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(CASE REPORT)

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Apeced's syndrome and lichen planus, is there a causal link? Clinical case and review of the literature (Case report)

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Abstract

- **Background:** Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy syndrome (APECED) is an autosomal recessive disorder characterised by the combination of autoimmune endocrine damage, mucocutaneous candidiasis and ectodermal tissue damage.
- **Case presentation:** we report the case of an 18-year-old female patient with APECED syndrome: the abnormalities found are in chronological order: primary hypoparathyroidism, mucocutaneous candidiasis, Addison's disease, Lichen planus, Biermer's anemia and autoimmune ovaritis. Lichen planus was diagnosed clinically and histologically.
- **Conclusion:** The occurrence of lichen planus is unusual in this syndrome. In this review, we first review the current knowledge of APECED syndrome and focus on the relationship between APECED syndrome and Lichen planus.

Keywords: APECED Syndrome; Lichen Planus; Genetics

1. Introduction

Autoimmune polyendocrinopathy type 1 (AEP1), also known as Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare autosomal recessive disease caused by mutations in the autoimmune regulatory gene (AIRE). Immunologically, APECED is characterized by the destruction of target organs by a cell-mediated and/or humoral attack (1). However, the association of APECED with lichen planus is unusual (2). The aim of this paper is to report the observation of a patient with APECED syndrome associated with Lichen planus, reviewing the clinical and therapeutic features of this syndrome and the possible link with Lichen planus.

2. Case presentation

Young 18-year-old patient from a consanguineous marriage, operated on for a bilateral cataract at the age of 2 years, diagnosed with APECED syndrome at the age of 6 years in the paediatric department of Casablanca after the discovery of hypocalcaemia secondary to primary hypoparathyroidism. Genetic exploration revealed a homozygous deletion of 10 base pairs on exon 6 of the AIRE gene. At the age of 18 the patient was admitted with acute adrenal insufficiency, after correction of the emergency and administration of corticosteroids, the questioning revealed the notion of secondary amenorrhea and the dermatological examination revealed onychodystrophy (F : A) as well as Lichen planus on the inner face of the cheek and both lower limbs (F : B+C). Hormonal assessment revealed hypergonadotropic hypogonadism and Biermer's anemia. The patient was put on alfa-calcidiol 2 ug/d + calcium 2 g/d + hydrocortisone 50

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mg/d + injection of vitamin B12 + oestroprogestatives + antifungal treatment. The evolution is marked by the normalization of the phosphocalcic balance but the persistence of onychodystrophy and Lichen planus.

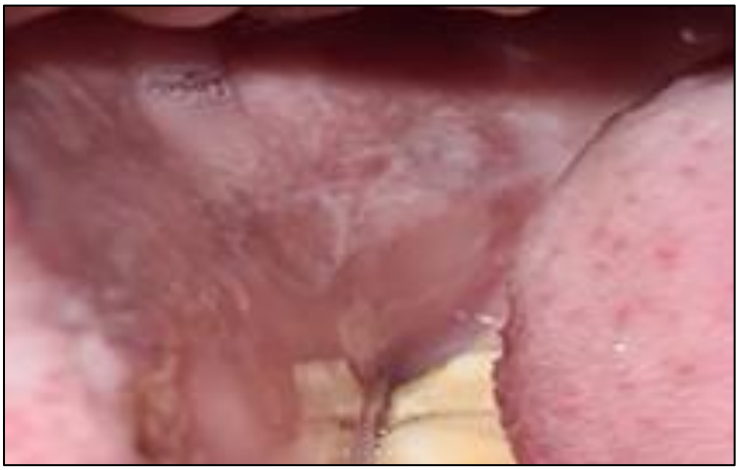

Figure 1 Lichen planus of the oral mucosa.

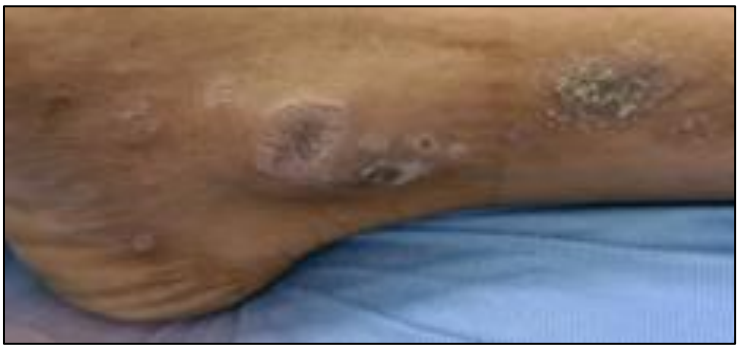

Figure 2 Appearance of lichen planus of the lower limb.

Figure 3 Bilateral onychodystrophy of all nails.

