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CASE REPORT

Oral manifestations of autoimmune polyglandular syndrome type 1

Jefferson R. Tenório[1] | **Marina Maués Tuma**[2] | **Natália Silva Andrade**[3] | **Thalita Santana**[4] | **Marina Gallottini**[5]

[1] Department of Oral Pathology and Diagnosis, School of Dentistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[2] Department of Oral Pathology, School of Dentistry, São Paulo University, São Paulo, Brazil

[3] Department of Dentistry, School of Dentistry, Federal University of Sergipe, Sergipe, Brazil

[4] School of Dentistry, Ceuma University, Sao Luis, Brazil

[5] Department of Stomatology, Special Care Dentistry Center, University of São Paulo, São Paulo, Brazil

Correspondence
Marina Gallottini, Department of Stomatology, Special Care Dentistry Center, University of São Paulo, Av. Prof. Lineu Prestes, 2227 - Butantã, Sãoscd12703 Paulo – SP 05508–900, Brazil.
Email: mhcgmaga@usp.br

Abstract

Aims: Autoimmune polyglandular syndrome type I (APS-I) is a rare condition of autosomal recessive and monogenic inheritance, which is characterized clinically by at least two signs of the classic triad: mucocutaneous candidosis, hypoparathyroidism, and Addison's disease. This study aims to report the oral manifestations of APS-I in a 42-year-old woman, who attended the Special Care Dentistry Center.

Methods and results: The patient presented with hypoparathyroidism, diabetes mellitus, and autoimmune hepatitis. Chronic hyperplastic candidosis (CHC) was the main oral manifestation and it was diagnosed based on clinical and cytologic characteristics. Microstomia, angular cheilitis, xerostomia, enamel hypoplasia, and microdontia were also present.

Conclusions: CHC was treated with topical nystatin and oral fluconazole, resulting in a significant improvement of the lesions.

KEYWORDS

autoimmune, autoimmune polyendocrinopathy candidiasis, candidosis, ectodermal dystrophy, hypoparathyroidism, polyendocrinopathies

1 | INTRODUCTION

Autoimmune polyglandular syndrome type I (APS-1) (OMIM: 240300), also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), is a rare condition of monogenic and autosomal recessive inheritance.[1] APS-1 affects about one in 90 000 to one in 200 000 individuals, with a slight predilection for females.[2]

Mutations in the autoimmune regulatory gene (AIRE) are linked to the pathogenesis of APS-1.[3] The AIRE gene is located on chromosome 21q22.3 and is expressed in the thymus and in peripheral lymphoid organs. This gene is responsible for encoding a transcription factor, which guarantees the maintenance of the central and peripheral tolerance through the elimination of auto-reactive T cells, controlling the function of antigen-presenting cells, regulating immune responses, among other functions.[4,5] Loss of function of the AIRE gene enables the escape of self-reactive T lymphocytes from the thymus to the periphery, which are directed against a variety of self-antigens, resulting in injuries to multiple organs and systems.[3]

APS-1 is clinically characterized by the presence of at least two signs of the classic triad: mucocutaneous candidosis, hypoparathyroidism, and Addison's disease, which usually appears in this sequence and with varying

severity.[6] As secondary manifestations, endocrine and nonendocrine autoimmune disorders are usually present, such as diabetes, hypothyroidism, hypergonadotrophic hypogonadism, autoimmune hepatitis, nail dystrophy, alopecia, keratoconjunctivitis, and among others.[7]

Individuals affected by APS-1 may present oral manifestations, and its clinical management represents a challenge to the dentist.[8]

2 | CASE REPORT

For this report, we followed the CARE guidelines (for CAse REports).[9] Data from the patient included in this paper were treated anonymously, and a statement of informed consent was signed by her allowing the use of her medical and dental records.

A 42-year-old White woman sought prosthetic rehabilitation, complaining of odynophagia and oral ulcerations. During anamnesis, the patient reported she was diagnosed with APS-1 during her childhood and that currently she was undergoing chemotherapy for intestinal cancer.

The patient presented hypoparathyroidism, hypocalcemia, chorea, onychomycosis, diabetes mellitus type I, liver cirrhosis due to autoimmune hepatitis, retinopathy, anemia, celiac disease, epilepsy, and depression. She was using calcium carbonate, insulin, calcitriol, vitamin B12, pancreatin, venlafaxine, and lamotrigine. Also, the patient had a history of multiple dental extractions and reported she had previously used mouthwashes for treating oral candidosis, however unsuccessfully.

