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CASO CLÍNICO

Immune Checkpoint Inhibitor-Induced Thyroidal, Pancreatic, and Pituitary Dysfunction: Diagnostic Challenges in a Cancer Patient

Disfunção Tiroideia, Pancreática e Hipofisária Secundária a Inibidores de Checkpoint Imunitário: Desafios Diagnósticos num Doente Oncológico

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ABSTRACT

Immune checkpoint inhibitors (ICPIs)-induced endocrine immune-related adverse events (irAEs) are common, can appear concurrently, and can be overlooked due to their nonspecific presentation overlapping with cancer-related symptoms. We describe the case of a 47-year-old woman with metastatic colorectal cancer treated with combined ICPI therapy. She presented thyrotoxicosis right after starting therapy, evolving into overt primary hypothyroidism, after two months, followed by abrupt-onset diabetes *mellitus* and hypophysisits-related secondary adrenal insufficiency and central hypothyroidism, six months after starting ICPIs. This case illustrates the complexity of diagnosing and managing overlapping endocrine irAEs, and the importance of high clinical suspicion. Clinical manifestations were attributed to the cancer and diabetes diagnosis, delaying recognition of adrenal insufficiency. Central hypothyroidism was initially interpreted as iatrogenic thyrotoxicosis. Glucocorticoid supplementation worsened diabetes management. Clinical and biochemical follow-up is essential in patients with ICPIs. Prompt recognition is essential to avoid life-threatening complications and ensure optimal long-term management.

Keywords: Endocrine System Diseases/chemically induced; Immune Checkpoint Inhibitors/adverse effects; Polyendocrinopathies, Autoimmune/chemically induced

RESUMO

Os efeitos adversos imunomediados (irAEs) endócrinos, secundários aos inibidores de *checkpoint* imunitário (ICPIs), são frequentes, podem surgir simultaneamente, e podem ser subdiagnosticados pela apresentação inespecífica, sobreponível à da doença oncológica. Descrevemos uma mulher de 47 anos com adenocarcinoma colorretal metastizado, sob terapêutica combinada com ICPIs. A doente apresentou tirotoxicose transitória imediatamente após iniciar terapêutica, que evoluiu para hipotiroidismo primário, após dois meses, seguida de diabetes *mellitus*, e insuficiência adrenal secundária e hipotiroidismo central, secundários a hipofisite, seis meses após iniciar ICPIs. Este caso ilustra a complexidade do diagnóstico e gestão de irAEs endócrinos simultâneos, e a importância da elevada suspeição clínica. Os sintomas atribuídos à neoplasia e diabetes atrasaram o reconhecimento da insuficiência adrenal. O hipotiroidismo central foi interpretado como tirotoxicose iatrogénica. Os glucocorticoides prejudicaram o controlo glicémico. A vigilância clínica e laboratorial é fundamental, especialmente em doentes sob combinações de ICPIs. O reconhecimento precoce é crucial para prevenir complicações e garantir uma gestão eficaz a longo prazo.

Palavras-chave: Doenças do Sistema Endócrino/induzidas quimicamente; Inibidores de Checkpoint Imunológico/efeitos adversos; Poliendocrinopatias Autoimunes/induzidas quimicamente

INTRODUCTION

Immune checkpoints play a critical role in modulating and regulating the immune system's response, preventing overstimulation and autoimmunity.[1,2] Immune checkpoint inhibitors (ICPIs) target these regulatory molecules, enabling immune recognition and subsequent destruction of cancer cells. However, their use can also lead to immune-related adverse events (irAEs) affecting any organ system.[3] The prevalence and nature of each endocrine irAE vary depending on the ICPI used, and they are more common in case of combined therapy with multiple ICPIs.[4]

Endocrine toxicities are amongst the most common, accounting for 8% of ICPIs' irAEs.[5] Unlike other irAEs, the inflammatory process is usually clinically silent and frequently results in permanent glandular damage. Clinical manifestations arise from the resulting hormone deficiency, often requiring lifelong hormone replacement therapy.[6] Although most frequently observed during the early phases of treatment, endocrine immune-related adverse events (irAEs) can arise at any time—even following discontinuation of ICPI therapy.[3]

Thyroid dysfunction is the most common endocrine irAE, followed by pituitary, pancreatic, and adrenal involvement and, less frequently, hypogonadism or hypoparathyroidism.[5]

We describe a case of multisystem endocrine dysfunction in a patient receiving combined therapy with ICPIs.

