Isolated adrenocorticotrophic hormone deficiency in a patient treated with checkpoint inhibitor therapy

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ABSTRACT

Treatment of advanced melanoma has significantly improved with the advent of checkpoint inhibitor therapy. With the widespread use of these agents, side effects are being increasingly recognized, including immune-related adverse events. We report the onset of adrenal insufficiency in a patient with advanced melanoma who was exposed to two checkpoint inhibitors: ipilimumab and nivolumab. His symptoms initially resolved with steroid replacement but he was unable to be weaned off hormone replacement and required long-term oral hydrocortisone treatment.

KEYWORDS Adrenal insufficiency; checkpoint inhibitor; cytotoxic T-lymphocyte antigen-4; hypophysitis; immune-related adverse events; ipilimumab; nivolumab; programmed death-1

Immunotherapy with checkpoint inhibitors has resulted in significant survival benefit in patients with metastatic melanoma.¹ Two checkpoint inhibitors commonly used in advanced melanoma are ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, and nivolumab, a programmed death-1 (PD-1) inhibitor. These treatments are associated with immune-related adverse events (irAE), commonly fatigue, dermatologic toxicities, gastrointestinal toxicities, hepatitis, hypothyroidism, and pneumonitis. Other less common toxicities include hyperthyroidism, primary adrenal insufficiency, insulin-dependent diabetes, and hypophysitis.^{2–5}

CASE PRESENTATION

A 59-year-old man with known hypertension presented with a pigmented skin lesion of the right distal dorsal forearm. Biopsy revealed malignant melanoma, and he underwent a wide-local excision and sentinel node biopsy in the right axilla. The pathology report revealed invasive melanoma of 19 mm in greatest dimension, tumor thickness of 11 mm, and a sentinel lymph node positive for metastatic melanoma. He subsequently underwent complete node

dissection, revealing 1/17 positive lymph nodes. His pathologic stage was T4bN1aM0 (stage IIIB).

He received one cycle of nivolumab plus ipilimumab. After 2 weeks, he was switched to nivolumab monotherapy. Three weeks after receiving nivolumab, he started experiencing mild abdominal pain, weakness, fatigue, headache, decreased appetite, nausea, and vomiting, which prompted him to go to the emergency department.

Baseline and postimmunotherapy laboratory values are reported in [Table 1](#). Administration of 250 µg intravenous cosyntropin showed a low cortisol response at 30 and 60 minutes. Magnetic resonance imaging of the brain with and without contrast revealed no evidence of hypophysitis and no evidence of intracranial metastatic disease. He was diagnosed with grade 3 toxicity of checkpoint inhibitor, given severe symptoms limiting activities of daily living and requiring hospitalization.

The patient was immediately started on hydrocortisone 50 mg intravenously every 8 hours for adrenal insufficiency and experienced significant improvement of his symptoms after 24 hours. He was discharged with a 4-day taper of hydrocortisone according to recommendations from the endocrinologist. He was later readmitted for hypoadrenal symptoms including fever, headache, myalgia, arthralgia, and

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Table 1. Laboratory values at baseline before and after receiving immunotherapy

Laboratory test	Reference range	Baseline	After immunotherapy
Sodium (mEq/L)	136–145	141	124
Potassium (mEq/L)	3.5–5.1	3.9	3.3
Chloride (mEq/L)	98–107	104	86
Bicarbonate (mEq/L)	21–32	28.6	27
Blood urea nitrogen (mg/dL)	7–18	19	6
Creatinine (mg/dL)	0.70–1.30	1.1	1.07
Albumin (g/dL)	3.4–5.0	3.9	3.7
Glucose (mg/dL)	70–99	111	104
Cortisol (μg/dL)	6.7–22.6	11.8*	<1.0**
ACTH (pg/mL)	0.0–46.0	19*	<5.0***
ACTH stimulation test:			
Cortisol (μg/dL) at 30 min		–	5.1
Cortisol (μg/dL) at 60 min		–	8.4
TSH (μIU/mL)	0.36–3.74	3.62	7.16
Free thyroxine (ng/dL)	0.76–1.46	0.89	0.77
FSH (mIU/mL)	1.5–9.3	–	5.1
Luteinizing hormone (mIU/mL)	1.4–18.1	–	7.3

*Collected at 8:47 AM.

