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Oral lesions in paediatric patients with COVID-19 and Paediatric Inflammatory Multisystem Syndrome: a review

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1. Introduction

The effects of COVID-19 pandemic have been devastating with over 20 million infected cases and over 4 million deaths reported worldwide [1]. The most prevalent features of SARS-Cov-2 infection are fever, continuous cough and change of taste and smell. The presence of these symptoms is well recognised as features of SARS-Cov-2 infection, however the viral infection may manifest itself as a variety of other symptoms in the affected host [2].

Oral manifestations are an important feature and may play a part in the diagnosis and management of the disease. A recent systematic review of the literature highlighted several oral mucosal lesions in SARS-Cov-2 infected patient [3]. The pathophysiology of oral manifestations of SARS-Cov-2 infection is currently unknown. Nevertheless, one hypothesis states the role of abundance of angiotensin-converting enzyme 2 and transmembrane protease serine 2 expressed in the respiratory tract and in the oral mucosa including tongue, gingiva and salivary glands. These cell receptors within the oral cavity have been shown to aid entry of the virus into the host [4].

At the beginning of the COVID-19 pandemic, it was suggested that the children infected with the virus had much milder symptoms compared to adults [5]. However, in April 2020 reports from the United Kingdom identified a new hyperinflammatory disease in children associated with the virus [6]. This condition was coined Paediatric Inflammatory Multi-System Syndrome (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C). An early symptom of this condition is mild oral ulceration; however, the disease progression can lead to serious consequences and, in some cases, can even result in fatality [6,7].

PIMS-TS classically presents with fever, gastrointestinal (GI) symptoms, alongside inflammatory changes throughout the body including skin rash, oral mucosal changes and conjunctivitis [6]. Although symptoms may be similar to those of Kawasaki Disease (KD) or toxic shock syndrome (TSS), GI symptoms and myocardial dysfunction are more common in PIMS-TS. The crucial diagnostic difference that separates them is the relationship of the condition and the infection with SARS-CoV-2. However, only 45% of the patients with PIMS-TS will have a positive polymerase chain reaction (PCR) test for SARS-CoV-2. Although this may be lower than expected, 75% of the patients have class-switched antibody to viral antigen indicating that all of these children with a diagnosis of PIMS-TS have occurred as a result of previous, current, or unrecovered coronavirus infection [8]. The World Health Organisation (WHO) published the criteria for a diagnosis of PIMS-TS in children and adolescents [9]. Several case reports and cohort studies suggest that patients can present with oral and facial symptoms before, during and after a diagnosis of PIMS-TS [3].

This article aims to review the oral manifestations of PIMS-TS and COVID-19 in children with an objective of increasing an awareness...
among the dental and medical profession to facilitate prompt referral, diagnosis and treatment.

2. Methods

A structured electronic literature search with keywords including “COVID-19 or SARS-CoV-2”, and “stomatognathic disease, mouth diseases, oral manifestation, oral lesions, oral ulcer or oral stomatitis”, and “child, paediatrics, adolescent or infant” was undertaken on MEDLINE to identify papers on the oral manifestations with SARS-CoV-2 in paediatric patients aged younger than 19 years. We included all types of studies including reviews and case series. Case reports were excluded.

3. Results

A total of five articles relating to oral manifestations of paediatric patients with SARS-CoV-2 infection, with or without a diagnosis of PIMS-TS, were identified. The data in these five articles was collected between January 2020 and January 2021, with a total combined sample size of 1274. The demographic and clinical data from the five articles included in this review has been summarised in Table 1.

All included studies except one reported on oral lesions in PIMS-TS. The most commonly affected oral sites were the lips and tongue and the most commonly reported symptoms were cheilitis, dry and red mucosal membranes, and tongue swelling. The studies also identified ‘oral mucosal changes’ in a large number of the study population, however the specific changes were not mentioned and therefore cannot be compared to the rest of the data [11]. Two of the five studies included in this review were systematic reviews, the first reported on oral lesions in patients with COVID-19 [3] and the second one reported on PIMS-TS [10].

The systematic review which reported on PIMS-TS in children also reported on oral lesions [10]. They appraised 39 studies with a total sample size of 662 presenting with PIMS-TS. The incidence of oral mucosal lesions in this paper were cheilitis in 32.6% and tongue swelling in 4.7% of the sample. Bhujel et al. [3] reported on oral mucosal lesions in both adult and paediatric patients with SARS-CoV-2 infection. Of the 12 studies appraised in this systematic review, a total of 84 paediatric patients were reported. The most common oral mucosal lesions in the paediatric patients from this systematic review were red or swollen lips reported in 27.3% and unspecified oral cavity changes in 19% [3].

A review article by Naka et al. [11] of recently published studies on PIMS-TS in Europe and the United States identified 13 large case series of which 8 reported on oral lesions. The sample size of these eight studies was 452, of which 185 had oral lesions reported. Oro-mucosal changes, dry and red lips were reported in 25%-87% of the patients, however the type of lesions remained unspecified [11].

The cohort study by Rekhtman et al. [12] included 31 paediatric patients out of which 19 had PIMS-TS and 12 had COVID-19 patients. From the PIMS-TS group 47% (n=9) had rash and/or mucositis and from the COVID-19 group 33% (n=4) had rash and/or mucositis. The case series of 58 children reported by Whittaker et al. [13] reported mucous membrane changes in quarter of the patients.

