A novel *AIRE* gene mutation in a patient with autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy revealed by alopecia areata

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INTRODUCTION

Autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy (APECED) syndrome is an autosomal recessive syndrome caused by biallelic mutations in the autoimmune regulator *AIRE* gene.[1] APECED is defined by at least 2 of the following conditions: hypoparathyroidism, chronic mucocutaneous candidiasis (CMC), and/or Addison disease.[1] Dermatologic manifestations of APECED syndrome are poorly reported.

CASE REPORT

Our patient, an 11-year-old boy of consanguineous parents, was referred to the dermatology department with a 6-month history of patchy alopecia. A family history for alopecia areata (AA) was found with a maternal aunt affected. Cutaneous examination found 2 oval patches of hair loss on the scalp with unscarred underlying skin. The hair loss involved other areas of the body: eyebrows, eyelashes, and arms. The nail examination found sandpaperlike fingernails. We did not notice dental enamel dysplasia. Immunologic investigations displayed positivity for autoantibodies to thyroid (antibodies against thyroglobulin and thyroperoxidase). One year later, cutaneous examination found *Candida* angular stomatitis and additional patches resulting in multiple areas of hair loss coalescing into a larger lesion. The follow-up examination found a recalcitrant angular stomatitis to local antifungal therapy, dysphagia, and AA that worsened into universalis form (Fig 1). APECED syndrome was suspected because of the presence of autoimmune disorders (AA and hypothyroidism) and CMC. Parathyroid and adrenal functions were normal. *AIRE* gene sequencing found a homozygous mutation in exon 2: *c.173 C>A*, p.Ala58Asp, a highly conserved amino acid among species with a PolyPhen score of 1 (probably damaging). The familial segregation is consistent with an autosomal recessive trait with complete penetrance (Fig 2). High levels of autoantibodies (auto-Abs) against

Abbreviations used:

AA:	alopecia areata
APECED:	autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy
Auto-Abs:	auto-antibodies
CMC:	chronic mucocutaneous candidiasis
IFN:	interferon
IL:	interleukin
Th:	T helper cell

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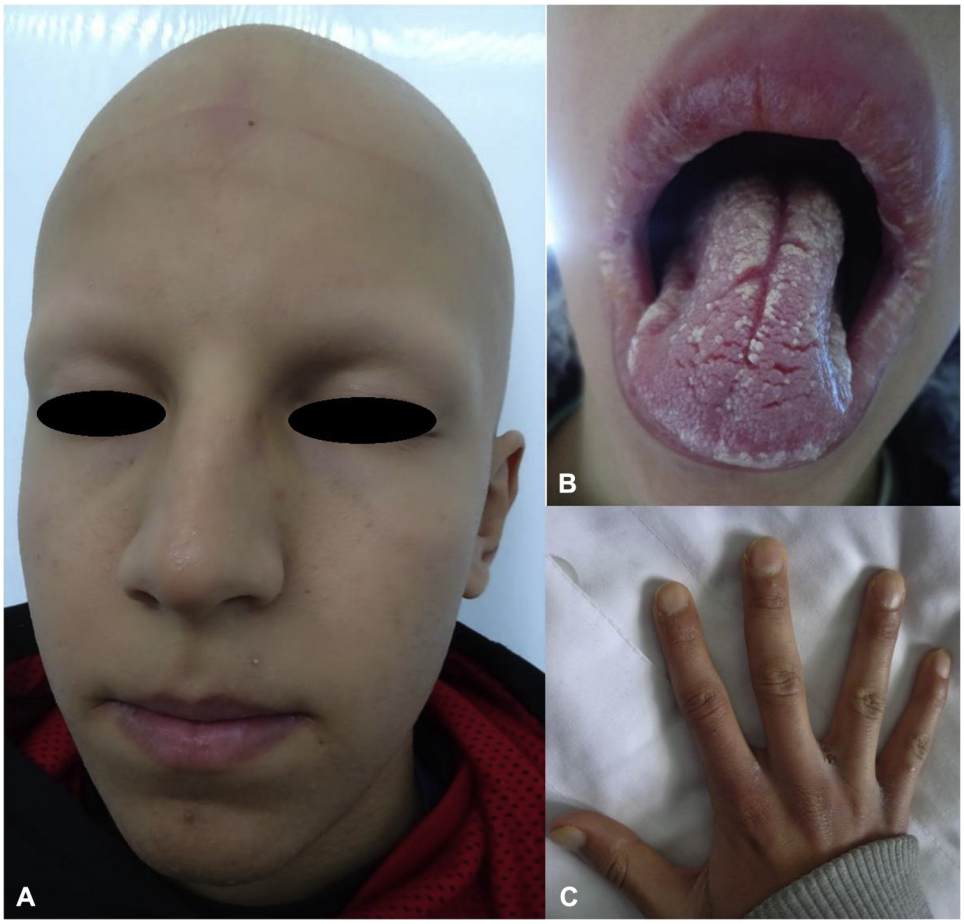

