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CASE REPORT

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An uncommon presentation of autoimmune polyglandular syndrome type 1 (APS-1)—A case report

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Key Clinical Message

Autoimmune polyglandular syndrome type 1 (APS-1) is a rare disorder defined by the presence of at least two of the following conditions: chronic mucocutaneous candidiasis (CMC), chronic hypoparathyroidism, and Addison's syndrome. Despite the lack of CMC and autoimmune history, APS-1 can be diagnosed using genetic testing.

We present the case of a 28-year-old female patient with a history of hypocalcemia due to hypoparathyroidism since the age of 2 years. She presented to the endocrine clinic with hypogonadism, primary amenorrhea, and primary ovarian insufficiency. Addison's disease was eventually diagnosed, despite a negative Synacthen test. The adrenal crisis required intravenous hydrocortisone therapy. No CMC was documented, and there was no family history of such conditions. The diagnosis of APS-1 was confirmed by genetic testing, revealing homozygous pathogenic variants of the autoimmune regulator gene. Management included oral calcium and calcitriol and oral hydrocortisone and fludrocortisone for Addison's disease. Hormonal induction of secondary sexual characteristics was initiated. The patient received combined oral estrogen and progesterone pills. This case highlights the critical significance of early recognition, thorough evaluation, and tailored treatment for patients with APS-1 to enhance their quality of life and mitigate potentially life-threatening complications. This underscores the importance of screening for associated minor autoimmune diseases as part of a holistic approach to care.

KEYWORDS

AIRE gene mutation, autoimmune diseases, endocrine disorders, hormonal replacement therapy, polyglandular autoimmune syndrome type 1, primary ovarian insufficiency

1 | INTRODUCTION

Autoimmune polyglandular syndrome type 1 (APS-1) is defined by the presence of at least two of three primary disorders during childhood: chronic mucocutaneous candidiasis (CMC), chronic hypoparathyroidism (CH), and Addison's disease.[1] APS-1 is an uncommon condition with an estimated prevalence of 10 cases per million people.[2] It is an uncommon autosomal recessive condition caused by autoimmune regulator (AIRE) gene mutations.[3,4] AIRE can eliminate autoreactive T cells by controlling the expression of several tissue-specific antigens in medullary thymic epithelial cells and drive regulatory T cell production to maintain central immunological tolerance.[5,6] As a result, various autoimmune disorders arise at a young age.[7,8]

Primary ovarian insufficiency (POI) affects approximately 60% of APS-1 women before the age of 30 years. Other associated conditions include enamel hypoplasia, enteropathy with chronic diarrhea or constipation, bilateral keratitis often accompanied by severe photophobia, recurrent fever with rash, autoimmunity-induced hepatitis, pneumonitis, nephritis, exocrine pancreatitis, and functional asplenia.[9–11] Patients may present with other autoimmune and non-autoimmune diseases and ectodermic dystrophy.[12] At onset, 80%–90% of patients had one or more major symptoms, while a small proportion (5%–20%) had additional disorders.[12,13]

The diagnosis of APS-1 is frequently delayed and sometimes made only after the patient's death, based on the diagnosis of a sibling.[14] Due to the availability of AIRE sequencing and particular autoantibody assays, milder and more unusual cases of APS-1 in people lacking two of the three core components have been discovered.[14] Because autoantibodies to type 1 interferon are present in more than 95% of APS-1 patients, comprehensive testing for such antibodies in suspected cases may be beneficial.[10,15]

2 | CASE HISTORY/EXAMINATION

A 28-year-old female patient presented with hypogonadism, primary amenorrhea, and a history of hypocalcemia since the age of 2 years due to hypocalcemia-induced tetany resulting from hypoparathyroidism, leading to recurrent hospital admissions. She has been treated with oral calcium and calcitriol for a long time since the diagnosis of hypoparathyroidism. Further testing revealed POI indicated by amenorrhea, low estradiol levels, and increased serum gonadotropin concentrations. No CMC had been documented, and there was no family history of such conditions.

