Case Report

Primary Adrenal Insufficiency during Immune Checkpoint Inhibitor Treatment: Case Reports and Review of the Literature

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Abstract
As the indications and clinical use of immune checkpoint inhibitors increase, it is expected that we will face some of their less frequently reported complications. Primary adrenal insufficiency is one of them, and given its unspecific symptoms and potentially serious consequences, it is important to have a high degree of clinical suspicion. We present 3 cases and a review of the literature concerning its main clinical characteristics, diagnostics, and management.

Introduction

Immune checkpoint inhibitors (ICI) have improved the prognosis of several solid tumor types, including melanoma, renal cell carcinoma (RCC), non-small cell lung cancer, and urothelial carcinoma, among others. Some of the drugs approved in this class are ipilimumab (CTLA-4 inhibitor), nivolumab and pembrolizumab (PD-1 inhibitors), atezolizumab, avelumab, and durvalumab (PD-L1 inhibitors) [1–3].
Even though they may confer significant clinical benefit by regulating immune response through the initiation of either inhibitory or stimulatory pathways that modulate T-cell function, they are also associated with significant immune-mediated adverse events (irAE), which can develop in any organ and can be challenging to diagnose and treat.

Within these irAE, the most frequent are endocrinopathies, which include thyroid disease, hypopituitarism, type 1 diabetes, and adrenal insufficiency, among others. Within these immune-related AEs, we want to highlight primary and secondary adrenal insufficiency, which is important to be mentioned due to its severity and mortality especially due to misdiagnosis and undertreatment. Therefore, we present 3 clinical cases of patients who developed adrenal insufficiency secondary to treatment with immunotherapy.

**Clinical Cases**

**Case 1**

Case 1 was a 60-year-old male with a medical history of hypertension since 2007 and a 30-pack-year history of smoking, who currently stopped smoking. In 2017, he was diagnosed with metastatic RCC (mRCC). He started treatment with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 2 weeks for the first 4 cycles, continuing with single-drug nivolumab 3 mg/kg every 2 weeks after that (Table 1). After cycle 10 of treatment, he developed severe asthenia and grade 3 hyponatremia, which led to the interruption of therapy. Bloodwork showed a sodium concentration of 117 mg/dL, renal function and thyroid function were within normal ranges, and morning cortisol was <1 μg/dL (reference range [RR]: 5–25 μg/dL). Adrenocorticotropic hormone (ACTH) stimulation test result was 7.38 μg/dL (RR: >18 μg/dL), thus confirming the diagnosis of primary adrenal insufficiency (PAI). Abdominal CT scan was normal (Table 1).

**Case 2**

Case 2 was a 65-year-old man with no medical history. He was diagnosed with mRCC in 2016. He decided to participate in a clinical trial and started treatment with nivolumab 3 mg/kg every 2 weeks plus cabozantinib 40 mg per day (Table 1). Best observed response was partial response by RECIST criteria, and treatment was well tolerated in general. After cycle 13, he developed asymptomatic grade 2 hyponatremia, which was corrected with treatment interruption and no additional measures; however, upon restarting treatment, he developed grade 4 hyponatremia with a sodium level of 112 mg/dL, which required hospitalization for management. Bloodwork showed a sodium concentration of 117 mg/dL, renal function and thyroid function were within normal ranges, and morning cortisol was <1 μg/dL (reference range [RR]: 5–25 μg/dL). Adrenocorticotropic hormone (ACTH) stimulation test result was 7.38 μg/dL (RR: >18 μg/dL), thus confirming the diagnosis of primary adrenal insufficiency (PAI). Abdominal CT scan was normal (Table 2).