**Collected at 8:05 AM.

***Collected at 10:07 AM.

ACTH indicates adrenocorticotropic hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone.

anorexia after a viral illness while on oral hydrocortisone treatment that was increased. He was unable to be weaned off oral steroid replacement.

DISCUSSION

It is well established that ipilimumab monotherapy causes endocrine irAEs more frequently than nivolumab monotherapy. This is a rare toxicity of immunotherapy that is expected to be more prevalent in combination therapy than in single-agent therapy. However, in our reported case, the patient received one cycle of anti-CTLA-4 plus a PD-1 blocking agent followed by PD-1 blocking agent monotherapy, which led to the emergence of this rare toxicity.^{5–7}

The mechanism of immune-checkpoint inhibitors causing irAEs appears to be autoimmune in nature. Blockade of CTLA-4 and PD-1 leads to loss of tolerance to self-antigens and causes autoimmunity. Impaired function and mutation of CTLA-4 is associated with multiple autoimmune diseases, including Graves' disease and Hashimoto's thyroiditis. In an autopsy study, a high level of pituitary expression of CTLA-4 along with T-cell infiltration and IgG-mediated complement fixation was found in patients with hypophysitis.⁸ Another study suggested that ipilimumab developed

autoantibodies against CTLA-4 expressed on pituitary endocrine cells, which led to complement activation with C3d and C4d deposition and inflammatory cascade, explaining the development of hypophysitis. The presence of CTLA-4 in normal pituitary cells may explain the high incidence of pituitary dysfunction with CTLA-4 blockade when compared to PD-1/PDL-1 blockade.⁹

Genetic polymorphism in PD-1 and PDL-1 has been associated with Addison's disease and autoimmune thyroid disease. In pembrolizumab (anti-PD-1)-associated thyroiditis, patients were found to have loss of PD1⁺, CD4⁺, and CD8⁺ T cells, an increase in peripheral CD56⁺CD16⁺ NK cells, and an increase in activated monocytes. Some studies have also shown circulating thyroid antibodies after anti-PD-1 therapy.⁹

In a recent meta-analysis, hypophysitis was observed in 6.4% of patients with combination therapy, 3.2% with CTLA-4 inhibitors, and 0.4% in PD-1 inhibitors. Most of these patients had metastatic melanoma.⁷ In patients with metastatic melanoma receiving combination treatment, approximately 75% diagnosed with hypophysitis received hormone replacement therapy, with 56% receiving high-dose corticosteroids for a median duration of 19 days.¹⁰ While our patient received only one cycle of ipilimumab plus

nivolumab, prior exposure to combination treatment may have put him at a higher risk of adverse events.

There are 2800 ongoing phase 1 clinical trials for development of new drugs for solid malignancies, and 75% of these trials are second- and third-generation immune-oncology drugs. We expect irAEs to become an increasingly common problem that clinicians will be managing in the clinic. Due to the insidious nature of the presentation, a high degree of clinical suspicion is warranted. Baseline thyroid-stimulating hormone, free thyroxine, 8 AM ACTH and serum cortisol, hemoglobin A1c, and serum glucose levels are acceptable standard of care. If an irAEs is clinically suspected, follicle-stimulating hormone, luteinizing hormone, and serum testosterone should be checked. Routine follow-up at 6 to 8 weeks is also recommended in these patients. The toxicities are easily reversible with prompt intervention but are fatal if unrecognized.

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Avocations

"Pink Dogwood blossom." Photo copyright © Rolando M. Solis, MD. Dr. Solis is co-medical director of the cardiopulmonary rehabilitation program at Baylor Scott & White Heart Hospital Plano, Plano, Texas (e-mail: rmsolis@mac.com).