

Do COVID-19 Patients Receiving Hospital Care in the ICU Develop Oral Complications? A Case Series Study

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ABSTRACT

Introduction: Following the global pandemic of coronavirus since 2019, oral lesions have been observed in infected patients. There is no clear answer about whether lesions are due to the virus itself or due to secondary manifestations from the patient's comorbidities.

Objective: This article aims to report some unique data since there is limited information regarding intubation in the ICU, coronavirus, and oral lesions.

Materials and Methods: Here we present oral complications developed in nine Covid-19 patients receiving hospital care in our ICU department in Athens, Greece. The oral findings of the patients were recorded by the doctors in charge of the department in the AsklepieionVoulas' general hospital.

Results: The main symptoms of the patients were hairy tongue, coated tongue, candidiasis, and cheilitis. Some other reported lesions were ulcers, gingivitis, atrophic tongue, and leukoplakia. All nine patients (except one) were taking anticoagulants, corticosteroids, and antibiotics intubated with an orotracheal tube. One of the patients was intubated with a nasotracheal tube. The prolonged mechanical ventilation devices and the immunosuppression state of the patients were the primary causative factors for the recorded oral complications.

Conclusion: The present case reports highlight the importance of routine oral examination in all infected patients to improve oral health and prevent any further general complications.

Keywords: Case series; Covid-19; Hospitalized/ICU patients; Oral lesions/complications; SARS-CoV-2

Introduction

Since 2019, a rapidly transmitted virus called coronavirus (SARS-CoV-2) has become a global threat. The knowledge and pathogenesis of this virus is rapidly evolving but we know for certain that coronavirus infects the respiratory, gastrointestinal, and central nervous system of humans and mammals [1]. Apparently, all ages are susceptible to this infection transmitted through respiratory droplets, aerosols, and contact surfaces [2]. Oral manifestations in patients infected by covid-19 are rare but several reports about oral lesions were published. However, the actual causes have not been established. The most common oral manifestations reported in the literature are taste impairment, oral mucosal changes (petechiae, ulcers, plaque-like lesions, bulla, vesicle, hemorrhagic crust, erythema), xerostomia, burning mouth syndrome, and candidiasis [2-6].

A cross-sectional study in Spain stated that taste disturbances are highly specific to SARS-CoV-2 infection but may or may not be accompanied by loss of smell. Moreover, younger patients may present taste disturbances more commonly than older ones and the differences are even more distinguishable when compared with age groups of 60-65 years old. However, more studies are still necessary to confirm the association between age and taste disorders in patients with COVID-19 [3,7].

One of this virus's possible mechanisms of action is that it uses angiotensin-converting enzyme 2 (ACE2) receptors to access the cells. These receptors are found in abundance in the oral

mucosa allowing the virus to infect the host [2,8]. Some of the most important predisposing factors for oral lesions in Covid-19 patients are opportunistic infections, stress, immunosuppression, vasculitis, medications, and xerostomia [5].

There is limited information on oral complications developed in patients hospitalized or treated in the ICU department with orotracheal intubation for any other infection/disease. Some prospective studies done in patients with prolonged endotracheal intubation found laryngeal injuries with the aid of direct endoscopic visualization [9]. These were mucosal ulcerations along the posteromedial aspect of the vocal cords, laryngeal edema, granulomas, or nodule [9,10,11]. Studies reported that ulceration may occur in up to 30-40% of patients intubated for longer than three or four days [10,11].

This study report provides information on critically ill patients both treated for Covid-19 but also intubated in the ICU department for 10 or more days.

Materials and Methods

The sample consisted of nine intubated (oropharyngeal) patients (except patient 4) with ages ranging from 52 to 65 years old (3 females and 6 males (Table 1). All the patients were intubated with an orotracheal tube except pt. 4 who was intubated with a nasotracheal tube. They were all examined on May 24, 2021. All nine patients were not vaccinated prior to hospitalization.

Table 1: Critically ill COVID-19 patients at Asklepion Voulas' General hospital- May 2021.