**Case 3**

Case 3 was a 76-year-old man with a medical history of hypertension since 2002. He was diagnosed with mRCC in 2019. He entered a clinical trial and started treatment with fixed-dose nivolumab 480 mg once per month (Table 1). After cycle 4, he presented with mild

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**Table 1. Patient characteristics**

| ID   | Age, years | Diagnostic          | Stage | Comorbidities | Tobacco habit | ECOG |
|------|------------|---------------------|-------|---------------|---------------|------|
| Patient 1 | 60 | renal cell carcinoma | IV    | hypertension   | 30 years       | 0    |
| Patient 2 | 65 | renal cell carcinoma | IV    | no            | no            | 0    |
| Patient 3 | 76 | renal cell carcinoma | IV    | hypertension   | no            | 0    |
fatigue and grade 1 hyponatremia; treatment was continued, and given the unspecific symptoms, no additional studies were requested at that time. After cycle 5, symptoms had progressed, he had severe fatigue and orthostatic hypotension; at that point, treatment was stopped and a morning cortisol was requested, which was <1 μg/dL (RR: 5–25 μg/dL). ACTH stimulation test result was 5.3 (RR: >18 μg/dL), confirming PAI. Plasmatic electrolytes were within reference ranges. He was referred to the endocrinologist, who requested additional testing: TSH, FSH, LH, IGF-1, prolactin, and total testosterone were all within normal ranges. Pituitary magnetic resonance imaging (MRI) was normal with no signs of hypophysitis (Table 2).

All 3 patients were started on steroid replacement therapy with hydrocortisone. They showed excellent clinical response with complete remission of symptoms. Considering that patients had shown a favorable oncological response to treatment, a clinical decision was made to restart immunotherapy once a stable dose of steroids was reached and no symptoms related to the adrenal insufficiency were present. All 3 patients are still on treatment with no further complications related to immunotherapy.

Review of the Literature

PAI is defined as the inability of the adrenal gland cortex to generate sufficient levels of glucocorticoids and/or mineralocorticoids. Given the critical role they play in salt, fluid, and energy homeostasis, this situation is potentially life-threatening. As the blood corticoid levels are reduced, the hypothalamic-pituitary axis responds with an increased secretion of ACTH [1–6].

Clinical signs and symptoms of PAI include fatigue, weight loss, orthostatic hypotension, and anorexia, and severe cases can also manifest with syncope, hypotension, and reduced consciousness. Laboratory tests can show low morning cortisol, high morning ACTH, hypotremia, and hyperkalemia [7, 8].

Although data on the incidence and prevalence of ICI-related toxicity are still being generated, PAI has been described with both anti-CTLA-4 and anti-PD-1/PD-L1 agents; most of these case reports come from melanoma patients treated with nivolumab, ipilimumab, and pembrolizumab [7–9].

Within irAEs, PAI is classified as extremely rare [7–9], although it may be underdiagnosed [7]. A systematic review with meta-analysis published in 2018 that included 38 randomized trials with 7,551 patients on the incidence of endocrinopathies caused by ICI.
showed a low frequency of adrenal insufficiency events: PAI of any grade was reported in 43 out of 5,831 patients (0.7%), but only 0.2% were grade 3 or higher. Patients who received combination ICI had a higher incidence of adrenal insufficiency (11 out of 262, 4.2%) [7, 8]. Wang et al. [10] reported fatal toxicity results from a global adverse drug reaction database (VigiLyze, VigiBase); they identified 614 fatal irAEs, out of which adrenal toxicity was identified as the cause in 8 patients treated with ipilimumab and 6 patients with anti-PD-1/PD-L1 agents [11].

Regarding timing, there is no clearly defined time frame for the development of PAI. It can develop in the first months of treatment, but some cases have been reported several years after starting treatment. In our series, PAI developed after 20, 13, and 16 weeks of treatment for case 1, 2, and 3, respectively.

Known risk factors for the development of irAE in general, and PAI in particular, are an area of active investigation. Medical history of previous autoimmune diseases increases the risk of developing irAE, even if they are inactive [10–12].

