future prospects are to analyze data with larger samples, also involving subjects with less serious clinical presentation than those analyzed in this research, with longitudinal follow up to evaluate the trend of these manifestations.

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