ORAL MUCOSA LESIONS IN CHILDREN WITH SARS-COV-2

Oana-Raluca Temneanu[1], Mihaela Roxana Popescu[2,*], Otilia Novac[3], Liliana Barbacariu[3], Luiza-Simona Pohaci-Antonesei[4], Roxana Șerban[5], Bianca Simionescu[6], Lorena Mihaela Manole[7,8]

1."Grigore T. Popa" University of Medicine and Pharmacy, Iași, România, Faculty of Medicine, Mother and Child Department
2."Grigore T. Popa" University of Medicine and Pharmacy Iași, România, Faculty of Medicine, Radiology Department
3."Grigore T. Popa" University of Medicine and Pharmacy, Iași, România, Faculty of Medicine, Preventive Medicine and Interdisciplinarity Department
4."Grigore T. Popa" University of Medicine and Pharmacy Iași, România, Faculty of Medicine, Morpho-Functional Sciences II Department
5."Grigore T. Popa" University of Medicine and Pharmacy Iași, România, Faculty of Medicine, Biochemistry Department
6."Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, România, -Faculty of Medicine, Department of Mother and Child
7."Saint Mary" Emergency Children Hospital Iași, România
8.I.O.S.U.D "Grigore T. Popa" University of Medicine and Pharmacy, Iași, România

*Corresponding Author: Mihaela Roxana Popescu, email: drpopescuroxana@yahoo.com

ABSTRACT

Objective: COVID-19, caused by the SARS-CoV-2 virus, has had far-reaching consequences globally, affecting people of all ages. While children generally experience mild or no symptoms, they can still be affected by the disease, in particular with oral manifestations. The understanding of oral manifestations related to COVID-19 is still limited and inconsistent. This review aims to gather and analyze data on the prevalence and clinical presentations of oral lesions in pediatric patients with SARS-CoV-2 infection, contributing to a better understanding of their relationship and classification within different forms of COVID-19. Material and Methods: A comprehensive search of medical databases was conducted to identify relevant articles published up to June 2023 searched using electronic databases such as PubMed, Medline, and Web of Science. Results: This review encompasses a systematic analysis of 33 relevant articles, with a focused examination of seven studies that specifically address the subject matter. The inclusion criteria involved thorough evaluation, with 15 articles read in their entirety and additional references searched manually for supplementary information. Discussions: Research on oral lesions in pediatric population affected by SARS-CoV-2 infection is limited, leading to potential underestimation or misdiagnosis. Oral mucosa lesions occur in 2-20% of cases, often alongside skin lesions. The most common oral lesions are erosions, ulcers, maculae, petechiae, and changes in the tongue, lips, and gingiva. Oral manifestations are also observed in Multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease associated with SARS-CoV-2. Dental care providers can play a role in identifying and monitoring MIS-C, but accurate diagnosis is crucial to prevent complications. Conclusions: Pediatric patients diagnosed with COVID-19 may not frequently exhibit recognized oral signs and symptoms, necessitating thorough evaluation and consideration of differential diagnoses. Oral healthcare professionals should assess and classify oral manifestations to prevent underestimation and misdiagnosis.

Keywords: SARS-CoV-2, COVID-19, oral mucosa lesions, children, oral cavity

INTRODUCTION

COVID-19, also known as the coronavirus disease 2019, is a severe condition characterized by the World Health Organization as an infectious illness caused by the SARS-CoV-2 virus[1]. This global pandemic has had a devastating impact on public health, the stability of economies and social well-being. Its effects continue to be observed in people of all age groups, including children and adolescents. COVID-19 primarily affects older individuals and those with pre-existing health conditions, but many studies confirms that, children have a lower chance of contracting the virus and typically experience either no symptoms or mild to moderate illness[2,3].