Pt	Intensive care days (on the day of examination)	Infection days (on the day of examination)	Sex/ age	Smoking	Underlying diseases	Medications	Oral lesions
1	42	61	M/59	No	No	anticoagulants, intravenous corticosteroids, carbapenems AB, aminoglycoside	ecchymoses, exfoliative cheilitis, leukoplakia on the dorsal surface of the tongue, fungiform papillae hypertrophy/swelling
2	24		M/ 55	No	HBP, high cholesterol	Anti-coagulants, IV and inhaled corticosteroids, AB β -lactams, polymyxin, nimesulide	exfoliative cheilitis and erosions, on the tip of the tongue- hyperplastic white areas and brown plaque (5x3 cm) (non-scrappable), brown plaques on palate
3	24	35	F/ 58	No	Obesity, diabetes, asthma, HBP	anticoagulants, inhaled corticosteroids, AB β -lactams, antifungal and polymyxin	generalized pigmentation of the mucosa, ecchymoses on buccal mucosa, hairy tongue, candidiasis, leukoplakic lesions on the hard palate (scrappable)
4	21	19	M/ 52	Yes	Hepatitis, HBP	anticoagulants, inhaled corticosteroids, AB β -lactams, polymyxin, glycopeptides	melanotic macules on the upper lip, multiple macules, brownish plaques, exfoliative cheilitis, and scattered pigmented lesions
5	12	24	M/55	Yes	No	anticoagulants, inhaled corticosteroids, β -lactam AB, glycopeptide, polymyxin, nimesulide	exfoliative cheilitis, desquamative gingivitis, hairy tongue with intense hyperplastic white plaques + erythematous areas, small ulcer at the mucosa of the lower lip
6	10	32	F/61	No	No	Anticoagulants, inhaled corticosteroids, antifungal, AB β -lactam, polymyxin, glycopeptide	Gingivitis, dry upper lip with erythema, crusts and peeling, hemorrhagic bullae/macules, hairy tongue, erythema, and atrophy at the periphery of the papillae, coated tongue-white plaques at the anterior surface (candidiasis), traumatic ulcer on the soft palate
7	10	22	M/ 65	Yes	Meningioma, diabetes mellitus, HBP, high cholesterol, glaucoma	anticoagulants, AB β -lactams, glycopeptides, polymyxin	erythematous areas on the alveolar ridge alternative with detached white plaques, brown non-removable plaques, hyperplastic red area+crusts-upper lip, fungiform papillae hypertrophy, erosion-lower lip, atrophic dorsal surface of tongue with white and red areas, pseudomembrane covering an extensive ulcerative lesion

8	7	Not available	F/ 64	Yes	Obesity, HBP, diabetes, high cholesterol, Parkinson's disease	anticoagulants, inhaled corticosteroids, AB β -lactams, macrolides	candidiasis, hairy tongue, and erythematous and white hyperplastic areas on the tongue.
9	6	10	M/60	Yes	Neuroglioma, high blood pressure, high cholesterol	anticoagulants, inhaled + IV corticosteroids, β -lactam AB, polymyxin, glycopeptide, echinocandin	linear ulcer in the hard palate(1 cm), exfoliative cheilitis, hemorrhagic macules at the vermillion lip (0.5 cm), candidiasis, coated tongue with multiple pigmented macules, white and brownish plaques alternatives with red areas (candidiasis)

Abbreviations: Pt=patient, AB= antibiotics, IV= intravenous, HBP=high blood pressure

Table 2: Oral complications and their frequencies out of 9 patients.

Oral Complication	Frequency	Oral Complication	Frequency
ecchymoses	2	atrophic tongue	1
exfoliative cheilitis	5	pigmented lesions/melanotic macules	5
ulcerations	4	gingivitis	2
White/leukoplakic areas	3	erosion	2
fungiform papillae hypertrophy	2	candidiasis	4
hairy tongue	3	hemorrhagic bullae/macules	2
lip crusts+peeling	2	dry lip	1

Moreover, it was not possible to have written consent from the patients' families since no visits were allowed, however, there was consent/approval from the Scientific Council of a hospital. There was no medical intervention to the patients from the clinical examiner, but just recording their oral manifestations and reporting them back to the director of the ICU department. There was only one examiner for all the nine patients, with a specialty in oral medicine and oral pathology assisted by a general dentist.