The patient presented multiple ephelides on the face. In the intraoral examination, we noticed ulcers on the upper and lower lip, microstomia, angular cheilitis, dry mouth, enamel hypoplasia on both superior second molars, and microdontia of the maxillary third molars (Figure 1). The ulcerated lesions were interpreted as ulcers of traumatic origin, as they appeared 5 days after the patient had traumatized the area while chewing. They were small, superficial, with flat edges, slightly reddish borders, and covered by a thin fibrinopurulent membrane. We also observed white plaques that could not be removed by scraping over the buccal mucosa, back, and lateral borders of the tongue. With the clinical hypothesis of chronic hyperplastic candidosis (CHC), we performed exfoliative cytology of the white lesions and angular cheilitis, which confirmed the presence of *Candida* spp. hyphae, endorsing the presumptive diagnosis of CHC (Figure 2).

The patient presented decreased occlusal vertical dimension. The panoramic radiographic examination

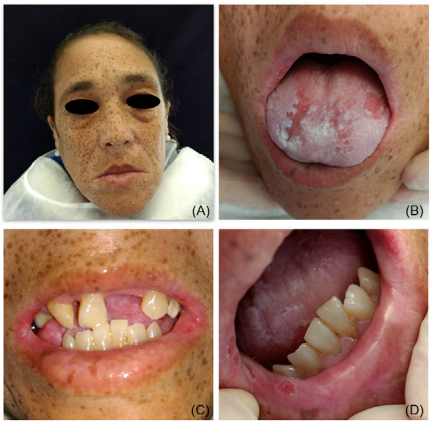

FIGURE 1 (A) Extraoral clinical aspect. (B) White plaques spread on the tongue. (C) Microstomia and angular cheilitis. (D) Ulcers on the upper and lower lip [Color figure can be viewed at wileyonlinelibrary.com]

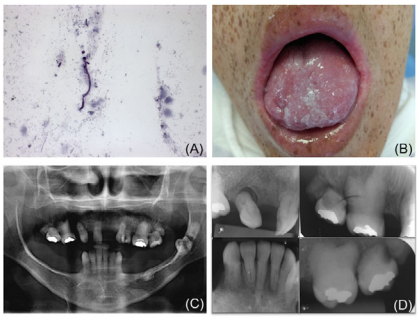

FIGURE 2 (A) (PAS, magnification: 200×) Cytopathological examination showing the presence of hyphae of *Candida* spp. (B) Clinical aspect of the lesions 14 days after local and systemic antifungal treatment. (C) Panoramic radiographic image showing multiple tooth absences and shortened roots. (D) Periapical radiographs showing periapical lesions, shortened roots, and obliteration of pulp chambers and root canals [Color figure can be viewed at wileyonlinelibrary.com]

revealed multiple shortened roots, periapical lesions, impacted inferior premolar and third molar, and obliteration of root canals and pulp chambers (Figure 2).

For treating CHC, a mouthwash with Nystatin Oral Suspension (100 000 IU) was prescribed four times a day associated with Fluconazole (oral route – 100 mg) once daily, both for 14 days. After this period, we observed an improvement of the condition (Figure 2), but not the complete remission of the lesion. As the ulcerated lesions were undergoing repair, our approach was clinical follow-up only.

Unfortunately, the patient died due to complications of intestinal cancer and was unable to complete the recommended dental treatment.

3 | DISCUSSION

The clinical management of patients with APS-1 is challenging, given the numerous complications related to failure in the mechanisms of self-tolerance, in addition to Addison's disease and hypoparathyroidism.

In APS-1, candidosis is usually caused by the yeast *C. albicans*. In a group of Finnish patients with APS-1, non-*C. albicans* spp. was reported in only 7/56 patients (12.5%).[10] Mucocutaneous candidosis probably occurs by depletion of Th17 lymphocytes, cells producers of interleukin (IL)-17 and IL-22, which are cytokines with antifungal capacity.[11] The management of this condition is usually carried out with polyenes, imidazoles, triazoles agents, used separately or in combination.[12]

Another aspect that may contribute to a greater propensity for persistent candidosis in this group of patients is dysbiosis in the oral ecosystem. Bruserud et al. (2018) described, among other findings, that patients with APS syndrome have altered salivary microbiota, characterized by a marked prevalence of the genus *Streptococcus* and *Gemella*.[13] Knowing that a healthy oral microbiota can prevent infections, the authors suggest the observed dysbiosis may influence candidosis in these patients.