This disease is mainly spread through droplets and close contact, but it can also be transmitted through fecal-oral route and aerosol transmission[4-6]. Pediatric patients require parental care due to their weaker resistance, quick changes in condition, and limited ability for medical cooperation and self-care. Furthermore, activities involving close proximity to the oral cavity, upper respiratory tract and secretions can facilitate the transmission of COVID-19 through respiratory droplets and close contact with infected individuals[7].

During the initial stages of the COVID-19 pandemic, the available evidence at that time indicated that pediatric patients often experienced either no symptoms or mild symptoms when infected with SARS-CoV-2[8]. However, subsequent research revealed that COVID-19 could progress to a severe form of the disease called "Multisystem Inflammatory Syndrome in Children" (MIS-C) in some pediatric cases[9]. In addition to the respiratory symptoms, COVID-19 has diverse clinical effects that vary among patients like oral manifestations, such as lesions on the oral mucosa, which have been observed in both pediatric individuals and adults in relation to SARS-CoV-2[10].

Despite the continuous emergence of new findings, the level of evidence regarding COVID-19 and associated oral mucosa lesions remains relatively low and inconsistent. Thus, the main objective of this review is to gather, analyze, and update the existing data on the prevalence of oral lesions among pediatric patients who have tested positive for the SARS-CoV-2 virus. Additionally, this study aims to assess the relationship between oral lesions and SARS-CoV-2 infection and classify the primary oral lesions based on their reported frequency, along with their clinical presentations related to different forms of COVID-19.

MATERIAL AND METHODS

This comprehensive review summarizes the most significant studies published in scientific literature, including original research papers and reviews reporting oral mucosa lesions in pediatric patients among SARS-CoV-2 cases, that have been identified and critically analyzed. To gather relevant information, the search was conducted using internationally recognized electronic databases such as PubMed, Medline, and Web of Science. The search focused on papers published up until June 2023, using specific keywords related to SARS-CoV-2, COVID-19, oral mucosa lesions, children, oral cavity, which align with the expertise of the authors. The resulting draft was thoroughly discussed among the authors to provide a theoretical perspective, and the final version was subsequently reviewed, communicated, and approved by all co-authors.

RESULTS

A comprehensive analysis was conducted using various databases, resulting in the identification of a total of 33 articles related to the subject matter. These articles were thoroughly studied and analyzed, and in the final analysis, 15 of them were read entirely. Additionally, a manual search was performed within the reference list of the selected papers to supplement our analysis. Three studies were excluded based on their abstracts. Ultimately, seven articles specifically addressing the topic were included in this review.

DISCUSSIONS

Oral lesions in pediatric SARS-CoV-2-positive subjects can occur, but research on mucosa lesions in pediatric cases is still limited, because most studies have focused on adult populations. However, some reports and case studies have provided insights into the oral manifestations observed in children with SARS-CoV-2 infection. The literature shows a wide range of terms used to describe primary oral lesions, which can be attributed to the fact that these lesions are often reported in the context of systemic syndromes. Consequently, healthcare providers who are not specialized in oral medicine encounter and describe these lesions, leading to potential underestimation/overestimation or even misdiagnosis of certain primary oral lesions[10]. Frequently, oral lesions have been reported alongside skin lesions, and their overall occurrence in pediatric patients affected by SARS-CoV-2 infection has been estimated to range from 2% to 20%[11].

The actual occurrence of oral lesions in pediatric SARS-CoV-2-positive

individuals may have been underestimated due to several factors. Many of these subjects were either asymptomatic or had only mild symptoms, resulting in a lack of diagnosis for COVID-19[8,9]. Additionally, those in home care might not have undergone oral examinations, further contributing to the potential underestimation of oral lesions in this population[12]. Moreover, there have been studies that reports a higher occurrence of oral lesions in pediatric cases with severe COVID-19. Similar to adult SARS-CoV-2-positive individuals, there is a higher prevalence of oral lesions in young males compared to females (with a male-to-female ratio of 1.33:1). Additionally, these young males are more likely to be hospitalized compared to females. The increased hospitalization rate of male pediatric patients likely resulted in the earlier detection of oral lesions, as it may be more challenging to identify such lesions in patients receiving home care[10].

