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SLOW EVOLUTION OF NON-FAMILIAL AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE II IN A 54-YEAR-OLD FEMALE, FIRST PRESENTING WITH ADDISON'S DISEASE, THEN HASHIMOTO'S THYROIDITIS, WHICH THEN TRANSITIONED TO GRAVES' DISEASE AND THEN THE DEVELOPMENT OF TYPE 1 DIABETES

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ABSTRACT

Background: Autoimmune polyglandular syndrome type II (APS-II) is a rare disorder defined by primary adrenal insufficiency in combination with autoimmune thyroid disease and/or type 1 diabetes mellitus. The dynamic nature of autoimmunity complicates diagnosis and management.

Case report: A 54-year-old woman presented in 2009 with Addison's disease, confirmed by very low cortisol and markedly elevated adrenocorticotropic hormone, despite negative adrenal antibodies. She remained stable on steroid replacement until 2019, when she developed hypothyroidism with elevated thyroid-stimulating hormone (TSH) and positive thyroglobulin antibodies, consistent with Hashimoto's thyroiditis. In 2023, she experienced new hyperthyroid symptoms with suppressed TSH, elevated free thyroxine, positive thyroid-stimulating immunoglobulin, and ultrasound evidence of diffuse hypervascularity, confirming Graves' disease. Concurrent screening revealed haemoglobin A1c 6.2% and positive GAD65 antibody, consistent with a risk of autoimmune diabetes, although without overt hyperglycaemia.

KEYWORDS

Autoimmune polyglandular syndrome type II, Addison's disease, Graves' disease, Hashimoto's thyroiditis, autoimmune diabetes

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LEARNING POINTS

- *Autoimmune polyglandular syndrome type II is progressive and unpredictable:* New endocrinopathies may develop years or even decades after the initial presentation, requiring lifelong surveillance.
- *Autoimmune thyroid disease can be dynamic:* Although rare (~1% of cases), transitions from Hashimoto's hypothyroidism to Graves' hyperthyroidism are well documented and should be considered when thyroid function changes unexpectedly.
- *Clinical vigilance is crucial:* Suppressed thyroid-stimulating hormone in a patient on levothyroxine is not always due to over-replacement; testing for thyroid-stimulating immunoglobulin should be considered to exclude evolving Graves' disease.
- *Adrenal insufficiency must be recognized before thyroid therapy:* Initiating levothyroxine without adequate glucocorticoid coverage can precipitate adrenal crisis in autoimmune polyglandular syndrome type II.
- *Multidisciplinary care improves outcomes:* Coordinated management between endocrinology, primary care, and other specialties ensures timely detection and treatment of evolving autoimmune conditions.

INTRODUCTION

Autoimmune polyglandular syndrome type II, or Schmidt's syndrome, is defined by the coexistence of primary adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes mellitus[1]. The prevalence is approximately 1.4–2 per 100,000 and it occurs predominantly in middle-aged women[2]. Autoimmune polyglandular syndrome type II (APS-II) has a strong genetic association with HLA-DR3, DR4, and D haplotypes[3].

We present a patient with Addison's disease who later developed Hashimoto's thyroiditis, followed by Graves' hyperthyroidism and emerging autoimmune diabetes. This case illustrates the dynamic shifts in autoimmune expression and the importance of long-term vigilance in APS-II.

CASE DESCRIPTION

A 54-year-old woman was diagnosed in 2009 with Addison's disease, presenting with fatigue, weight loss, and anorexia. Initial evaluation revealed adrenocorticotropic hormone at >1250 pg/ml, cortisol at 0.7 µg/dl and high plasma renin activity (281 ng/ml/hour). She was started on fludrocortisone 0.1 mg and prednisone 5 mg daily. Vital signs were stable, with a low blood pressure of 94/70 mmHg and no orthostatic symptoms. Initial laboratory tests, including a complete blood count, and comprehensive metabolic panel were within the normal range.

