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Adrenal Crisis Associated With Graves' Disease Relapse After Levothyroxine Reintroduction in Established Autoimmune Polyglandular Syndrome Type 2: A Case Report and Review of Thyroid-Adrenal Interactions

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Abstract

Thyroid hormone excess is a recognized precipitating factor for adrenal decompensation in patients with primary adrenal insufficiency because it increases cortisol metabolism and glucocorticoid requirements. In some patients, autoimmune thyroid disease may fluctuate between hypothyroid and hyperthyroid states, creating additional challenges in the management of autoimmune polyglandular syndrome type 2 (APS-2). This case also provides an opportunity to review the clinical interactions between the thyroid and adrenal axes.

A woman in her forties with APS-2, including primary adrenal insufficiency and Graves' disease, presented with fatigue, dizziness, nausea, and hypotension. Two months earlier, she was euthyroid with negative thyroid-stimulating immunoglobulins (TSI), but subsequently developed subclinical hypothyroidism for which levothyroxine 50 µg/day was reintroduced. One month later, she presented with adrenal crisis. Laboratory evaluation showed hyponatremia, mild hyperkalemia, and elevated adrenocorticotropic hormone (ACTH) concentrations. Thyroid function tests revealed overt thyrotoxicosis with suppressed thyroid-stimulating hormone, markedly elevated free thyroid hormones, and TSI, consistent with relapse of Graves' disease. No alternative precipitating factor was identified. The patient improved rapidly following glucocorticoid replacement, fluid resuscitation, and antithyroid therapy.

This case highlights the dynamic nature of autoimmune thyroid disease in APS-2 and reinforces the close physiological interaction between thyroid and adrenal function. Together with a focused review of the literature, it illustrates how abrupt changes in thyroid status may substantially increase glucocorticoid requirements and contribute to adrenal decompensation in susceptible patients. Careful reassessment of adrenal status should be considered during major changes in thyroid function and after reintroduction of levothyroxine therapy.

Categories: Internal Medicine, Endocrinology/Diabetes/Metabolism, Allergy/Immunology
Keywords: adrenal crisis, autoimmune polyglandular syndrome type ii, graves relapse, levothyroxine therapy, thyroid-adrenal axis interaction

Introduction

Autoimmune polyglandular syndrome type 2 (APS-2) is characterized by the coexistence of primary adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes mellitus [1,2].

The condition presents unique diagnostic and therapeutic challenges because changes in one endocrine disorder may influence the clinical course of another [2].

In some patients, autoimmune thyroid disease may fluctuate between hypothyroid and hyperthyroid states as a result of evolving thyroid autoimmunity. These fluctuations may manifest clinically as transitions between hypothyroidism and Graves' hyperthyroidism over time [3,4].

This phenomenon may be particularly relevant in APS-2, where changes in thyroid hormone availability can alter glucocorticoid requirements and destabilize previously compensated primary adrenal insufficiency.

Thyroid hormone excess increases cortisol metabolism and clearance, potentially precipitating adrenal decompensation in patients with limited adrenal reserve [2,4]. While both levothyroxine therapy and endogenous thyrotoxicosis have individually been associated with adrenal crisis, less attention has been given to the broader implications of rapidly changing thyroid status in patients with established primary adrenal insufficiency. This issue may be particularly relevant in APS-2, where fluctuations in thyroid

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function can substantially alter glucocorticoid requirements and increase the risk of adrenal decompensation [2,4].

We report the case of a patient with APS-2 who developed adrenal crisis shortly after reintroduction of levothyroxine for subclinical hypothyroidism, in the setting of rapidly recurring Graves' disease. This case, together with a focused review of the literature, highlights the need for close monitoring of adrenal function during major changes in thyroid status in patients with APS-2.

Case Presentation

A woman in her forties with APS-2, consisting of primary adrenal insufficiency and autoimmune thyroid disease, was followed in the endocrinology clinic. Her adrenal insufficiency was treated with hydrocortisone 25 mg daily in three divided doses and fludrocortisone 100 µg daily. Adherence and tolerance to replacement therapy had been consistently documented as excellent during follow-up. She had a previous history of Graves' disease that had entered remission after antithyroid drug treatment.

Two months before admission, the patient was euthyroid with normal thyroid-stimulating immunoglobulin (TSI) concentrations. One month before admission, levothyroxine 50 µg/day was reintroduced because of progressive subclinical hypothyroidism characterized by high thyroid-stimulating hormone (TSH) concentrations and low-normal free thyroxine (FT4) levels. Approximately four weeks later, she was admitted with adrenal crisis and was subsequently found to have overt thyrotoxicosis and elevated TSI levels consistent with recurrent Graves' disease.

Relevant biochemical data at admission are summarized in Table *1*.