Adrenal insufficiency has varying presentations, from asymptomatic laboratory alterations to a serious medical emergency [10, 13]. Clinical symptoms are usually vague and nonspecific, just as adrenal insufficiency from any other cause: fatigue, dizziness, orthostatic symptoms, anorexia, weight loss, and abdominal pain are the most frequent. Severe cases usually manifest as refractory hypotension, altered state of consciousness, generalized weakness, abdominal pain, shock, and, potentially, death. Frequently reported laboratory abnormalities include hyponatremia and hyperkalemia, while hypoglycemia and hypercalcemia are less frequent [10, 13, 14].

Differential diagnoses include central (immune-mediated hypophysitis with secondary adrenal insufficiency, hypophysary metastases) and peripheral (adrenal metastases, adrenal hemorrhage) potential causes, while also infections, drugs, and infiltrative diseases should be considered [10, 14].

Laboratory tests to consider are morning cortisol, morning ACTH, and ACTH stimulation test, which should indicate the degree of adrenal insufficiency. Additional tests, such as post-ACTH stimulation levels of renin and aldosterone, can be useful to determine the level of mineralocorticoid deficiency. The clinical utility of measuring adrenal autoantibodies has not been sufficiently studied in this setting, and it is not currently recommended [10, 14].

Imaging studies can also be helpful in some situations. Hypophysis MRI should be requested in case of new neurological symptoms or clinical suspicion of a secondary cause. Adrenal glands CT can show an increased volume of the adrenal glands with smooth contours, although this is not always present. Imaging studies will also help to rule out metastatic lesions. Radiological adrenalitis, which refers to radiological alterations on adrenal glands without endocrine function abnormalities, has also been described, which could potentially indicate a subclinical presentation of this complication [15].

Management depends on the clinical severity. All patients should stop ICI treatment. Patients with mild signs and symptoms can be started on oral hydrocortisone (15–25 mg/day) in 2 or 3 divided oral doses per day, with progressive tapering afterwards at least for 1–2 weeks [7, 10, 13, 16, 17]. Patients with suspected adrenal crisis should receive an immediate dose of 100 mg intravenous hydrocortisone plus fluid resuscitation, followed by 200 mg/24 h of hydrocortisone either by continuous infusion or 6-hourly injection; when clinically stable, the previously described recommendations with oral therapy can follow. Adding fludrocortisone 50–100 μg/day can be effective in the context of low aldosterone levels with orthostatic hypotension and refractory hyponatremia and hyperkalemia. Dose can be titrated according to symptoms [15, 17].

Monitoring of steroid supplementation is critical and can be complemented with morning cortisol and ACTH levels. It is important to identify potential situations which demand
increased steroid supplementation, such as fever, acute infections, and physical activity [9, 15].

Early diagnosis algorithms have been proposed, which include adrenal, pituitary, and thyroid axis tests before starting ICI agents and during follow-up. There is currently no agreed standard on this topic. Serial electrolytes, fasting cortisol and glucose can help to detect abnormalities before clinical symptoms occur.

Conclusions

Adrenal insufficiency, an immune-mediated treatment complication of novel oncology therapies, can have very serious effects if not diagnosed and treated appropriately. Its incidence is low, and there are few reported cases in the literature so far. It can occur with any of the currently approved ICIs.

Active surveillance of this potentially life-threatening atypical complication with a high degree of clinical suspicion is important. Restoring the hypothalamic-pituitary-adrenal axis with lifetime glucocorticoids is the treatment of choice, with excellent clinical results. Long-term follow-up is necessary, along with patient education to identify symptoms and self-supplementation in case of acute stress situations.

Statement of Ethics

Written informed consent was obtained from the patients for the publication of this case report.

Disclosure Statement

Alex Renner: travel, accommodations, expenses: Roche. Suraj Samtani: travel, accommodations, expenses: Roche. Mauricio Burotto: consulting: Genentech, Bristol-Myers Squibb, Merck, Astrazeneca. Carlos Rojas: honoraria: Bristol-Myers Squibb, Astrazeneca, Roche. No other potential conflicts of interest were reported.

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Author Contributions

All authors have been involved in the work conception, data acquisition, and manuscript drafting.
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