Autoimmune adrenal antibodies were negative, and a computed tomography scan of the abdomen revealed normal adrenal glands. There was no family history of autoimmune disease or adrenal insufficiency. Her past medical history was significant for vitiligo. Genetic testing was not performed.

She remained stable until 2016, when she developed symptoms of hypothyroidism. Testing revealed elevated thyroid-stimulating hormone (TSH) and positive thyroglobulin antibodies, consistent with Hashimoto's thyroiditis. Levothyroxine therapy improved her symptoms.

In 2023, she presented with palpitations, weight gain, and thyroid enlargement. Thyroid function tests showed suppressed TSH (0.005 mIU/l) and elevated thyroxine (T4). A 24-hour radioactive iodine uptake (RAIU) was 38%, indicating Graves' disease, and thyroid-stimulating immunoglobulin (TSI) was elevated (0.96 IU/l). She responded well to methimazole.

Autoimmune screening showed antinuclear antibody (ANA) positivity and elevated ribonucleoprotein antibody (RNP). Her haemoglobin A1c (HbA1c) was 6.2%, and GAD65 antibodies were positive, increasing the probability of developing autoimmune type 1 diabetes. However, the

Parameter	Value	Reference range
Blood pressure (mmHg)	94/70	90–120/60–80
Sodium (mmol/l)	138	135–145
Potassium (mmol/l)	5.5	3.5–5
CBC	Normal	–
CMP	Normal	–
Morning cortisol (µg/dl)	0.7	6–23
ACTH (pg/ml)	>1200	10–60
Plasma renin activity (ng/ml/h)	281	0.6–4.3

Abbreviations: CMP, complete metabolic panel; CBC, complete blood count; ACTH, adrenocorticotropic hormone.

Table 1. Initial laboratory evaluation and clinical parameters.

Year	Clinical event	Diagnostic findings	Intervention
2009	Addison's disease	- ACTH >1200 (pg/ml); - Cortisol 0.7 µg/dl; - High renin	Prednisone, fludrocortisone
2019	Hashimoto's thyroiditis	- ↑ TSH; - Positive Tg-Ab	Levothyroxine
2023	Graves' disease	- ↓ TSH; - ↑ T4; - ↑ TSI; - US: hypervascularity	Methimazole
2023	Increase the probability for autoimmune diabetes (latent)	- HbA1c 6.2%; - GAD65 Ab positive	Monitoring, lifestyle advice

Abbreviations: ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; TSI, thyroid-stimulating immunoglobulin; US, ultrasound; Ab, antibody; HbA1c, haemoglobin A1c.

Table 2. Timeline of autoimmune events.

patient did not report any symptoms, including polyuria or polydipsia, and glucose readings remained within normal limits. *Table 1* summarizes the initial laboratory findings. *Table 2* provides a timeline of autoimmune events.

DISCUSSION

The case highlights a rare but increasingly recognized phenomenon in autoimmune thyroid disease: the transition from Hashimoto's thyroiditis, a typically hypothyroid state, to Graves' disease, characterized by hyperthyroidism. While autoimmune thyroid disease traditionally presents as either Hashimoto's thyroiditis or Graves' disease, emerging literature indicates that these phenotypes may represent points along a dynamic autoimmune spectrum rather than distinct, immutable entities.

This transition is particularly significant in autoimmune polyglandular syndrome type II (APS-II), where immune dysregulation may intensify antibody switching and lead to unusual thyroid trajectories. Though Hashimoto's thyroiditis is the dominant thyroid manifestation in APS-II - affecting up to 75% of cases - conversion to Graves' disease is uncommon, with cohort estimates suggesting a prevalence of ~1% among Hashimoto thyroiditis patients[4].