CASE REPORT

A 47-year-old-woman, receiving combination therapy with ipilimumab and nivolumab for progression of metastatic colon adenocarcinoma (CRC), after incomplete surgical resection (pT4bN1aM0) and palliative chemotherapy

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(FOLFIRI-bevacizumab), was referred to the endocrinology clinic for thyrotoxicosis (Table 1). She complained of a transient episode of diarrhea, agitation, and tremor, right after starting ICPIs. Past medical history included hypertension and dyslipidemia. She was not taking any regular medication and had no relevant family history.

On physical examination, body mass index (BMI) was 28.3 kg/m^2, blood pressure was 139/70 mmHg, and heart rate 86 bpm. The thyroid gland was palpable, without nodules or bruit. On her second visit, two weeks after starting therapy, she was asymptomatic. Given the most likely diagnosis of ICPI-induced thyrotoxicosis, no treatment was instituted.

Two months after starting treatment, the patient developed fatigue and cold intolerance. Blood tests revealed overt primary hypothyroidism (Table 2), and levothyroxine replacement therapy was implemented, with clinical improvement. Low thyroid-stimulating hormone (TSH) levels persisted even after levothyroxine dose adjustment.

Six months after starting ICPIs, the patient presented to the emergency department with severe fatigue, anorexia and myalgia, and mild weight loss. She was hemodynamically stable, afebrile, and had no nausea or abdominal pain. Blood tests showed hyperglycemia (Table 3) without diabetic ketoacidosis, prompting hospital admission for new-onset diabetes *mellitus*. Plasma glucose and HbA1c levels were within normal range three months before. Additional testing revealed low C peptide levels and mildly elevated glycated hemoglobin (Table 3). Measurement of islet antibodies was not available.

Given the possibility of ICPI-induced diabetes, further endocrine work-up was performed (Table 3). The patient was diagnosed with secondary adrenal insufficiency, with low cortisol and adrenocorticotropic hormone (ACTH) levels, likely due to ICPI-induced hypophysitis. She had no headaches or visual disturbances. Based on the persistently low TSH levels with normal free T4 levels despite levothyroxine dose reduction, secondary hypothyroidism was suggested.

The patient improved significantly after therapy implementation and was later discharged on hydrocortisone replacement therapy, an adjusted levothyroxine dose and a basal-bolus insulin regimen.

At the time of writing this article, the patient was still under nivolumab maintenance therapy, with stable oncologic disease. Current medications include hydrocortisone 20 mg/day, levothyroxine 100 µg/day, and an insulin regimen comprising glargine and lispro; however, glycemic control remains suboptimal.

DISCUSSION

This case report illustrates multiple endocrinopathies after combined ICPI therapy.

Thyroiditis is the most common ICPI-related endocrinopathy, usually developing after anti-PD-1/PD-L1 treatment, but even more after combination therapy.[3,5,6] Thyrotoxicosis, when present, is typically mild and transient or asymptomatic.[3]

In our patient, a biphasic thyroiditis unfolded, with an initial thyrotoxicosis phase with symptoms consistent with thyroid hormone excess. This inflammatory process typically leads to rapid and complete destruction of the gland,[6] resulting in primary hypothyroidism and need for thyroid hormone replacement.[5] Thyroid autoimmunity was present, a condition associated with an increased risk of immune checkpoint inhibitor (ICPI)-induced thyroid dysfunction.[5]

Diabetes *mellitus* is a rare but potentially life-threatening irAE of ICPIs, associated with diabetic ketoacidosis (DKA) in 70% of cases,[3] primarily associated with PD-1/PD-L1 inhibitors or combination therapy.[7] The sudden onset of hyperglycemia, low C peptide values and only slightly elevated HbA1c made the diagnosis of ICPI-induced diabetes *mellitus,* likely. The discrepant values reflect the rapid destruction of pancreatic beta cells, faster than what can be translated through the HbA1c value.[3,7]

