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CASE REPORT

Autoimmune Polyglandular Syndrome Type 2 Presentation with Alopecia Universalis, Hashimoto's Disease, and Addison's Disease

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Abstract: Autoimmune polyglandular syndrome type 2 (APS2) is characterized by the coexistence of primary adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes. APS2 frequently includes conditions affecting non-endocrine organs, such as alopecia, vitiligo, celiac disease, and autoimmune gastritis associated with vitamin B12 deficiency. We report the case of a 30-year-old male with a history of Hashimoto's disease and alopecia universalis, who presented with diarrhea, anorexia, hypoglycemia, and abdominal pain. Physical examination revealed orthostatic hypotension, a non-tender abdomen, and generalized hair loss. Initial laboratory workup showed hyponatremia and hyperkalemia. Further testing, including serum cortisol, ACTH, aldosterone, and 21-hydroxylase antibodies, confirmed the diagnosis of Addison's disease. The patient was treated with prednisone and fludrocortisone. Only two previous cases of APS2 associated with alopecia universalis have been reported: one with concurrent Crohn's disease and another with hypoparathyroidism. This case highlights the importance of recognizing non-endocrine manifestations in patients with autoimmune endocrinopathies to facilitate earlier diagnosis and management.

Keywords: autoimmune polyglandular syndrome type 2, alopecia universalis, Addison's disease, adrenal crisis

Introduction/Background

Autoimmune polyglandular syndromes are characterized by circulating autoantibodies and lymphocytic infiltration of the affected tissues or organs, eventually leading to organ failure. Autoimmune polyglandular syndrome type 2 (APS2) is characterized by the coexistence of primary adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes.[1] APS2 is a rare disease, with an incidence of 1–2 per 100,000 cases per year. When associated with thyroid disease, 50% will start as Hashimoto's disease.[2] APS2 is a condition that appears in adulthood. Most reported cases are women between the third and fourth decades of life.[3] The heritability of APS2 is complex. Single-nucleotide polymorphisms are associated with various organ-specific autoimmune diseases. Genes encoding key regulatory proteins in both the adaptive and innate immune systems, particularly those in the major histocompatibility complex, confer a significant risk of developing endocrinopathies. APS2 frequently includes conditions that affect non-endocrine organs, such as alopecia, vitiligo, celiac disease, and autoimmune gastritis with vitamin B12 deficiency.[1]

Alopecia universalis (AU) is defined as an inflammatory scarring hair loss disorder.[4] AU is the severe form of alopecia areata characterized by the complete loss of hair on the scalp and body. AU is rare, with an incidence of 0.02%.[5] A recent systematic review found insufficient data to assess autoimmune comorbidities and the overall prevalence of AU.[5]

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Due to the rare occurrence of APS2 and its association with non-endocrine autoimmune conditions, we report a case of a patient with APS2, AU, and Hashimoto's disease who subsequently developed Addison's disease.

Case Description

A 30-year-old-male identical twin with a past medical history of alopecia universalis diagnosed in 2007, Hashimoto's thyroiditis diagnosed in 2016, treated with levothyroxine 200mcg daily, and had multiple previous admissions for hyponatremia and dehydration.

He presented to the emergency department with two days of diarrhea, anorexia, and abdominal pain. Initially, he had six loose stools accompanied by anorexia and lower abdominal pain. His condition progressed to twelve stools in 24 hours. The following day, he was found unconscious at work, and he was brought to the emergency department. His capillary glucose level was at 26 mg/dl, and his consciousness was restored after administering a 5% glucose solution.

The physical examination revealed on admission a blood pressure of 100/54 mmHg, heart rate of 76 bpm, weight of 70 kg, height of 1.76 m, and BMI of 22.6. He was alert and awake. No oral ulcers or rash were noted. The cardiovascular exam showed normal S1 and S2, no murmurs, and normal pulses in all four extremities. Abdominal examination showed normal abdominal circumference, soft and non-tender. It revealed hair loss on the scalp (Figure 1) and eyebrows (Figure 2), both arms (Figure 3A and B), both legs (Figure 3C and D), and upper and lower body (Figure 4).

He presented with a sodium of 126 and a potassium level of 7.4. The spot urinary electrolyte levels were sodium of 143 mmol/L, potassium of 16 mmol/L, and chloride of 151 mmol/L. As he revealed orthostatic hypotension, he was admitted to the general internal medicine ward with nephrology and endocrinology consultations.

Clinical Course

On admission, He developed restlessness, feeling the urge to move or change from a supine to a seated position, and frequently reported abdominal pain; however, the abdominal examination was otherwise unremarkable. His blood work showed a random serum cortisol of 1.5 µg/dL, ACTH of 1250 pg/mL, and aldosterone of 3.33 ng/dL, leading to the diagnosis of primary adrenal insufficiency.