Fig 1. **A**, Alopecia universalis. **B**, Oral candidiasis and angular cheilitis. **C**, Sandpaperlike nails, intertriginous candidiasis of interdigital spaces.

cytokines (interleukin [IL]-17A, IL-17F, IL-22) and circulating auto-Abs against interferon (IFN)-α were found. The CMC was first treated with 100 mg/d of fluconazole during 4 months without any response. Voriconazole (200 mg/d) was administered orally during 2 months resulting in a significant regression of the angular stomatitis candidiasis. Intravenous systemic steroids were not effective for the treatment of alopecia universalis. On the latest examination at 16 years of age, there were no significant psychological impacts of alopecia universalis. Addison's disease and hypoparathyroidism were biologically excluded. Our patient was receiving replacement therapies for thyroid dysfunction and systemic antifungal therapy (fluconazole, 150 mg/wk) as a maintenance treatment of *Candida* infections.

DISCUSSION

The ectodermal manifestations in APECED syndrome refer to enamel hypoplasia of permanent teeth, nail dystrophy, tympanic membrane calcification, and dermatologic disorders (vitiligo and AA).[1] AA is a multifactorial autoimmune disease causing nonscarring hair loss. AA was variously reported as a minor component of APECED syndrome but was rarely described as the first sign of APECED. AA is reported in about 13% to 40% of patients with APECED.[1-3] The occurrence of AA in association with APECED syndrome does not seem to differ in prognosis from isolated cases of AA. Other skin diseases in APECED syndrome are represented mainly by CMC, a major diagnostic criterion.[3,4] CMC is the most prevalent and the earliest manifestation of APECED syndrome. Severity ranges from intermittent angular cheilitis to extensive variants.[3,4] Most patients do not respond to systemic antifungal therapies.[3] In our patient, CMC did not occur as the first manifestation of APECED syndrome and was represented by an isolated recurrent angular cheilitis that resisted topical antifungal drugs. Different cell-mediated anomalies were variously reported during CMC. It is frequently related to T-cell immunodeficiencies that alter the effectiveness in clearing mucocutaneous candidiasis.[5] Recently, investigators discovered auto-Abs against