Parameter	Result	Units	Reference Range
Sodium	130 ↓	mmol/L	135-145
Potassium	5.0	mmol/L	3.5-4.5
Glucose	112	mg/dL	70-140
Lactate	2.2 ↑	mmol/L	0.5-2.0
ACTH (admission)	564 ↑	ng/L	10-60
Cortisol (admission)	186	µg/L	62-180
ACTH (day 4)	426 ↑	ng/L	10-60
Cortisol (day 4)	0.54 ↓	µg/L	62-180
TSH	0.025 ↓	mIU/L	0.4-4.0
Free T4 (FT4)	52.7 ↑	pmol/L	10-22
Free T3 (FT3)	16.2 ↑	pmol/L	3.5-6.5
TSI	18 ↑	U/L	<1.75

TABLE 1: Laboratory findings at admission and during hospitalization

TSI: thyroid-stimulating immunoglobulins; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone.

Initial laboratory investigations demonstrated hyponatremia, mild hyperkalemia, and elevated adrenocorticotropic hormone (ACTH) concentrations. Cortisol measured at admission was obtained after administration of 100 mg intravenous hydrocortisone and therefore was not considered representative of endogenous adrenal function. Subsequent morning cortisol measurements, obtained at day 4 before the daily hydrocortisone dose, remained markedly low (Table *1*).

At the same time, thyroid function testing revealed overt thyrotoxicosis with suppressed TSH and markedly elevated FT4 and FT3 concentrations. TSI levels, previously normal, showed a marked increase and remained elevated during follow-up, supporting recurrence of Graves' disease rather than simple thyroid hormone over-replacement.

A diagnosis of adrenal crisis in the setting of recurrent Graves' hyperthyroidism was made. The patient was

treated with intravenous fluids and stress-dose glucocorticoids, resulting in rapid clinical improvement. Because of the severity of the thyrotoxicosis and the additional ability of propylthiouracil to inhibit peripheral conversion of thyroxine (T4) to triiodothyronine (T3), antithyroid treatment was initially started with propylthiouracil. Following clinical stabilization, treatment was transitioned to thiamazole (Strumazol®) 30 mg/day, which is generally preferred for long-term management because of its more favorable safety profile.

During follow-up, thyroid hormone concentrations gradually improved under antithyroid therapy, while TSI concentrations remained elevated for several months before progressively declining.

Discussion

This case illustrates adrenal crisis occurring during a rapid transition from subclinical hypothyroidism to overt Graves' hyperthyroidism in a patient with APS-2. The sequence of events was characterized by euthyroidism, followed by progressive biochemical hypothyroidism requiring levothyroxine reintroduction, and subsequently by severe thyrotoxicosis associated with a marked increase in TSI concentrations. The development of adrenal crisis in this setting highlights the close physiological relationship between thyroid and adrenal function.

Thyroid hormone excess increases cortisol metabolism and clearance, thereby increasing glucocorticoid requirements. In patients with intact adrenal function, this effect is usually compensated by increased endogenous cortisol production. However, in primary adrenal insufficiency, the inability to augment cortisol secretion may result in relative glucocorticoid deficiency and, in some circumstances, adrenal crisis [4,5].

Both endogenous thyrotoxicosis and initiation of thyroid hormone replacement have previously been reported as precipitating factors for adrenal decompensation in susceptible individuals [6,7]. To contextualize the present case, a focused literature search was performed in PubMed using combinations of the terms “adrenal crisis”, “Addison’s disease”, “primary adrenal insufficiency”, “Graves’ disease”, “thyrotoxicosis”, “hyperthyroidism”, and “levothyroxine”. Additional relevant reports were identified through manual screening of the reference lists of retrieved articles. Published cases describing adrenal crisis associated with endogenous or exogenous thyroid hormone excess were reviewed and are summarized in Table *2*.

First Author	Year	Age/Sex	APS-2	Underlying Condition	Thyroid Trigger	Trigger Type
Rupp [8]	1957	42/Female	No	Addison's disease	Thyrotoxicosis	Endogenous
Burke [9]	1965	40/Female	No	Addison's disease	Graves' disease	Endogenous
Newrick [10]	1984	65/Male	No	Addison's disease	Thyrotoxicosis	Endogenous
Fonseca [11]	1986	47/Female	Yes	APS-2	Levothyroxine 50 µg initiation	Exogenous
Fonseca [11]	1986	24/Male	Yes	APS-2	Levothyroxine 100 µg initiation	Exogenous
Graves [12]	2003	44/Female	Yes	APS-2	Levothyroxine (dosage N.A.) initiation	Exogenous
Graves [12]	2003	23/Man	Yes	APS-2	Levothyroxine (dosage N.A.) initiation	Exogenous
Shaikh [13]	2004	15/Female	Yes	APS-2	Levothyroxine 75 µg initiation	Exogenous
Wang [14]	2016	38/Female	Yes	APS-2	Levothyroxine 37.5 µg initiation	Exogenous
Naik [15]	2016	42/Female	No	Addison's disease	Graves' disease	Endogenous
Attaye [16]	2018	67/Female	Yes	APS-2	Graves' disease	Endogenous
Schulz [17]	2020	15/Male	Yes	APS-2	Graves' disease	Endogenous
Patel [18]	2021	34/Female	Yes	APS-2	Levothyroxine (dosage N.A.) initiation	Exogenous
Lassoued [19]	2023	28/Female	Yes	APS-2	Thyrotoxicosis	Endogenous
Tsinopoulou [20]	2025	13/Female	Yes	APS-2	Levothyroxine 37.5 µg initiation	Exogenous
Present case	2026	40/Female	Yes	APS-2	Levothyroxine 50 µg reintroduction + Graves relapse	Uncertain

TABLE 2: Published cases of adrenal crisis precipitated by endogenous or exogenous excess of thyroid

APS-2: autoimmune polyglandular syndrome type 2; N.A.: not available.