According to Di Spirito et al. the primary oral lesions accounted for 18.61% of all 35 study participants (20 males and 15 females, aged between 10 days and 14 years and mean age of 5.98) and the oral mucosa lesions are: nonspecific erosions and ulcers (6.98% of cases), maculae and petechiae (11.63% of cases), with erythema (4.65% of cases), purpura (2.33% of cases), ecchymosis (2.33% of cases), and petechiae (2.33% of cases). Other oral lesions, reported in 81.4% of cases, included fissures (4.65% of cases), hypertrophic papillae (2.33% of cases), oral candidiasis (11.63% of cases), geographic tongue (2.33% of cases), coated tongue (4.65% of cases), hyperemic pharynx (23.26% of cases), crusts (2.33% of cases), swollen (2.33% of cases), and nonspecific oral mucosal changes (27.91% of cases)[13]. The most affected sites were the lips, pharynx, tongue, and gingiva. However, specific details about the affected site were not clearly defined in some cases. None of the nine included studies recorded any cytological or histological investigations related to these oral lesions[13].

"Multisystem Inflammatory Syndrome in Children" (MIS-C) is a newly recognized condition that has emerged during the COVID-19 pandemic. The diagnostic criteria for MIS-C include several symptoms: (1) fever lasting for more than 5 days, (2) redness of the palms and soles or more commonly swelling of the hands and feet, (3) peeling of the skin around the nails, (4) widespread rash, (5) redness and inflammation of the conjunctiva (conjunctival injection), (6) redness of the lips and oral cavity, (7) swollen lymph nodes in the neck (cervical lymphadenopathy), and (8) exclusion of

other diseases. Also, MIS-C can also involve abnormalities in the coronary arteries, such as dilation and aneurysms[14-16].

As stated by the systematic literature review of Nascimento et al. which analyzed a total of 624 pediatric cases diagnosed with either MIS-C or Kawasaki disease (KD) associated with SARS-CoV-2 infection the clinical and laboratory changes are similar to KD[16]. Oral manifestations were found to be one of the most common signs observed in both MIS-C and KD cases, with no notable differences between the two conditions. Changes in the oral cavity were identified as early symptoms in both diseases, including erythema (redness) of the oral mucosa and tongue, often accompanied by aphthous (ulcerative) lesions in some instances. The lips were also affected, showing symptoms such as erythema, edema (swelling), dryness, or superficial scaling. However, reports of burning or pain that hindered or limited normal food intake were infrequent[12,16].

Kawasaki disease (KD) is the most commonly observed primary vasculitis in childhood[17,18]. While the exact cause of KD is still unknown, studies conducted in 2014, 2015, and 2020 suggest that it may be a result of viral infection[19-21]. To diagnose KD, the presence of fever lasting for more than 5 days and at least 4 out of 5 specific physical examination findings is required. These findings include conjunctival injection, changes in the oral mucous membranes (such as redness of the lip vermilion and labial mucosa, redness of the oral and oropharyngeal mucosa, and the presence of a "strawberry tongue"), changes in the peripheral extremities (such as redness and swelling), a polymorphous rash, or cervical lymphadenopathy. KD is typically diagnosed by ruling out other potential causes, making it a diagnosis of exclusion[18,22]. In the review of Halepas et al. with a cohort of 47 patients positive for SARS-CoV-2 infection, 23 individuals were found to have documented symptoms of swelling, redness, or cracking of the labial mucosa during oral examination. However, only 5 patients exhibited a strawberry tongue. It remains uncertain whether the absence of a documented strawberry tongue represents a genuine negative finding or an omission error. Nevertheless, it is noteworthy that the lack of documented cases with a strawberry tongue in our patient cohort was observed much more frequently compared to other diagnostic criteria for MIS-C, such as fever (observed in all 47 patients), systemic rash (present in 32 patients), and conjunctivitis (reported in 27 patients)[23].