3. Discussion

APECED syndrome is a rare disease of autosomal recessive inheritance. In the last decade, great interest has been shown in the pathogenesis of this syndrome. Indeed, APECED represents a paradigm of genetically determined systemic autoimmunity. It has long been known that APECED is linked to a mutation in the AIRE gene, located at 21q22.3 (3). This gene encodes the AIRE protein, a transcription factor, which plays a role in central thymic tolerance and T-cell activation by dendritic cells (4, 5). However, the great variability that characterises APECED, independently of the AIRE genotype, implies that several factors are involved in the phenotypic expression of the disease (7). Susceptibility to infections, especially candidiasis, has long remained unexplained (8).

The clinical picture of APECED is polymorphic, the positive diagnosis being classically based on the presence, in a single individual, of two of the following three conditions: mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency. However, several recent notions suggest that this criterion needs to be reviewed (9).

Mucocutaneous candidiasis is the most common manifestation, except in Iranian Jews where it is rarely described. It most often occurs before the age of 5 years, frequently revealing the disease. It preferentially affects the oral mucosa (up to 100% of patients), the nails (in 2/3 of cases), and more rarely the genitals (10). The lesions described as oral candidiasis in APECED syndrome could in some patients be inflammatory lesions of the lichen planus type with a mycotic superinfection. This hypothesis would also explain the resistance described with long-term antifungal drugs due to the persistence of lichen planus lesions. The other hypothesis is the confusion of lichen planus with chronic candidiasis [11,12]. Lichen planus could be an unrecognised manifestation of APECED syndrome. The age of the patient does not correspond to the usual epidemiological data on the prevalence of oral lichen planus (incidence is higher in women with an average age of 50 years) [2,13]. Pathophysiologically, oral lichen planus is a chronic inflammatory disease characterised by the destruction of basal cells of the epithelium by Langerhans cells, macrophages and T cells [14], whereas in APECED syndrome there is no destruction of autoreactive T cells. These arguments suggest a possible link between APECED and lichen planus [13,15].

Hypoparathyroidism is the most common autoimmune disorder found in all studies. It is usually the first endocrine manifestation, most often present before the age of 10 (16).

Autoimmune ovaritis is classic in autoimmune polyendocrinopathies (AEP) (17). Its prevalence varies according to the type of syndrome, and is higher in APECED (>40%), in which the development of Addison's disease tends to precede that of premature ovarian failure (POI) (18). These results highlight the potential benefit of testing for anti-StCA antibodies in patients diagnosed with APECED. This test should allow the risk of developing POI in these patients to be stratified (19).

Other non-endocrine autoimmune visceral disorders can be seen such as: chronic gastritis which is complicated in severe forms of Biermer's anaemia, vitiligo, alopecia, ectodermal dystrophy, intestinal malabsorption, autoimmune hepatitis, splenic atrophy, tubulointerstitial nephritis.... (3).

The therapeutic management of APECED syndrome has a threefold aim: to substitute endocrine deficits; to control the consequences of the immune deficiency; and to control the autoimmune aggression with immunosuppressive therapies (20).

Substitution of hormonal deficiencies will be based on: compensation of hypoparathyroidism by active metabolites of vitamin D and calcium intake, intake of hydrocortisone and 9-alpha-fluorohydrocortisone in case of Addison's disease, correction of hypogonadism... Intestinal malabsorptions may justify iron, magnesium and vitamin D supplementation. Bacterial infections should be treated locally with antibiotics. Candidiasis infections require the usual oral or systemic anti-fungals, sometimes in sequential courses. Eradication of oropharyngeal candidiasis is essential for the prevention of loco-regional cancers. Pneumococcal vaccination is recommended in cases of documented splenic atrophy or recurrent bacterial infections (21, 22, 23).

Immunosuppressive therapy is essential for the control of autoimmunity in order to prevent irreversible damage to affected organs, and should only be prescribed after a thorough evaluation of the initiation, benefits and risks of preventive immunomodulation (22, 23).

The prognosis of APECED syndrome is quite severe, the disease is early progressive, usually from childhood to adulthood. The factors that contribute to its severity are not well understood. The risk of multi-visceral damage is greater the earlier the onset of the disease. The life expectancy of patients is reduced, although it is tending to improve.

Severe infections, oral or oesophageal carcinoma, hepatitis, complications related to hypoparathyroidism and adrenal insufficiency are the specific causes of death (21,22).

In the coming decades, research should focus on the prevention and targeted treatment of autoimmune diseases through early immunomodulatory therapy to stop the autoimmune process before irreversible organ damage occurs. Work is currently underway to generate thymic epithelial tissue from stem cells that could potentially be used to correct IAR expression and help reverse immunopathology (24).

Abbreviations

- APECED: Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy syndrome;

4. Conclusion

APECED syndrome is a rare condition that is difficult to diagnose because of its polymorphic nature and its ever-widening spectrum. Through this observation we highlight two points: the first is the possible link between APECED syndrome and lichen planus, the latter is probably an unrecognised manifestation of the syndrome; the second is the crucial interest of an early recognition and diagnosis of the different anomalies of this syndrome in order to allow a rapid intervention, a precise genetic counselling and thus to avoid the emergence of serious and irreversible autoimmune complications.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of informed consent

Patient informed and consent for publication obtained including images with written consent.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author.

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