Immune checkpoint inhibitor-induced hypophysitis is most commonly seen after CTLA-4 inhibitors or combination therapy,[5] usually resulting in panhypopituitarism. ACTH deficiency is the most common manifestation, followed by TSH and gonadotrophin deficiency.[6]

The clinical symptoms of cortisol deficiency were initially misattributed to the underlying cancer and newly diagnosed diabetes mellitus, leading to delayed recognition of adrenal insufficiency, which was ultimately identified through biochemical evaluation. This aligns with findings from several reviews and prospective studies, which emphasize that overlapping symptoms in cancer patients can hinder timely recognition of endocrinopathies—particularly adrenal insufficiency, which may rapidly progress to life-threatening states if not promptly diagnosed.[8-11]

Central hypothyroidism emerged as a likely concurrent diagnosis. Retrospectively, the persistently low TSH levels, which prompted multiple levothyroxine dose adjustments, may have represented the early biochemical manifestation of central hypothyroidism, characterized by inappropriately low TSH and low thyroid hormone concentrations.

This report highlights the need for a high index of suspicion regarding the non-specific symptoms of endocrine irAEs. This is particularly relevant in patients in the oncology setting, in which cancer-related complaints can overlap and mask symptoms of ICPI-induced endocrinopathies, with life-threatening consequences. Regular clinical and biochemical evaluation is crucial in ensuring a prompt diagnosis and timely treatment.

This case also emphasizes the complexity of managing multiple, concurrent endocrine irAEs. Overlapping clinical features can delay diagnosis, and the management of one condition may directly complicate the diagnosis and treatment of another. In our patient, the diagnosis of central hypothyroidism was initially delayed due to the prior history of primary hypothyroidism and ongoing levothyroxine therapy, which led to the assumption that the suppressed TSH levels reflected iatrogenic hyperthyroidism. Moreover, lifelong glucocorticoid replacement for adrenal insufficiency can interfere with glycemic management in the setting of ICPI-induced type 1 diabetes *mellitus*.

A multidisciplinary approach is essential for early detection, management and mitigation of long-term complications in patients with ICPIs' irAEs. Implementation of follow-up protocols may prove beneficial in these patients.

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AUTHOR CONTRIBUTIONS

SGS: Study design, data collection, analysis and interpretation, drafting and critical review of the manuscript.
RC, APS, II, JO: Study design, critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained**.**

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Table 1 – Blood tests two weeks after starting ICPI combination therapy

Parameters	Results	Reference values
TSH	0.014	0.270 - 4.200 uUI/mL
Free T4	4.39	0.72 - 1.56 ng/dL
Free T3	10.5	2.00 - 4.40 pg/mL
Anti-thyroglobulin antibodies	367	0 - 115 U/mL
Anti-thyroid peroxidase antibodies	52.3	0 - 35 UI/mL

Table 2 – Blood tests two months after starting ICPI combination therapy

Parameters	Results	Reference values
TSH	69.000	0.270 - 4.200 uUI/mL
Free T4	0.0743	0.72 - 1.56 ng/dL
Free T3	0.510	2.00 - 4.40 pg/mL

Table 3 – Blood tests six months after starting ICPI combination therapy

Parameters	Results	Reference values
Glucose	492	76 - 115 mg/dL
Creatinine	0.78	0.51 - 0.95 mg/dL
Sodium	126	135 - 145 mmol/L
Potassium	4.2	3.8 - 5.0 mmol/L
C peptide	0.0362	1.1 - 5.0 ng/mL
A1c hemoglobin	7.4	4.0% - 6.0%
ACTH	< 1.50	7.2 - 63.3 pg/mL
Plasma cortisol	0.311	5.0 - 25.0 ug/dL
TSH	0.170	0.270 - 4.200 uUI/mL
Free T4	0.766	0.72 - 1.56 ng/dL
Free T3	3.10	2.00 - 4.40 pg/mL
FSH	20.5	2.4 - 12.6 mUI/mL
LH	7.87	3.5 - 12.5 mUI/mL
IGF-1	58.4	80.2 - 218 ng/mL
Prolactin	0.419	4.79 - 23.30 ng/mL