The general clinical examinations of the patients were performed under room lights. Oral examinations were performed to record any oral lesions present in the oral cavity. Due to several difficulties and challenges faced during the clinical and oral examinations of the patients, no specific examinations were performed for the submandibular lymphadenitis nor photographic documentation, except for one case (Figures 1-3).

All patients were receiving anticoagulants, corticosteroids (except pt.5), and antibiotics (AB). Two of the nine patients passed away at the end of May 2021. Moreover, patients were then transferred to other ICU departments in other hospitals since our department returned to the ICU-surgical department and not ICU-Covid-19 patients. The data collected were from April 13, 2021, to May 20, 2021.



Figure 1: A round hyperplastic mixed white and red area (3.5x2.5 cm) in the middle dorsal surface of the tongue.



Figure 2: Crusts on the upper lip and a round hyperplastic mixed white and red area (3.5x2.5 cm) in the middle dorsal surface of the tongue.



Figure 3: Pseudomembrane covering extensive ulcerative lesion on the upper jaw.

Case Presentations

Case 1

A 59 years old man from Greece was referred to our ICU department on April 13, 2021. He was a non-smoker with no underlying diseases. This patient was intubated with a nasotracheal tube and not orotracheal like the rest of

the patients. On the day of the examination, he was taking anticoagulants, intravenous corticosteroids, carbapenems AB, and aminoglycoside. The oral manifestations were recorded on the 61st day of infection and were ecchymoses, exfoliative cheilitis, large areas of leukoplakia on the dorsal surface of the tongue, and fungiform papillae hypertrophy/swelling. The patient passed away on the 24th of May 2021.

Case 2

A 55 years old man from Greece was referred to our ICU department on April 30, 2021. He was a non-smoker. His underlying diseases were high blood pressure and dyslipidemia. On the day of the examination, he was taking anticoagulants, IV and inhaled corticosteroids, AB β -lactams, polymyxin, and nimesulide. The oral manifestations were exfoliative cheilitis and erosions on the upper and lower lip. On the tip of the tongue, there were hyperplastic white areas and in the middle of the dorsal surface of the tongue, there was a brown plaque (5x3 cm) that was not scrapable alternative with small erythematous areas. On the soft palate and the anterior part of the hard palate, there were brown plaques.

Case 3

A 58 years old woman from Greece was referred to our ICU department on April 30, 2021. She was a non-smoker. Her underlying conditions were obesity, diabetes mellitus, asthma, and high blood pressure. On the day of the examination, she was taking anticoagulants, inhaled corticosteroids, AB β -lactams, antifungal, and polymyxin. The oral manifestations were recorded on the 35th day of infection and were generalized pigmentation of the mucosa, and ecchymosis on the left commissural and left buccal mucosa. Also, there was an intense hairy tongue on the whole dorsal surface, candidiasis, and leukoplakic lesions on the hard palate that were scrapable. The patient passed away 26th of May 2021.

Case 4

A 52 years old dark-skinned man from Greece was referred to our ICU department on May 4, 2021. He was a heavy smoker for 25 years (20 cigarettes/day) and an alcoholic. His underlying diseases were hepatitis C and high blood pressure. On the day of the examination, he was taking anticoagulants, inhaled corticosteroids, AB β -lactams, polymyxin, and glycopeptides. The oral manifestations were recorded on the 19th day of infection. The oral manifestations were melanotic macules on the upper lip (7 cm in length) and on the vermilion lower lip multiple macules. On the right anterior hard palate and on the dorsal surface of the tongue there were brownish plaques, exfoliative cheilitis, and scattered pigmented lesions on buccal mucosa.

Case 5

A 55 years old man was referred to our ICU department on May 13, 2021. He was smoking for 39 years and has stopped smoking in 2017 but used vape smoking. No underlying diseases were presented. He was taking anticoagulants, inhaled corticosteroids, -lactam AB, glycopeptide, polymyxin, and nimesulide. The oral manifestations were recorded on the 24th day of infection and were exfoliative cheilitis, desquamative gingivitis, hairy tongue with intense hyperplastic white plaques located at the left lateral border and tip of the tongue alternative with erythematous areas, and small ulcer at the mucosa of the lower lip.