Regardless of the variations in terminology used in the systematic reviews, it was observed that macules/petechiae,

predominantly in erythematous forms, as well as ulcerative/erosive lesions, were the most frequently encountered oral lesions among pediatric individuals who tested positive for SARS-CoV-2. This was observed irrespective of whether they developed SARS-CoV-2-associated syndromes[12,13,16].

It's important to recognize that these oral lesions are not unique to COVID-19 and can occur in other viral infections or even non-infectious conditions. The prevalence and specific characteristics of these lesions in pediatric SARS-CoV-2-positive individuals require further investigation and research.

Dental care providers have the potential to play a significant role in the initial identification of MIS-C, both in inpatient and outpatient settings[23]. With the reopening of dental practices and the resumption of elective treatments, it is possible that dentists may come across patients who are either experiencing or have received a diagnosis of COVID-19 with features of MIS-C. This is particularly relevant for those working in pediatric or family dental practices. Since oral manifestations are believed to be among the early signs of MIS-C, dental professionals may be consulted in the inpatient setting to assess subtle changes in the oral mucosa. Equally important, dental care providers can assist frontline workers in ruling out oral changes unrelated to MIS-C[24]. An example of such an oral manifestation is strawberry tongue, which can be challenging to detect and may be mistaken for similar-looking lesions on the dorsal tongue, such as oral thrush or a coated tongue. Early diagnosis and close monitoring of MIS-C are crucial because, similar to KD, cardiac abnormalities have been observed[25]. While the long-term consequences of MIS-C are still not fully understood, accurate and timely detection of patients with MIS-C can help prevent future complications[25,26]. Furthermore, it is important to report the presence of any oral manifestations, especially given the limited knowledge in this area. Understanding oral signs and symptoms could significantly contribute to more accurate screening of patients and early diagnosis in dental settings. For instance, dental practitioners should routinely include questions about "recent onset of taste disturbance" or "oral ulcers" in their medical questionnaires, helping to identify individuals at higher risk and preventing their attendance at primary healthcare environments.

Further research is needed to explore the epidemiology, histopathology, and clinical characteristics of oral lesions in relation to age, gender, comorbidities, and associated treatments in individuals

affected by SARS-CoV-2 infection. Additionally, it is important to investigate the impact of COVID-19 vaccination on the occurrence and characteristics of oral lesions in the pediatric population, including the type and number of vaccine doses administered. By delving into these aspects, a more comprehensive understanding of oral manifestations in relation to SARS-CoV-2 infection and vaccination can be gained.

CONCLUSIONS

In conclusion, it was observed that pediatric patients with COVID-19 are not frequently recognized and the oral signs and symptoms not reported specifically by the parents, and these manifestations may not be specific to this disease. In this context, it is advisable to consider a differential diagnosis with other chronic conditions and thoroughly assess the patient's medical history.

Nevertheless, several diseases manifest oral involvement as their initial and sole symptom. Therefore, it is crucial to evaluate and consider this aspect in relation to the new infection. To address this, it would be beneficial for oral healthcare professionals to evaluate and classify all oral manifestations of coronavirus infection. Such action would prevent the underestimation and misdiagnosis of oral signs and symptoms. Based on these findings, it is suggested that all specialists involved in oral health, particularly dentists and dermatologists, perform oral examinations in patients suspected or affected by SARS-CoV-2.

Oral professionals must be aware of COVID-19 and their crucial role in controlling outbreaks. By applying updated triage protocols and identifying early oral signs and symptoms of COVID-19, healthcare professionals can promptly refer patients for further investigation and expedite self-isolation procedures.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICT OF INTEREST AND FUNDING