The present case is notable because adrenal crisis occurred shortly after reintroduction of levothyroxine for subclinical hypothyroidism and in the context of a rapid transition from hypothyroidism to recurrent Graves' hyperthyroidism. As summarized in Table *2*, adrenal crisis has been described in association with both endogenous and exogenous thyroid hormone excess. Most published reports involve either untreated thyrotoxicosis or initiation of levothyroxine therapy in individuals with known or unrecognized adrenal insufficiency. However, cases combining reintroduction of levothyroxine with the simultaneous emergence of recurrent Graves' hyperthyroidism appear to be unusual. To our knowledge, and based on the cases identified in the literature review summarized in Table *2*, no previously published report has described adrenal crisis occurring after levothyroxine reintroduction together with documented recurrence of Graves' disease in a patient with established APS-2.

Although causality cannot be established, the temporal association between levothyroxine reintroduction and the abrupt rise in TSI concentrations is unusual and noteworthy. Current evidence suggests that the onset of Graves' disease after initiation of thyroid hormone replacement is more likely to reflect pre-existing or evolving thyroid autoimmunity than a causal effect of the treatment itself. In our patient, the marked increase in TSI concentrations from normal levels to 18-24 U/L provided strong evidence of recurrent autoimmune Graves' disease. Furthermore, the degree of thyrotoxicosis observed would be difficult to explain solely by levothyroxine over-replacement. Although a contributory effect of levothyroxine cannot be completely excluded, these findings support recurrence of Graves' disease as the principal mechanism underlying the hyperthyroidism.

An additional noteworthy feature was the persistence of markedly elevated ACTH concentrations. Although high ACTH levels may raise suspicion of inadequate glucocorticoid replacement, interpretation should be made cautiously. Current management guidelines for primary adrenal insufficiency do not recommend normalizing ACTH as a therapeutic target, and treatment adjustment is guided primarily by clinical assessment rather than ACTH concentrations alone [6,7]. Substantial interindividual variability in ACTH concentrations has been reported among patients receiving replacement therapy, with some individuals

maintaining persistently elevated ACTH levels despite apparent clinical stability. This variability may reflect differences in glucocorticoid pharmacokinetics, sampling timing relative to hydrocortisone administration, and individual sensitivity of hypothalamic-pituitary feedback mechanisms. In our patient, elevated ACTH concentrations had been documented repeatedly over several years, including long before the index admission, and remained elevated after recovery from adrenal crisis. This chronic pattern argues against abrupt treatment discontinuation immediately preceding presentation as the sole explanation for the biochemical abnormalities. While periods of relative under-replacement cannot be completely excluded, the longitudinal biochemical profile suggests that chronic ACTH elevation was a pre-existing feature of the patient's disease course rather than a specific marker of the acute event.

From a practical perspective, this case emphasizes that APS-2 should be regarded as a dynamic rather than static condition. Significant changes in thyroid status may alter glucocorticoid requirements and destabilize previously compensated adrenal insufficiency. Clinicians should therefore maintain a high level of suspicion for adrenal decompensation whenever major changes in thyroid function occur. They should reassess adrenal replacement therapy during overt thyrotoxicosis or after initiating or restarting levothyroxine.

Conclusions

This case, together with the cases identified in our literature review, highlights the complex interaction between thyroid hormone excess and adrenal function in patients with primary adrenal insufficiency. Following reintroduction of levothyroxine for subclinical hypothyroidism, our patient developed recurrent Graves' hyperthyroidism and adrenal crisis within a short period of time. Although causality cannot be established, the marked rise in TSI concentrations supported recurrent autoimmune hyperthyroidism rather than simple levothyroxine over-replacement. Clinicians should therefore consider evolving Graves' disease when thyrotoxicosis develops after levothyroxine initiation or reintroduction, particularly in patients with APS-2. In this setting, closer clinical and biochemical monitoring of adrenal function may be warranted, as thyroid hormone excess can substantially increase glucocorticoid requirements and contribute to adrenal decompensation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Alberto Papaleo, Floor Bracquez, Corina E. Andreescu

Acquisition, analysis, or interpretation of data: Alberto Papaleo

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Critical review of the manuscript for important intellectual content: Alberto Papaleo, Floor Bracquez, Corina E. Andreescu

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