He was started on IV normal saline 0.9% at a rate of 125mL per hour, hydrocortisone 100 mg IV TID along with treatment for hyperkalemia with polarizing solution (insulin lispro 10UI with glucose 50%), furosemide 20mg IV TID, 3 g of magnesium sulphate, and empirical ciprofloxacin for a suspected gastrointestinal infection due to his abdominal symptoms and a procalcitonin of 0.25 ng/mL.

The nephrology consult continued the hyperkalemia treatment and initiated zirconium silicate. Nonetheless, the patient responded appropriately to hydrocortisone. The restlessness resolved within 6 hours of hydrocortisone administration. The rest of the laboratory values are in Table 1.

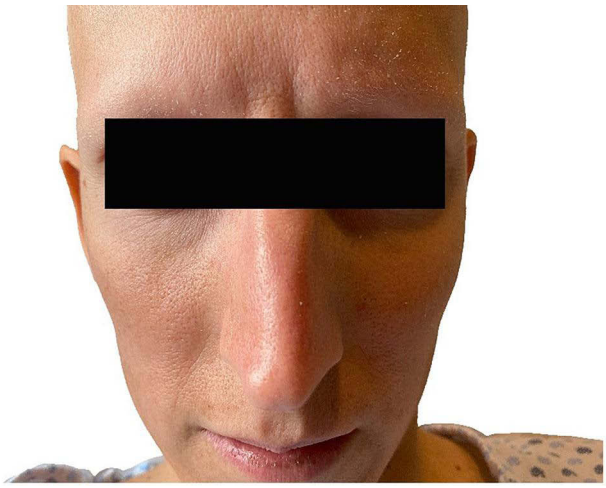

Figure 1 Image of the patient with hair loss in eyebrows. Non-scarring loss of eyebrow hair with no signs of local inflammation.

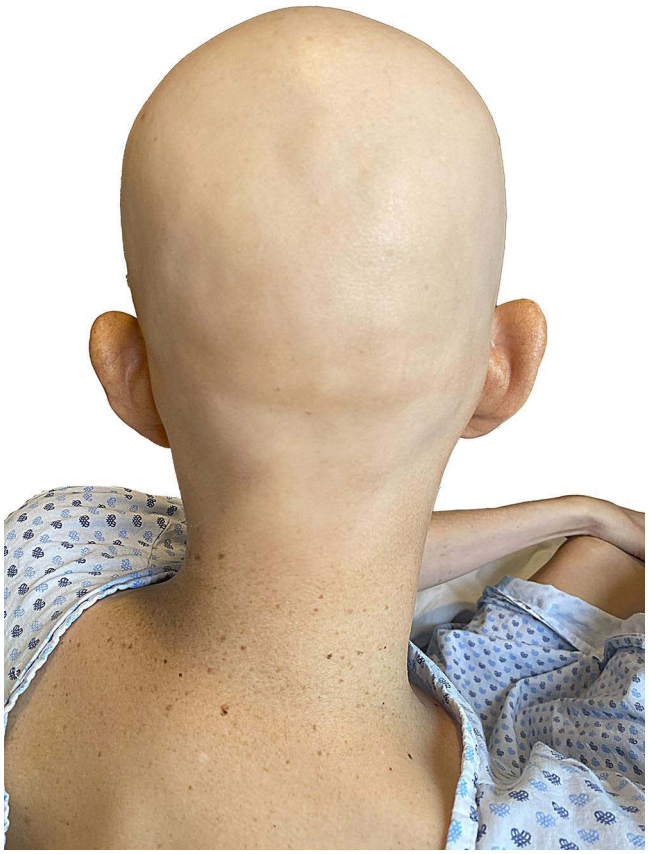

Figure 2 Image of the patient with hair loss in the scalp. Complete scalp alopecia consistent with alopecia universalis.

On day 2 of hospitalization, a CT scan of the abdomen and adrenal glands with intravenous contrast showed medullary calcifications and three 3–4mm pulmonary nodules. His hyponatremia and hyperkalemia resolved without additional medication. The endocrinology consult ordered thyroid function and thyroid antibodies and reported TSH at 0.0065 mIU/L (reference value 0.35–4.94), normal free T4 levels, TPO antibodies at 172.74 UI/mL (reference value 0–5.61), and antithyroglobulin antibody at 133.15 UI/mL (reference value 0–4.11). Modifying his levothyroxine dose to 112.5 mcg daily.