In the present case, the patient had mucocutaneous candidosis in the nails and multiple sites of the oral mucosa. Mucocutaneous candidosis within the context of APS-1 may present in different clinical subtypes, including CHC, which is characterized by persistent clinical behavior.[14]

The World Health Organization defines CHC as a potentially malignant oral disorder.[15] Although there is still a discussion as to whether CHC is a form of candidosis superimposed on leukoplakia or if the infection by *Candida* spp. can induce dysplastic epithelial changes; what is known is that antifungal treatment can promote total or partial resolution of CHC lesions.[14]

Since mucocutaneous candidosis has an early appearance in APS-1, a critical point in the treatment of these lesions lies in the fact that many patients need to use topical and systemic antifungals for long periods throughout their lives, which can result in microbial resistance.[12] Currently, the recommendation for the use of azole antifungals is not to exceed two to three treatments per year.[16] It is important to emphasize that there are currently no clinical trials that provide evidence of a standard protocol for the treatment of oral candidiasis in APS-1 patients. Therefore, many of the case reports or case series show expert experiences in the treatment of this condition. We suggest, based on our experience, the combined use of topical antifungal agents such as nystatin 100.000 IU mouthwash four times daily and systemic fungal agents such as Fluconazole (100 mg) once daily. This regimen should be continued for 4–6 weeks or for at least 1 week after the resolution of symptoms.

Enamel hypoplasia is another finding of dental interest that has been described in the present case and by other authors. The enamel defects in APS-1 have variable frequency and their etiopathogenesis is still not fully understood.[17] It is not known for certain whether these defects occur due to hypoparathyroidism with a consequent imbalance in the calcium-phosphate metabolism during amelogenesis, or if it is a result of the action of autoantibodies against enzymes that participate in the formation of the enamel.[18] Late tooth eruption, hypodontia, and incomplete root formation are other findings observed in the present case and they were reported in previous studies.[19] Different techniques are available for the treatment of enamel hypoplasia, such as crowns/veneers, traditional restorative treatments, microabrasion, whitening, remineralizing agents, and infiltration techniques. The choice between one technique and another must be made judiciously and must take into account the intensity of the defect and the available resources.

The first signs and symptoms of APS-1 are manifested in childhood and, according to a Norwegian cohort, the median age of death from complications of APS-1 is 34 years.[17] In our case, the poor oral health condition seemed to be part of the clinical picture of a long and persistent period of systemic health impairment. The literature also reports that many patients may develop reduced salivary flow and xerostomia, in a clinical setting that resembles Sjögren's syndrome, but in the absence of specific autoantibodies.[20] This salivary glandular dysfunction can be associated with the development of caries lesions and periodontal disease. In addition to these factors, there is a discomfort caused by CHC, which can impair oral hygiene. As there are little data available on the treatment of xerostomia/hyposalivation in this specific group of patients, we recommend the treatment proposed by Gil-Montoya et al. (2016) in their systematic review, which shows that pilocarpine is the most effective sialogogue agent to treat this condition. The dose of 5 mg of pilocarpine four times a day has been most commonly recommended and effective, especially when the tablets are dissolved in the mouth, with no significant adverse effects of this treatment.[21]

Because it is a rare syndrome, there is a lack of studies that adequately assess the biological plausibility between the observed genetic defect and the occurrence of other oral manifestations presented here. The few studies that try to establish these relationships are speculative and reflect the need for further in-depth studies on this topic.

The presence of damage to target organs such as the pancreas, liver, thyroid, and adrenals requires specific

adjustments to the dental treatment plan, which points to the need for a multiprofessional approach.[22] These adjustments could include an assessment of the effects of the patient's medical problems and drug therapy on dental care. We should also investigate specific oral problems that have arisen from either the underlying medical condition and the patient's medication, and possible interaction between the patient's oral health and their general health.[23]

4 | CONCLUSION

Mucocutaneous candidosis is one of the most persistent and characteristic oral manifestations of APS-1. Poor oral health, enamel defects, xerostomia, and dental development disorders are common in this condition.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ORCID

Jefferson R. Tenório https://orcid.org/0000-0002-6986-9148
Marina Maués Tuma https://orcid.org/0000-0002-7841-257X
Natália Silva Andrade https://orcid.org/0000-0001-5945-8401

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