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Eric Shiffrin, MD
Thomas Jefferson University, eric.shiffrin@jefferson.edu

Melinda Ukrainski, MD
Thomas Jefferson University, melinda.ukrainski@jefferson.edu

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A Case of Ipilimumab Induced Hypophysitis

Eric Shiffrin, MD and Melinda Ukrainski, MD

INTRODUCTION
Ipilimumab (Yervoy®) is a human monoclonal antibody that has been shown to significantly improve survival in cases of metastatic melanoma. Ipilimumab blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4), a protein receptor on the surface of T-cells, resulting in their activation, proliferation and an anti-tumor response. Commonly reported immune-related side effects of ipilimumab are enterocolitis, dermatitis, and hepatitis. However, different endocrinopathies, including autoimmune hypopituitarism, have become emerging clinical entities in patients taking ipilimumab. We present a case of ipilimumab induced hypophysitis in a 62-year-old male presenting with fatigue and hypotension.

CASE PRESENTATION
A 62-year-old male with a history of melanoma metastatic to the lung and brain status-post frontal craniotomy and whole brain radiation, as well as a recent diagnosis of hypothyroidism, presented from the oncology office with hypotension after receiving his fourth dose of ipilimumab therapy. The patient had a routine blood pressure check after the chemotherapy infusion and was found to be hypotensive at 80/58 mmHg. He reported increasing fatigue over the past week. He denied chest pain, shortness of breath, dizziness and headache. He was given one liter of normal saline solution, but remained hypotensive and was directly admitted to the hospital.

On physical exam, the patient was tachycardic to 102 beats per minute with a regular rhythm, clear lungs, and positive orthostatics. Laboratory studies were significant for a thyroid stimulating hormone of <0.02 uIU/mL (normal range = 0.3 – 5 uIU/mL), free T4 of 1.2 ng/dL (normal range = 0.7 – 1.7 ng/dL), follicle stimulating hormone of 0.9 mIU/mL (normal range 1.5 – 12.4 mIU/mL), adrenocorticotropic hormone (ACTH) of <9 pg/mL (normal range 9 – 46 pg/mL), total testosterone of 4 ng/dL (normal range 250 – 1100 ng/dL), and a free testosterone of 0.4 pg/mL (normal range 35 – 155 pg/mL). His white blood cell count, hemoglobin and electrolytes were within normal limits. A noon cortisol was 0.3 mcg/dL (normal A.M. range 16 – 20 mcg/dL and P.M. range 2 – 12 mcg/dL)

Figure 1. Postcontrast T1-weighted magnetic resonance image of the brain two days prior to the fourth dose of ipilimumab and hospital admission, demonstrating diffuse enlargement of the pituitary gland (arrow).

Figure 2. Postcontrast T1-weighted magnetic resonance image of the brain three months before presentation and prior to starting ipilimumab, demonstrating normal pituitary gland architecture and size (arrow).
MRI findings in ipilimumab-induced hypophysitis are non-specific and are typically characterized by a diffuse enlargement and homogeneous enhancement of the pituitary gland. Less commonly, heterogeneous enhancement has also been described. While it is common to have radiographic evidence of hypopituitarism, a normal MRI is possible. Follow-up imaging often shows resolution of abnormal findings after hormone replacement.

Pituitary hormone replacement with corticosteroids is critical to treatment, assuming ACTH is low. Either high dose or physiologic replacement dose corticosteroids are needed. Current recommendations advocate for high dose (1-2 mg/kg/day of prednisone or equivalent) steroids for moderate to life threatening symptoms. However, it is not clear whether initial high doses of corticosteroids are beneficial in treating hypophysitis. While they may play a role in reducing inflammation, they do not improve neuro-endocrine function compared to physiologic doses. However, high doses of corticosteroids may increase morbidity through side effects. Mineralocorticoid replacement is not needed since the renin-angiotensin-aldosterone system is still intact. It should be at the discretion of the oncologist and endocrinologist as to whether ipilimumab should be continued based on the condition of the patient and response to hormone replacement. Hormone deficiencies can improve, although corticotroph function seems to be the least likely to recover. Many doctors recommend close monitoring for hormone abnormalities in patients receiving ipilimumab, especially after the third infusion.

KEY POINTS

Hypophysitis is a well recognized side effect of ipilimumab therapy. A high clinical suspicion for hypopituitarism in patients receiving the drug is imperative due to the non-specific symptoms and potentially life threatening consequences. Corticosteroids should be promptly initiated as soon as secondary adrenal insufficiency is detected. While ipilimumab has many side effects, the drug has improved survival in metastatic melanoma and remains an important treatment option.
REFERENCES