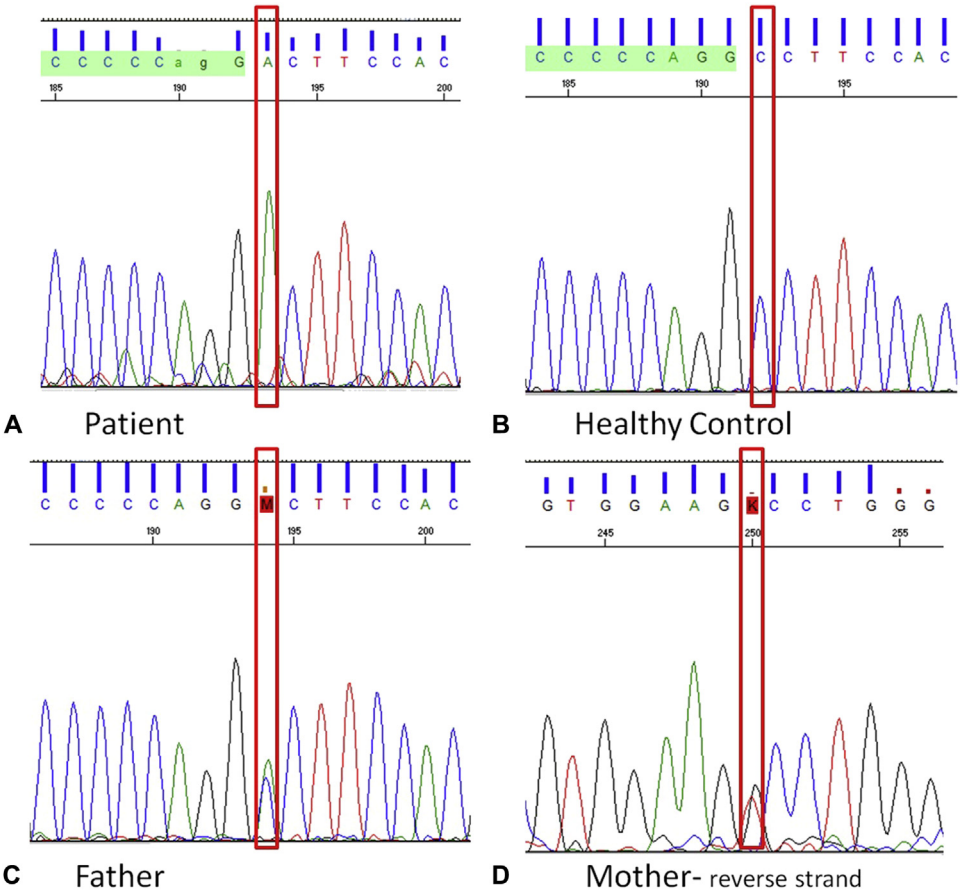

Fig 2. *AIRE* gene sequencing in exon 2. **A**, The novel homozygous mutation observed in our patient (c.173C>A, p.Ala58Asp), **B**, A WT control sequence. **C**, Heterozygous state for the novel mutation (c.173C>A, p.Ala58Asp) in the father's DNA. **D**, Heterozygous state for the novel mutation (c.173C>A, p.Ala58Asp) in the mother's DNA.

T helper cell 17 (Th17)-related cytokines (IL-22, IL-17A, IL-17F) in the sera of APECED patients, suggesting a probable role of impaired IL-17–mediated immune responses in the pathogenesis of this disease.[6,7] In our patient, high titers of auto-antibodies against Th17 cytokines were found. The presence of auto-antibodies against IFN-α was also found. In fact, auto-Abs against some IFNs, including IFN-α and IFN-ω, are present in all patients with APECED syndrome.[8,9] These auto-Abs are a hallmark of APECED syndrome and are therefore useful for diagnostic purposes.[9] The underlying genetic defect most often associated with APECED are mutations in the *AIRE* gene located in chromosome 21q22.3. In our Tunisian patient, molecular analysis of the *AIRE* gene found on exon 2 a new homozygous missense mutation *c.173C >A* (p. Ala58Asp). Vitiligo may occur alone or in association with AA. It is reported less commonly than alopecia, ranging from 8% to 25% of APECED cases.[1,3] Nail dystrophy is reported as an ectodermal manifestation, but its pathogenesis is still conflicting: investigators report the possibility that this occurs as a manifestation of ungueal candidiasis or in association with AA.[1,3] The enamel hypoplasia is multifactorial and may be secondary to recurrent oral infections, malnutrition, or prolonged hypocalcemia rather than a primary failure of morphogenesis.[3,4,10] No history of middle ear disease is reported in association with the calcium salt deposit in the tympanic membrane.[10] The recent understanding of the *AIRE* gene and the current identification of several autoantigens associated with APECED syndrome does not support that APECED is a primary ectodermal dysplasia, and the autoimmune origin of these manifestations seems conceivable.[3,4] Thus, the term *ectodermal dystrophy* seems misleading.

This case is quite original in that the patient exhibited a nonclassical clinical picture with atypical manifestations and way of onset. In such a case, we think it is appropriate to perform an analysis of the *AIRE* gene to diagnose APECED early.

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