In one of the largest studies, González-Aguilera et al. reported that approximately 1.2% of 2000 Hashimoto 's thyroiditis patients eventually developed Graves' disease, with a mean interval of 38 months, suggesting the need for long-term vigilance[5]. A recent review by Daramjav et al. compiled over 50 published cases of conversion of Hashimoto's thyroiditis to Graves' disease, finding a median interval of 7 years, which parallels our patient's disease timeline[6]. Vassallo et al. also emphasized this transition in the context of polyglandular autoimmunity, where systemic immune imbalance may facilitate antibody profile changes[7].

This phenomenon is attributed to shifts in the dominance between TSH receptor-blocking antibodies —which inhibit thyroid activity—and stimulating antibodies, which drive hyperthyroidism. A change in immune regulation—due to infections, stress, or even levothyroxine therapy—may tip the balance toward Graves' disease[8]. Earlier research by Takasu et al. described patients oscillating between hypothyroid and hyperthyroid states, reinforcing the concept of autoimmune thyroid disease as a spectrum rather than a binary diagnosis[9].

While rare, case reports substantiate this shift. For instance, Asano and Kenzaka described a patient with a 16-year history of Hashimoto's thyroiditis who developed Graves' disease during Guillain-Barré syndrome, suggesting that broader immune disturbances can trigger this conversion[10].

In APS-II, where immune surveillance is disrupted by coexisting endocrinopathies such as Addison's disease and autoimmune diabetes, such transitions may occur more readily, though still unpredictably.

Clinically, the conversion from Hashimoto's thyroiditis to Graves' disease can cause diagnostic confusion, particularly in patients on levothyroxine. Hyperthyroid symptoms in such individuals are often misattributed to over-replacement. However, persistent TSH suppression despite dose reduction should raise suspicion of underlying Graves' disease, warranting TSH receptor antibody testing and thyroid ultrasound for clarification. Accurate recognition avoids inappropriate levothyroxine adjustments and allows prompt initiation of antithyroid therapy[5-7].

Importantly, this transition has implications for broader APS-II management. Hyperthyroidism can exacerbate cortisol clearance, potentially unmasking or worsening adrenal insufficiency. This underscores the need for reassessment of adrenal function and adequate glucocorticoid coverage before initiating Graves' disease treatment, especially antithyroid drugs or radioiodine[3].

This case highlights the progressive and unpredictable course of APS-II. The sequential emergence of Addison's disease, Hashimoto's thyroiditis, subsequent Graves' disease, and the early stages of autoimmune diabetes underscores the need for clinicians to maintain a high index of suspicion for evolving autoimmune endocrinopathies even many years after the initial diagnosis.

In summary, the evolution from Hashimoto's thyroiditis to Graves' disease, though uncommon, is now well-documented and should be part of the differential diagnosis

in APS-II patients who develop signs of hyperthyroidism after years of hypothyroidism. This case adds to the growing literature about APS-II and reinforces the importance of lifelong antibody and hormonal monitoring, particularly in syndromes of immune dysregulation.

CONCLUSION

A key lesson from this case is that thyroid disease in APS-II may not follow a static course. Our patient's transition from hypothyroidism due to Hashimoto's thyroiditis to hyperthyroidism with Graves' disease reflects the dynamic nature of autoimmune thyroid disorders and illustrates the importance of repeated testing and clinical re-evaluation when symptoms change.

Furthermore, this case demonstrates the value of proactive antibody screening. The detection of GAD65 antibodies before the onset of overt hyperglycaemia allowed for anticipatory monitoring and patient education, reducing the risk of a delayed or crisis presentation of autoimmune diabetes. Such an approach should be incorporated into the long-term management of APS-II.

Ultimately, APS-II requires a multidisciplinary strategy, involving internists, endocrinologists, and often immunologists, to ensure comprehensive surveillance and timely intervention. Early recognition of new endocrine dysfunctions, careful coordination of hormone replacement, and patient education are crucial to preventing life-threatening complications such as adrenal crisis, inappropriate thyroid management, and diabetic ketoacidosis.

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