During clinical examination, the patient was stable. She had no fever and her vitals were normal. Her heart rate was regular at 83 beats per minute, body temperature was 37.1°C, and blood pressure was within the normal range while standing (117/71 mmHg) and sitting (113/68 mmHg). She did not report orthostatic hypotension. Her height was 156 cm and her weight was 48 kg (body mass index = 19.72). Oxygen saturation in room air was recorded as healthy at 99%. Breast examination revealed delayed development corresponding to Tanner stage II. No other noticeable findings were observed on physical examination.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT)

The patient's calcium and phosphorus levels were 1.6 mmol/L (range: 2.2–2.6 mmol/L) and 1.75 mmol/L (range: 0.81–1.45 mmol/L), respectively, while parathyroid hormone was undetectable. Vitamin D was measured at 33.63 ng/mL (range: 30–74 ng/mL), and urinary calcium was observed at 5.1 mg/dL (range: 2.5–6.2 mg/dL), suggesting hypoparathyroidism. Hormonally, the patient exhibited low levels of estradiol (42.13 pmol/L; range for premenopausal women: 73.8–859.0 pmol/L), elevated levels of gonadotropins, follicle-stimulating hormone (FSH) at 108.4 IU/L (range for premenopausal women: 3.5–12.5 IU/L), and luteinizing hormone at 57.28 mIU/mL (range for premenopausal women: 2.4–12.6 mIU/mL). The thyroid function markers indicated a thyroid stimulating hormone (TSH) of 2.43 mIU/L (range: 0.4–4.0 mIU/L) and a free thyroxine level (free T4) level of 16.19 pmol/L (range: 9.0–19.0 pmol/L). Cortisol levels were notably elevated at 424.9 μmol/L (range: 138–635 μmol/L). Additionally, electrolyte values, including sodium and potassium, fell within normal ranges, as did magnesium, creatinine, and glycosylated hemoglobin levels.

Pelvic transabdominal ultrasound revealed a small uterus measuring 4 × 1.7 cm, characterized by a homogenous myometrium without focal lesions. The uterinary bladder appeared empty, and the endometrial thickness was 3 mm (Figure 1). Visualization of both ovaries was challenging during this examination, limiting the assessment of their condition. The patient underwent screening for other autoimmune diseases as part of the comprehensive evaluation of her autoimmune status. These included tests for type 1 diabetes mellitus (islet cell antibodies,

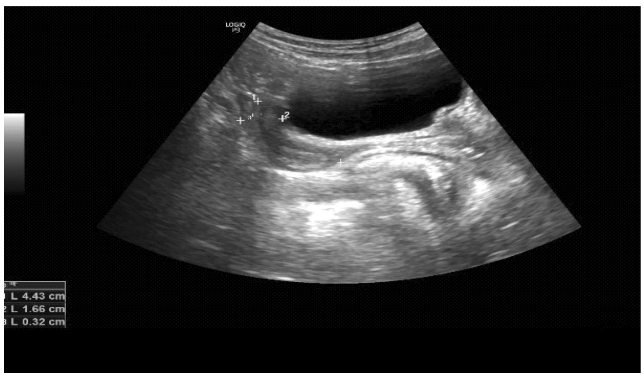

FIGURE 1 Pelvic ultrasound showing a small anteverted flexed uterus (4 × 1.7 cm) with homogenous myometrium. The endometrium thickness is 3 mm.

insulin autoantibodies, and glutamic acid decarboxylase antibodies), celiac disease (anti-tissue transglutaminase antibodies and anti-endomysial antibodies), and autoimmune adrenal insufficiency (21-hydroxylase antibody test). The results revealed the presence of antibodies against 21-hydroxylase, indicating autoimmune involvement of adrenal glands.