4. Discussion

To the best of our knowledge, this is the first review article specifically discussing oral manifestations in paediatric patients with SARS-CoV-2 infection, including those with PIMS-TS. The systematic review by Bhujel et al. [3] on the oral mucosal lesions in patients with SARS-CoV-2 identified three studies [14-16] reporting on paediatric patients, of which two [15,16] specifically reported on PIMS-TS. The cohort study by Rekhtman et al. [12] is possibly the only study to date which categorised the mucocutaneous lesions in hospitalised PIMS-TS and COVID-19 paediatric patients in separate groups. Mucocutaneous morphologic patterns differed in PIMS-TS from SARS-CoV-2 group with papillitis of the tongue observed only in the PIMS-TS group. It is worth noting that in this study none of the 19 PIMS-TS patients met the criteria for KD [12]. This indicated the need to have distinct criteria for diagnosis for this condition which were later published by the Royal College of Paediatrics and Child Health, US Centers for Disease Control and Prevention [17] and WHO [9] in May 2020.

PIMS-TS is a rare complication of SARS-CoV-2 in children which resulted in 71% of children requiring admission to intensive care and a mortality rate of up to 1.7% [10] compared to 0.01% in KD [18]. It is not known if oral lesions are related to the severity of SARS-CoV-2 infection or pre-existing medical conditions. It is also not known if oral lesions are a complication of the viral infection or a result of the treatment received [3]. Ahmed et al. [10] found that 52% (n=290 of 558) of PIMS-TS patients did not have underlying medical conditions.

Cant et al. [19] reported on a case of a 9-year-old child who had two episodes of lip swelling and ulceration which was treated with topical steroids, however despite an improvement in the oral lesions the patient

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**Table 1**

Summary of published studies on oral manifestations of paediatric patients with SARS-CoV-2.

| Study                          | Design          | Data Collection Date | Sample n=                      | Age, y, | Location of oral lesions | Type of oral lesions                                    | PIMS-TS |
|-------------------------------|-----------------|----------------------|--------------------------------|---------|--------------------------|---------------------------------------------------------|---------|
| Ahmed et al. (2020), USA [10] | SR              | Jan-July 2020        | 662 (39 studies)               | Mean 9.3 ± 0.5 | Lips, Tongue             | Chelitis (n=216, 32.6%)                                 | Yes     |
| Bhujel et al (2021) UK [3]    | SR              | Mar 2020             | 84 (3 studies reported paediatric patients) | Range 3 months to 20 years | Tongue, lip | Oral pseudomembranous candidiasis (n=2, 2%), Geographic tongue (n=1, 1%), Coated tongue (n=2, 2%), Red or swollen lips (n=23, 27%), Strawberry tongue (n=5, 6.0%), Oral cavity changes unspecified (n=16, 19.0%) | Yes (2 studies) (Falah et al., 2020 & Halepas al. 2021) |
| Naka et al. (2021), USA [11]  | Review article  | Jan 2021             | 452 (8 case series)            | Median 8 to 12 | Oral mucosa and lips     | Dry and red lips and/or other mucosal changes in 25%-87% in children with MIS-C (n=185 affected) | Yes     |
| Rekhtman et al. (2020), USA [12] | Cohort        | May 2020             | 31 (M: 19, F:11)               | Range 1.75 to 16 | Tongue, Lips             | MIS-C group: Lip fissuring (n=4, 21%), tongue papillitis (n=2, 11%), COVID-19 group: Lip fissuring (n=1, 8%) | Yes     |
| Whittaker et al. (2020), Europe & USA [13] | CS          | Mar-May 2020         | 58                             | Median 9 | Lips                    | Mucous membrane changes and red cracked lips (n=11, 25%) | Yes     |

SR: systematic review; CR: case report; CS: case series; NS: not specified.
was admitted to intensive care with PIMS-TS. The authors suggested that eight children admitted with PIMS-TS to St Thomas’ Hospital in London presented with oral ulceration as an early feature of PIMS-TS [19].

There is a need for healthcare professionals working with children to understand this novel disease which has similarities to KD and TSS. However, recent data has described the clinical, immunological and microbiological findings in PIMS-TS with PIMS-TS occurring in older children and with different laboratory features including higher C-reactive protein, white blood cell and neutrophil count [13]. Whittaker et al. [13] also found that most patients were negative for detection of the virus but had antibodies against SARS-CoV-2 as the illness generally manifests 3–4 weeks after the infection. This suggests that PIMS-TS could possibly arise from an acquired immunity to the virus which has implications for developing vaccines [13]. Due to the nature of PIMS-TS being a multisystem illness, a multidisciplinary approach is crucial in the management of these patients. As oral manifestations have been reported in several studies, we would highly recommend early inclusion of experts experienced in managing oral lesions in the care of these children. Many of the studies did not specify the exact nature of the mucosal changes in PIMS-TS and this highlights the need for oral screening to be undertaken as part of the diagnosis and management for these patients. There are a number of limitations of this review. The use of a single electronic database (MEDLINE) would have resulted in selection bias and exclusion of other important studies. The inclusion of case series, which was to facilitate wider capture of published literature on the subject, may have resulted in a lower quality of evidence. Only descriptive analysis was undertaken, and no statistical analysis was performed. Despite the potential flaws, this review article uniquely intends to provide an up-to-date summary of the oral manifestations in children infected with SARS-CoV-2 and those with PIMS-TS.

5. Conclusion

Oral mucosal lesions may be a feature in children with SARS-CoV-2 and PIMS-TS, which has resulted in mucosal changes being part of the diagnostic criteria for patients with PIMS-TS. This may highlight the need for oral screening to be conducted by healthcare professionals involved in the care of these patients for early diagnosis and appropriate management.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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