Case 6

A 61 years old woman from Greece was referred to our ICU department on May 15, 2021. She was a non-smoker with no underlying diseases. On the day of the examination, she was taking anticoagulants, inhaled corticosteroids, antifungals, AB β -lactam, polymyxin, and glycopeptide. The oral manifestations were recorded on the 32nd day of infection and were gingivitis, gingival bleeding during palpation, dry upper lip with erythema, crusts and peeling, hemorrhagic bullae/macules on the right buccal mucosa at the occlusal plane level, petechiae, hairy tongue, white plaques, erythema and atrophy at the periphery of the papillae, coated tongue-white plaques at the anterior surface of the tongue indicating candidiasis and traumatic ulcer at the right posterior soft palate.

Case 7

A 65 years old man from Albania was referred to our ICU department on May 15, 2021. He was a heavy smoker until 2007. His underlying diseases were meningioma with valve, diabetes mellitus, hypercholesterolemia, glaucoma (blindness), and high blood pressure. On the day of the examination, he was taking anticoagulants, AB β -lactams, glycopeptides, and polymyxin but no corticosteroids. The oral manifestations were recorded on the 22nd day of infection and were erythematous areas on the alveolar ridge alternative with detached white plaques. On the palate, there were bilateral brownish non-removable plaques. Also, on the vermilion of the upper lip on the right side, there was a hyperplastic red area. On the tongue, there was fungal fungiform papillae hypertrophy. The vermilion of the lower lip was erythematous and the mucosa had erosions probably due to traumatic reasons. The tongue was red and had an atrophic dorsal surface and in the middle of the dorsal surface of the tongue, there was a round hyperplastic mixed white and red area (3.5x2.5 cm). On the upper jaw, there was a pseudomembrane covering an extensive ulcerative lesion (Figures 1,2,3).

Case 8

A 64 years old woman from Greece was referred to our ICU department on May 19, 2021. She was a smoker for 25 years. The patient's underlying conditions were obesity, high blood pressure, high cholesterol, Parkinson's disease, and diabetes mellitus. On the day of the examination, he was treated with anticoagulants, inhaled corticosteroids, AB β -lactams, and macrolides. The oral manifestations recorded (we do not know the first day of infection) were candidiasis, hairy tongue, and erythematous and white hyperplastic areas on the dorsal surface of the tongue.

Case 9

A 60 years old man from Albania was referred to our ICU department on May 20, 2021. He was a smoker and alcoholic. His underlying diseases were neuroglioma (chemo and radiation therapy received-paralysis), high blood pressure, high cholesterol, and hypertension dyslipidemia. He was taking anticoagulants, inhaled and intravenous corticosteroids (corticosteroids were taken for neuroglioma), β -lactam AB, polymyxin, glycopeptide, and echinocandin. The oral manifestations were recorded on the 10th day of infection. The oral manifestations were linear ulcer in the middle of the hard palate (1 cm), exfoliative cheilitis, hemorrhagic macules (0.5 cm) at the left vermilion lip, and coated tongue with multiple pigmented macules, and white and brownish plaques alternatives with red areas indicating candidiasis.

Discussion

In this case series, we reported nine cases of COVID-19 patients who were intubated in the ICU developing oral manifestations during the infectious period of the disease. It is obvious that COVID-19 patients receiving hospital care in the ICU develop oral complications and the most common symptoms being exfoliative cheilitis, pigmented lesions, ulcerations and candidiasis. (Table 1) In general, there were diverse clinical findings in various locations in the oral cavity like buccal mucosa, tongue, lips, gingiva, hard and soft palate. Some other reported lesions were ecchymoses, white/leukoplakic areas, fungiform papillae hypertrophy, hairy tongue, lip crusts and peeling, atrophic tongue, gingivitis, erosions, hemorrhagic bullae and dry lip. (Table 2) No unexpected findings were found in our clinical examination since the cause of these oral lesions is multifactorial. The reported oral lesions are not clinically different in our patients based on age (average age was 58.7) or gender and they appear widespread on all patients.