The patient's medical history became more complex during this assessment when Addison's disease, triggered by urinary tract infection, was diagnosed (with ACTH level of 65 pg/mL [range: 7–50 pg/mL], cortisol level of 18.7 nmol/L [range: 123–626 nmol/L], glucose level of 92 mg/dL [range: 70–99 mg/dL], sodium level of 132 mmol/L [range: 135–145 mmol/L], and potassium level of 4.6 mmol/L [range: 3.5–5.1 mmol/L]). Interestingly, despite having a negative Synacthen test, she later developed an adrenal crisis, necessitating immediate intravenous hydrocortisone treatment. Testing revealed two of the three primary criteria for APS-1, which included hypoparathyroidism and Addison's disease. Genetic testing revealed homozygous pathogenic variants of the AIRE gene, providing conclusive evidence to confirm the diagnosis of APS-1.

4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW-UP)

The patient's treatment strategy was comprehensive, addressing various endocrine problems and immunological components. To control her hypocalcemia, she was administered oral calcium (calcium carbonate 1200 milligrams Three times a day) and calcitriol regularly (3 micrograms (μg) Once a day). To restore hormonal balance in Addison's disease, the patient was prescribed oral hydrocortisone at a dose of 10 mg in the morning and 5 mg in the afternoon, along with fludrocortisone at a daily oral dose of 0.1 mg. Furthermore, given the diagnosis of POI, a low dose of estradiol was used to initiate hormonal induction of secondary sexual characteristics. We gave ethinyl estradiol 2 mg every other day. Now, she is on Climen, which is a preparation that contains 2 mg estradiol valerate and 1 mg cyproterone acetate.

5 | DISCUSSION

The patient presented with a complex medical history characterized by hypocalcemia in early childhood, leading to tetanic episodes and, subsequently, in adulthood, the development of premature ovarian failure. A diagnosis of APS-1 was established based on the presence of two major clinical features of the syndrome: hypoparathyroidism and Addison's disease. CMC, another major characteristic of APS-1, was absent in this case. The diagnosis was further confirmed by genetic sequencing, which revealed mutations in the AIRE gene, a hallmark of the syndrome. Importantly, no other concomitant endocrine or immunological conditions were identified and the patient reported no family history of similar medical conditions, underscoring the uniqueness and complexity of this case.

In general, APS-1 is managed with hormone replacement therapy and the treatment of comorbidities. A multidisciplinary team directed by an endocrinologist in a tertiary care center is best suited for patients with APS-1.[2] Due to the complexity of the condition, patients should have at least two follow-up visits each year, and asymptomatic carriers of mutations should be observed at least annually. All siblings of APS-1 patients must be tested, even if they are adults, and appear healthy. Screening for 21-hydroxylase and NALP5 autoantibodies can help determine the risk of developing adrenal insufficiency and hypoparathyroidism.[2,16]

Patients with hypoparathyroidism must be administered calcium and vitamin D derivatives in amounts sufficient to maintain plasma calcium in the lower half or slightly below normal and urine calcium in the normal range. Adrenal insufficiency should be diagnosed as a life-threatening disorder as soon as the symptoms appear. Glucocorticoid replacement must be initiated quickly, and doses must be increased during periods of acute stress, such as infection or surgery. When glucocorticoid replacement is increased, it is critical to be aware of the possibility

of hypocalcemia and to alter hypoparathyroidism treatment accordingly.[16]

Mineralocorticoid deficiency is treated with fludrocortisone acetate. L-thyroxine supplementation is administered in cases of hypothyroidism, always after ruling out or treating adrenal insufficiency. Thyroid hormones increase hepatic clearance of cortisol, which may precipitate an adrenal crisis in undiagnosed adrenal insufficiency. In addition, patients with untreated adrenal insufficiency may display a reversible increase in thyrotropin levels, because glucocorticoids inhibit thyrotropin secretion. Estrogen or androgen replacement should be started at pubertal age in hypogonadal children. Doses should be gradually increased, and treatment should be maintained during adulthood. Vitamin B12 replacement therapy should be administered whenever necessary. Notably, intestinal disturbances can lead to inadequate and unpredictable drug absorption. This can pose challenges in maintaining the proper levels of hormones and other substances. In some cases, malabsorption can be addressed by taking pancreatic enzymes or by modifying dietary fat intake, such as reducing fat consumption or replacing typical fats with medium-chain triglycerides.[17]