On day 3, his hydrocortisone dose was reduced to 100 mg twice daily and on day 4 to 100 mg once daily. He no longer developed hypotension, hyperkalemia or hyponatremia. His hemoglobin remained at 8 g/dL, and his C-reactive protein levels remained normal. As a possible diagnosis of pernicious anemia, the measurement of vitamin B12 levels was 2405.8 pg/mL (reference value 187–883), folate levels were 4.47 ng/mL (reference value 3.10–20.5), intrinsic factor antibody of 2.76 UI, and parietal cell antibodies of 110.9 UI (reference value 0–20).

He was discharged for ambulatory follow-up on day 5 with prednisone 10 mg and fludrocortisone 0.1mg. He did not develop orthostatic hypotension and his mean arterial pressure remained above 65 mmHg.

This patient presented acute symptoms compatible with Addison's disease. His history of alopecia universalis, Hashimoto's disease, abdominal signs, and elevated C-reactive protein levels suggested the possibility of a concomitant infection and/or inflammatory process at the time of presentation. However, the positive antibody tests of the adrenal test confirmed the autoimmune cause of adrenal insufficiency.

Discussion

Schmidt described in 1962 two cases of Addison's disease with cortical atrophy and lymphocytic infiltration of the adrenal glands, as well as lymphoid infiltration of the thyroid gland. These cases were later recognized as APS2.[6] The association between autoimmune endocrinopathies and dermatological manifestations such as alopecia universalis

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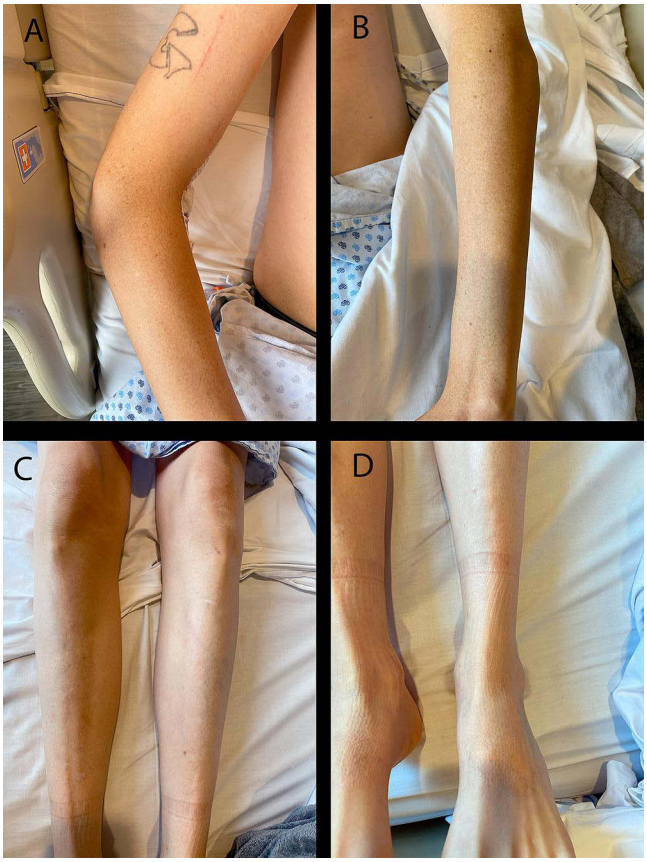

Figure 3 Images of the patient showing hair loss on the right arm (**A**), left arm (**B**), upper legs (**C**), and lower legs (**D**). Widespread non-inflammatory alopecia involving upper and lower extremities.

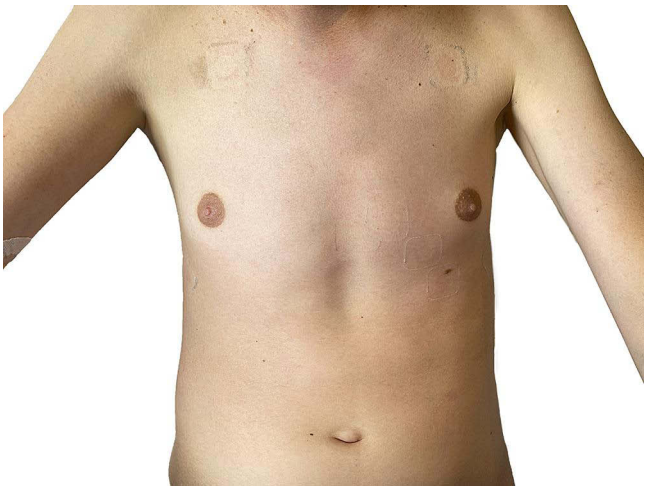

Figure 4 Image of the patient with hair loss in upper and lower body. Diffuse alopecia affecting the trunk and extremities, with no evidence of erythema or scarring.