Our findings are in agreement with Lucas Alves da Mota Santana et al., who also reported no sex or age predilection and the oral lesions presented mostly on tongue, lips and palate like our cases with their main clinical presentation being ulcerations. The main causative factor they mentioned was based on a probable hypothesis that covid-19 has a capacity of reactivating viruses like the HSV family [12].

Generally, we know from the published bibliography and our case reports that SARS-CoV2 can affect the oral cavity in various ways and the patients suffering from this virus develop oral lesions. It can be related directly to the virus or as a coinfection, the result of the immunosuppression, or an adverse reaction to medications and medical devices [6]. More possible causes for developing oral complications in ICU intubated patients are xerostomia, secondary manifestations from systemic diseases, opportunistic infections, susceptibility of the patient, or the combination of the above. To confirm this association, prospective and longitudinal studies are further needed, together with a larger number of patients, complemented by histopathological examination of these lesions. Additionally, molecular techniques, such as immunohistochemistry and in situ hybridization, may be necessary to perform the differential diagnosis with other oral lesions [13,14].

Vascular lesions in Covid-19-positive patients could be due to a direct action of the virus on endothelial cells; this involves immune or autoimmune reactions, such as thrombocytopenic purpura or cytokine storm, leading to microvascular dysfunction, increased vasoconstriction, organ ischemia, and inflammation. These reactions could also alter the oral keratinocytes and salivary gland ducts, leading to increased permeability of cell walls to pathogens replicating in oral cells [15]. Thrombocytopenia due to COVID-19 infection or the prescribed drug were suggested as possible causes of petechiae. Older age and severity of COVID-19 disease seem to be the most common factors that predict the severity of oral lesions in these patients [5].

It is believed that the virus is associated with the interference in hematopoiesis, excessive destruction of platelets by antibodies, and platelet consumption because of hypercoagulability causing macules, petechiae and hemorrhagic lesions [13].

Dry mouth is also very common and is possibly linked to the destruction of salivary glands caused by the binding of the virus to ACE-2 receptors on the glands. Oral manifestations in patients with COVID-19 might be due to SARS-CoV-2-

mediated hemolysis (erythrocytes have ACE-2 receptors). The virus might compete with hepcidin causing increased levels of serum ferritin and, paradoxically, anemia and iron deficiency. Like patients with iron deficiency, they could experience ulcers and a burning sensation in the mouth [3]. Regarding the occurrence of xerostomia in COVID-19, other authors also suggested the association with medications, nasal congestion, mouth breathing, nutritional deficiency, diabetes, and the anxiety and distress related to the pandemic or long-term hospitalization [7]. Candidiasis due to long-term AB and/or corticosteroids therapy, deterioration of general status, immunosuppression, and decline in oral hygiene can be the cause of candida growth in the form of white or red patches/plaques. Therefore, it is likely that this fungal infection is not directly related to COVID-19 but is secondary to the use of medications and the patients' immunosuppression condition [13].

Treatment with systemic drugs, such as glucocorticosteroids, broad-spectrum AB, immunosuppressants, and antineoplastics, may alter the oral flora, giving rise to a predisposition to the appearance of oral fungal or bacterial infections. The prolonged use of broad-spectrum AB may cause the appearance of candidiasis. Certain drugs can cause gingival hemorrhage directly or indirectly. The gums may bleed spontaneously after brushing or other activities such as mastication. This can occur in patients under treatment with anticoagulants like heparin, acenocoumarol, or warfarin. Anticoagulant drugs that are Vitamin K antagonists interfere with the production of vitamin K-dependent coagulation factors (II, VII, IX, and X) [16].

Oral lesions are observed in both non-hospitalized and hospitalized patients while perioral pressure ulcers, macroglossia, blisters, and oral candidiasis were more frequent in patients during their hospitalization. The first could be directly related to COVID-19, while the other could be caused by medical devices, treatments, prone position, and immunological impairment [6].

