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Headache in the Setting of Immunotherapy Treatment for Metastatic Melanoma

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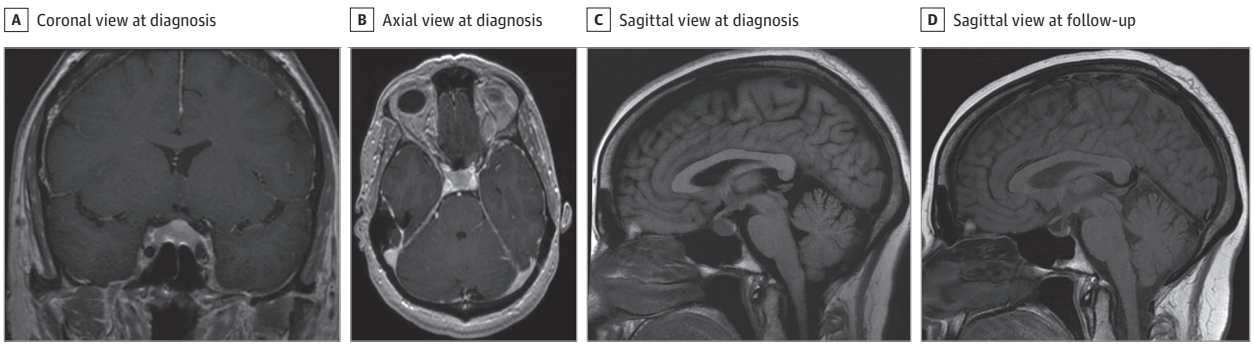

Figure. Magnetic resonance imaging (MRI) of the brain obtained 8 weeks after initiating ipilimumab (A-C) and nivolumab treatment and at follow-up (D).

A 56-year-old woman with metastatic melanoma receiving ipilimumab and nivolumab every 3 weeks developed headaches during the course of her treatment. In the week following her first treatment, the patient reported a few mild morning headaches that improved with acetaminophen. After receiving 3 cycles of ipilimumab, 3 mg/kg, and nivolumab, 1 mg/kg, and 8 weeks after her first treatment, the patient reported experiencing daily headaches for at least the prior week and a half. The location of her headaches varied, and there was no associated eye or temple pain. At best, with taking nonsteroidal anti-inflammatory drugs, the headache decreased to pain rated 3 on a scale of 1 to 10. Also at this time, the patient reported low energy levels and difficulty reading; however, physical examination showed no gross visual field defects. Laboratory workup conducted 8 weeks after initiating treatment included adrenocorticotropic hormone (ACTH) and cortisol levels that were measured at 25 pg/mL (reference range, 10-60 pg/mL) and 16.8 µg/dL (reference range, 6-24 µg/dL), respectively. Thyroid-stimulating hormone (TSH) level was 0.82 mIU/L (reference range, 0.5-5.0 mIU/L), which was gradually decreasing compared with 1.41 mIU/L 5 weeks earlier and 1.21 mIU/L 2 weeks earlier. Her total triiodothyronine level was measured at 73 ng/dL (reference range, 80-200 ng/dL) and free thyroxine level was 1.0 ng/dL (reference range, 0.9-1.7 ng/dL). Her serum sodium level was measured at 138 mEq/L; 1 week later it was measured at 135 mEq/L (reference range, 135-145 mEq/L). Contrast-enhanced magnetic resonance imaging (MRI) of the brain was performed for further assessment (**Figure**).

WHAT IS THE DIAGNOSIS?

A. Brain metastasis

B. Immune-related hypophysitis

C. Pituitary adenoma

D. Mucocele

Diagnosis

B. Immune-related hypophysitis

Discussion

Magnetic resonance images at 8 weeks after initiating ipilimumab and nivolumab therapy demonstrate an enlarged ovoid-shaped pituitary gland and thickening of the infundibulum. Based both on the constellation of imaging, laboratory, and clinical findings and the known association of hypophysitis during immune-checkpoint inhibitor treatment, the diagnosis of immune-related hypophysitis was made in this patient treated with ipilimumab and nivolumab. The laboratory abnormalities associated with hypophysitis can include low or inappropriately normal levels of TSH, low levels of ACTH, thyroid hormones, or gonadal hormones. Disruptions of the pituitary can lead to secondary adrenal insufficiency, hypothyroidism, or hypogonadism. Hypophysitis is one of the many adverse effects that has been related to immunotherapies; posterior reversible encephalopathy syndrome, aseptic meningitis, and other neurologic adverse effects have also been reported.[1]

The patient was started on steroid therapy with 20/10-mg doses (AM/PM replacement dose) of hydrocortisone. The treatment of hypophysitis was complicated when at 3 days following her last cycle of ipilimumab and nivolumab she was admitted to the hospital for colitis. She was hospitalized for 3 weeks and treated with Solu-Medrol and infliximab. She was discharged receiving a high-dose of prednisone and later tapered to a maintenance dose of hydrocortisone. In total, she completed 4 cycles of ipilimumab and nivolumab.

The patient's clinical symptoms resolved, including headache and fatigue. A follow-up MRI demonstrated resolution of the pituitary enlargement (Figure). She continues to be monitored for adrenal insufficiency and thyroid abnormalities, and more than a year after initiation of treatment her adrenocorticotropic hormone level was 5 pg/mL (reference range, 10-60 pg/mL) and morning cortisol level was 12.9 µg/dL (reference range, 6-14 µg/dL).

Mechanistically, ipilimumab is a monoclonal antibody that binds cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), and nivolumab is a monoclonal antibody directed against programed cell death protein-1 (PD-1). CTLA-4 and PD-1 normally function as immune checkpoints by downregulating pathways involved in T lymphocyte activation. By binding CTLA-4 and PD-1, ipilimumab and nivolumab increase the activation of the immune system by inactivating these immune checkpoints. Immune-checkpoint inhibition has been associated with a unique set of adverse events termed *immune-related adverse events* (irAEs) that can involve multiple organ systems in the body.[2,3] Immune-related hypophysitis during immune-checkpoint inhibitor therapy is an uncommon but increasingly recognized form of irAE. Various studies examining patients treated with monotherapy ipilimumab have reported an incidence of immune-related hypophysitis ranging from 1% to 13%.[4-8] The median time of onset for hypophysitis after beginning ipilimumab was found to be 9 weeks (range, 5-36 weeks).[7] In a study analyzing nivolumab and ipilimumab combination therapy, 11.7% of patients developed hypophysitis.[9]

The treatment of ipilimumab-induced hypophysitis is often with systemic high-dose corticosteroids, although the supportive-treatment with hormone replacement for hypophysitis-related hormone deficiencies could also be considered as a treatment strategy. It was noted that frequency of hypophysitis resolution and time to resolution did not differ significantly between the 2 treatment strategies, nor did either group recover from persistent adrenal insufficiency.[7]

This case highlights the clinical and radiographic presentation of immune-related hypophysitis during ipilimumab and nivolumab combination therapy for metastatic melanoma. As the use of immune-checkpoint inhibitor therapies rapidly increases in clinical oncology practice, heightened awareness of and familiarity with the manifestations of various forms of irAEs, including hypophysitis, will be important for clinicians involved in immuno-oncology patient care.

ARTICLE INFORMATION

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