remains underreported. This case highlights the progression from Hashimoto's thyroiditis to Addison's disease over several years, consistent with the latency period described in APS2. The clinical presentation of autoimmune polyglandular syndromes is often preceded by a prolonged asymptomatic phase characterized by the isolated presence of circulating antibodies. The evolution of APS2 from the initial onset of Hashimoto's thyroiditis to the development of an additional endocrinopathy has a mean latency of 10.3 ± 8.7 years, as demonstrated in a retrospective cohort study.[7]

Table 1 Laboratory Results on Admission, Day 1, and Day 5

Test	On Admission	Day 1	Day 5	Reference Value
Glucose (mg/dL)	68	68	100	70–99
BUN (mg/dL)	27	18	11	9–20
Urea (mg/dL)	57.78	38.5	23.5	19–43
Creatinine (mg/dl)	1.20	1.10	0.6	0.66–1.25
Urate (mg/dl)	8.8	–	4.2[a]	2.5–6.2
Na (mmol/L)	125	124	136	137–145
K (mmol/L)	7.5	6.5	3.3	3.5–5.1
Cl (mmol/L)	98	100	107	98–107
P (mg/dL)	5.9	4.4	2.8	2.5–4.5
Mg (mg/dL)	1.16	1.1	1.9	1.6–2.3
Ca (mg/dL)	9.2	8.3	8.1[a]	8.4–10.2
Albumin (gr/dl)	–	–	2.9[a]	3.5–5
Ph	7.21	–	7.35[a]	7.32–7.42
HCO3	14.1	–	20[a]	21–23
C-reactive protein (mg/L)	48	–	8	0–10
Hemoglobin (gr/dl)	–	10.67	8.1	13–17
Platelets ($x10^3$ /mm^3)	–	112.8	134	150–450
Leukocytes ($x10^3$ /mm^3)	–	4.7	5.1	4.5–11.5

Note: [a]Indicates data obtained on day 3.
Abbreviations: Na, sodium; K, potassium; Ca, Calcium; Mg, magnesium; Cl, Chloride; P, Phosphate; BUN, blood urea nitrogen.

Patients diagnosed with one autoimmune endocrinopathy should undergo annual screening for the first two years, followed by evaluations every two years over the next six years, to assess for other associated conditions such as type 1 diabetes, celiac disease, rheumatoid arthritis, chronic atrophic gastritis, systemic lupus erythematosus, vitiligo and additional thyroid disorders.[7] While alopecia is a known extra-endocrine manifestation of APS2, alopecia universalis is exceedingly rare in this context. There have been only two previously published case reports describing the association between APS2 and AU, which highlights the rarity of this clinical association. In one case, the patient had Crohn's disease; in the other, hypoparathyroidism was present.[8,9]

Additionally, this case underscores the relevance of early screening and monitoring in patients with autoimmune diseases. The timely measurement of ACTH and cortisol, along with antibody testing, allowed for rapid diagnosis and initiation of life-saving treatment. Interestingly, the elevated vitamin B12 levels—along with positive parietal cell and intrinsic factor antibodies—suggest a subclinical phase of autoimmune gastritis or pernicious anemia, even in the absence of anemia or symptoms, reflecting the broader autoimmune dysregulation in APS2.

A limitation of this report is the absence of longitudinal follow-up to evaluate the long-term response to therapy and monitor for additional autoimmune conditions. However, this case serves as a clinical reminder to maintain a high index of suspicion for adrenal insufficiency in patients with established autoimmune diseases presenting with non-specific gastrointestinal symptoms or electrolyte imbalances.

Considering the elevated risk of developing additional autoimmune diseases, further exploration of genetic mechanisms and immunological mechanisms could allow for a more precise subclassification of autoimmune polyglandular syndromes, ultimately improving treatment strategies and prognosis.

Conclusion

This case highlights the importance of considering autoimmune polyglandular syndrome type 2 as a differential diagnosis in patients presenting with multiple endocrinopathies and non-endocrine conditions. Providing clinical clues for identifying non-endocrine-associated conditions in patients with at least one autoimmune endocrinopathy, aiming to raise awareness among clinicians.

The coexistence of alopecia universalis, Hashimoto's disease, and Addison's disease in a single patient underscores the clinical complexity of autoimmune diseases and the need for a multidisciplinary approach to their diagnosis and management.

Timely recognition and treatment of these conditions can prevent severe complications and improve the patient's quality of life. This report not only emphasizes the relevance of initial clinical manifestations, such as electrolyte imbalances and dermatological features but also suggests the necessity of ongoing monitoring in patients with autoimmune endocrinopathies to detect potential future comorbidities.

Ethical Approval

This case report didn't require review by the Ethics committee at Hospital Español de Veracruz.

Consent Statement

Written informed consent was obtained from the patients for publication and accompanying images. A copy of the written consent is available for review.

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Disclosure

All authors declared no conflicts of interest in this work.

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