Previous studies such as the one by Reis, Vanessa Paiva, et al. have also pointed out the ability of SARS-CoV-2 to trigger an unregulated activation of the immune system, causing an excessive release of cytokines. This storm of cytokines causes defense cells to migrate to the affected area. Without a feedback mechanism to control this process, the action of the immune system begins to cause damage to the patient's tissues. It has been suggested that the pathogenesis of recurrent aphthous stomatitis is associated with an immune reaction mediated by T cells and an increase in cytokines as the tumor necrosis factor-alpha. Therefore, the production of cytokines triggered by the virus may induce an immune reaction that culminates in the destruction of the oral mucosa [13,14].

SARS-CoV-2 may infect nasal and oral mucosal cells, which may explain the occurrence of smell and taste dysfunctions early in the course of the disease. Two mechanisms may explain the development of such lesions: directly through the effects of the replicating virus, where these lesions will be SARS-CoV-2-specific; and indirectly through COVID-19-associated physical and psychological stress or secondary to the drugs used for its treatment. For the above-reported patients, the anosmia and dysgeusia weren't noted because of their intubation state.

It is important to be noted that oral lesions may be different between orotracheal and nasotracheal intubation. In nasotracheal intubation, we did not expect to see traumatic ulcers from the tube and indeed patient 4 did not have any ulcers in the mouth.

Other infectious, inflammatory, and autoimmune disorders

could not be excluded from the diagnosis. Therefore, oral mucosal lesions seemed to develop as secondary manifestations and coinfections related to a weakened systemic condition of the patients. The peripheral nervous system is affected by the coronavirus, and as gustatory buds are innervated by cranial nerves, related functions may be impaired, resulting in taste disorders [17].

One of the strengths of these case reports is that there are very limited cases reported of critically ill patients on mechanical ventilation devices with oral complications reported in the bibliography that can be used as a reference. Also, the severity of the patients' condition was similar as all patients were treated in the intensive care unit and we were able to compare their symptoms.

There was great difficulty to proceed with the oral examination due to the personal protective equipment required, the risk of spread of the infection, the intubation/ventilator, the position of the patients, and their inability to cooperate. As a result, recording oral findings were difficult due to exposure and contamination risk during photographic image conduction.

Another limitation of the cases is that there was a small number of patients that didn't represent the population. Also, a variety of oral lesions were recorded which gets kind of confusing as to which lesions are commonly found. There was a limited range of the age of the patients as there was no recorded data for young people. During the examination, any underestimation was possible due to obstructions from the tube, lack of adequate lighting, and cooperation from the patients. Moreover, many of the brown plaques were due to the betadine staining done for oral hygiene reasons so it is possible that the plaques recorded were white fungal lesions that got stained.

Finally, we didn't take samples to evince the presence of SARS-CoV-2 in oral lesions or to investigate the immunoexpression of ACE2 either. Also, we did not have the chance to observe the healing of the oral lesions together with the resolution of COVID-19 infection so that we can conclude that they are directly related.

Conclusion

SARS-CoV-2 can be found in saliva and oropharyngeal secretions, although the transmission pathways in the oral and oropharyngeal mucosa are still poorly understood. Oral manifestations have shown to be both the first sign of the infection but also secondary to medications, immunosuppression, co-infections, comorbidities, or systemic deterioration caused by the medications needed for treatment.

In conclusion, more data and research are needed regarding oral manifestations of patients infected with covid-19 either hospitalized or intubated in ICU departments to determine whether oral lesions are an incidental complication of COVID-19 progression or a direct result of SARS-CoV-2 infection. This is needed to confirm the correlation between them and look for the appropriate diagnosis, underline cause, and risk factors for developing oral complications.

An early thorough clinical oral examination and appropriate laboratory tests are required in confirmed COVID-19 patients during their hospital admission. Managing COVID-19 patients in ICU units requires a multidisciplinary approach, the use of teledentistry, and frequent follow-ups to prevent any life-threatening complications while navigating through this pandemic.

Acknowledgements

Data availability Statement

Data are available upon request

Ethical approval and patient consent statement

Approval by the Scientific Council of the Hospital. The patients themselves have not signed for the obvious reasons and also because the intervention involved a dental examination which was part of a "routine" examination, to determine the existence of lesions/diseases that needed treatment (e.g. candidiasis) so as not to further affect their general health.

Conflicts of interest

None to declare.

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