All authors read and approved the final manuscript. All authors have equal contribution.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19). URL: https://www.who.int/health-topics/coronavirus#tab=tab_1. [data accesării, mai 2023]
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021; 19: 141-154 doi: 10.1038/s41579-020-00459-7
3. O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, Fontanet A, Cauchemez S, Salje H. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 2021; 590: 140-145 doi: 10.1038/s41586-020-2918-0
4. Li Q, Guan XH, Wu P, Wang XY, Zhou L, Tong YQ, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199–207.
5. Chan JF, Yuan SF, Kok KK, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395:514–23.
6. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. Ann Intern Med. 2021;174:69–79.
7. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Euro Surveill. 2020 Jan;25(4):2000058.
8. Nikolopoulou, G.B.; Maltezou, H.C. COVID-19 in Children: Where do we Stand? Arch. Med. Res. 2022, 53, 1–8.
9. Nakra, N.A.; Blumberg, D.A.; Herrera-Guerra, A.; Lakshminrusimha, S. Multi-System Inflammatory Syndrome in Children (MISC) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. Children 2020, 7, 69.
10. Di Spirito, F.; Iandolo, A.; Amato, A.; Caggiano, M.; Raimondo, A.; Lembo, S.; Martina, S. Prevalence, Features and Degree of Association of Oral Lesions in COVID-19: A Systematic Review of Systematic Reviews. Int. J. Environ. Res. Public Health 2022, 19, 7486.
11. Brandini, D.A.; Takamiya, A.S.; Thakkar, P.; Schaller, S.; Rahat, R.; Naqvi, A.R. COVID-19 and Oral Diseases: Crosstalk, Synergy or Association? Rev. Med. Virol. 2021, 31, e2226.
12. Di Spirito F, D'Ambrosio F, Di Palo M.P, Giordano F, Coppola N, Contaldo M. COVID-19 and Related Vaccinations in Children: Pathogenic Aspects of Oral Lesions. Children 2023, 10, 809.
13. Di Spirito F, Caggiano M, Di Palo M.P, Contaldo M, D'Ambrosio F., Martina S, Amato A. Oral Lesions in Pediatric Subjects: SARS-CoV-2 Infection and COVID-19 Vaccination. Appl. Sci. 2022, 12, 8995.
14. Heidemann SM, Tilford B, Bauerfeld C, et al. Three cases of pediatric multisystem inflammatory syndrome associated with COVID-19 due to SARS-CoV-2. Am J Case Rep. 2020;21:e925779.
15. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017;135(17):e927–e999.
16. Nascimento R.B, Araujo N.S, Silva J.C, Xavier F.C.A. Oral Manifestations of Multisystemic Inflammatory Syndrome in Children (MIS-C) and Kawasaki Disease Associated to COVID-19: A Systematic Review. Spec. Care Dent. 2022, 42, 266–280.
17. Schnabel A, Hedrich CM. Childhood vasculitis. Front Pediatr. 2018;6:421.
18. Shackelford PG, Strauss AW. Kawasaki syndrome. N Engl J Med. 1991;324(23):1664-1666.
19. Rowley AH, Baker SC, Arrollo D, et al. A protein epitope targeted by the antibody response to Kawasaki disease. J Infect Dis. 2020;222(1):158-168.
20. Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148-154.
21. Turnier JL, Anderson MS, Heizer HR, Jone P-N, Glodé MP, Dominguez SR. Concurrent respiratory viruses and Kawasaki disease. Pediatrics. 2015;136(3):e609-e614.
22. Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. Int J Rheum Dis. 2018;21(1):36-44.

23. Halepas S, Lee KC, Myers A, Yoon RK, Chung W, Peters SM. Oral manifestations of COVID-2019–related multisystem inflammatory syndrome in children: a review of 47 pediatric patients. The Journal of the American Dental Association. 2021; -152(3):202–8.
24. Meng L, Hua F, Bian Z. Coronavirus disease 2019 (COVID-19): emerging and future challenges for dental and oral medicine. J Dent Res. 2020;99(5):481-487.
25. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142(5):429-436.
26. Capone CA, Subramony A, Sweberg T, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory disease of childhood (MIS-C) associated with SARS-CoV-2 infection. J Pediatr. 2020; 224:141-145.