In conclusion, the patient's journey emphasizes the complexity of PAS-1 and underscores the critical need for comprehensive evaluation in clinical practice. Tailored management strategies are essential to optimize patient well-being and quality of life while also preventing potential complications associated with this rare autoimmune syndrome. Monitoring and screening for other potential minor autoimmune diseases associated with this disease will be integral to patient care.

AUTHOR CONTRIBUTIONS

Ali M. Alrufaidi: Conceptualization; methodology; supervision; visualization; writing – original draft; writing – review and editing. **Mohammed Mosa Alnashery:** Methodology; supervision. **Ageel Ahmad Alghanimi:** Conceptualization; methodology; supervision; visualization; writing – original draft; writing – review and editing. **Rash Elamin Ahmed Elmansor:** Conceptualization; methodology; supervision; visualization; writing – original draft; writing – review and editing. **Ramy Mohamed Ghazy:** Conceptualization; validation; writing – review and editing.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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REFERENCES

1. Neufeld M. Polyglandular autoimmune diseases. *Symposium on Autoimmune Aspects of Endocrine Disorders*. Academic Press; 1980.
2. Husebye ES, Anderson MS, Kämpe O. Autoimmune polyendocrine syndromes. *N Engl J Med*. 2018;378(12):1132-1141.
3. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet*. 1997;17(4):399-403.
4. Nagamine K, Peterson P, Scott HS, et al. Positional cloning of the APECED gene. *Nat Genet*. 1997;17(4):393-398.
5. Weiler FG, Dias-da-Silva MR, Lazaretti-Castro M. Autoimmune polyendocrine syndrome type 1: case report and review of literature. *Arq Bras Endocrinol Metabol*. 2012;56:54-66.
6. Fierabracci A. Recent insights into the role and molecular mechanisms of the autoimmune regulator (AIRE) gene in autoimmunity. *Autoimmun Rev*. 2011;10(3):137-143.
7. Bruserud Ø, Oftedal BE, Wolff AB, Husebye ES. AIRE-mutations and autoimmune disease. *Curr Opin Immunol*. 2016;43:8-15.
8. Passos GA, Speck-Hernandez CA, Assis AF, Mendes-da-Cruz DA. Update on AIRE and thymic negative selection. *Immunology*. 2018;153(1):10-20.
9. Ahonen P, Myllärniemi S, Sipilä I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med*. 1990;322(26):1829-1836.
10. Bruserud Ø, Oftedal BE, Landegren N, et al. A longitudinal follow-up of autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab*. 2016;101(8):2975-2983.
11. Ferre EM, Rose SR, Rosenzweig SD, et al. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *JCI Insight*. 2016;1(13):e88782.
12. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev*. 2002;23(3):327-364.

13. Guo C-J, Leung PSC, Zhang W, Ma X, Gershwin ME. The immunobiology and clinical features of type 1 autoimmune polyglandular syndrome (APS-1). *Autoimmun Rev*. 2018;17(1):78-85.
14. Wolff AS, Erichsen MM, Meager A, et al. Autoimmune polyendocrine syndrome type 1 in Norway: phenotypic variation, autoantibodies, and novel mutations in the autoimmune regulator gene. *J Clin Endocrinol Metab*. 2007;92(2):595-603.
15. Orlova EM, Sozaeva LS, Kareva MA, et al. Expanding the phenotypic and genotypic landscape of autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab*. 2017;102(9):3546-3556.
16. Sperling MA, Angelousi A, Yau M. Autoimmune polyglandular syndromes. 2015.
17. Perheentupa J. APS-I/APECED: the clinical disease and therapy. *Endocrinol Metab Clin N Am*. 2002;31(2):295-320.

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