CLINICAL VIGNETTE

Hypophysitis Caused by Monoclonal Antibody Treatment of Metastatic Melanoma

Jennifer Han, M.D., and Yaroslav Gofnung, M.D.

Case

A 75-year-old male was diagnosed with melanoma in December 2013 after a one month history of left nostril discomfort and epistaxis. Initial positron emission tomography–computed tomography (PET-CT) showed vague metabolic activity involving the posterior aspect of the nasal septum and soft palates with no discrete mass or distant metastases. An excisional biopsy of the left nasal area revealed malignant melanoma. One month later, he underwent a total nasal septectomy followed by adjuvant radiation therapy.

He developed a painless left neck mass six months later that enlarged over 3 weeks. CT scan of the neck revealed a 3.2 x 2.5 cm left level 1 lymph node. Magnetic resonance imaging (MRI) of the brain revealed postoperative changes in the nose and no evidence of brain metastases or pituitary abnormality. Fine needle aspiration of the mass showed malignant cells consistent with melanoma. The patient underwent a left neck dissection with resection of the tumor followed by another course of radiation.

Postoperative imaging showed no evidence of disease, and the patient appeared to be in remission. Unfortunately just over a year later, CT imaging demonstrated 4 new peri- and subcentimeter pulmonary nodules in the right middle lobe, left lower lobe, and right lower lobe that were suspicious for metastatic disease. A lung biopsy was consistent with metastatic melanoma. He was started on a systemic therapy of pembrolizumab, an anti-programmed cell death 1 (anti-PD 1) antibody.

Baseline thyroid testing prior to pembrolizumab initiation and throughout treatment remained within normal limits. Pituitary function tests on pembrolizumab were also normal. Despite treatment, there was radiologic evidence of disease progression with an increase in lung nodule size and a new left paraesophageal 2.8 x 2 cm lymph node.

Due to disease progression, he was switched to experimental combination immunomodulatory therapy with nivolumab and ipilimumab every 3 weeks. After his third infusion with this combination therapy, he noted acute onset of constipation, decreased appetite, weakness necessitating wheelchair, and a decrease in morning erections and libido. Laboratory evaluation (Table 1) showed a markedly decreased cortisol of 0.3ug/dL (normal 8-22ug/dL for morning draw), mild hyponatremia with sodium 134mmol/L (normal 135-146mmol/L), decreased free T4 level of 0.48 (normal 0.8-1.6ng/dL), and decreased TSH level of 0.15 (0.3-4.7mcIU/mL). He was diagnosed with panhypopituitarism and started on glucocorticoid and thyroid replacement therapy with an immediate improvement in his symptoms.

Discussion

Monoclonal Antibodies (mAbs) have been increasingly used as targeted therapies for a variety of hematologic and solid malignancies.[1] mAbs used as monotherapy or in combination with other cytotoxic drugs have improved outcomes in patients with malignancies.[1] Ipilimumab is a mAb that acts as an inhibitor of the cytotoxic T-lymphocyte antigen-4 (anti-CTLA4) receptor.[1] CTLA4 is a key immune checkpoint molecule that downregulates T-cell activation and proliferation.[1,2] Anti-CTLA4 agents inhibit this checkpoint leading to improved anti-tumor immunity through increased T-cell activation.[2-4]

In addition to treating malignancies, inhibition of CTLA4 can cause immune-related adverse events (IRAEs) by autoimmunity.[3] Frequently IRAEs include enterocolitis, rash, and hepatitis.[1-3,5] Endocrine IRAEs include thyroid dysfunction, thyroiditis, and hypophysitis.[1,3] Hypophysitis has become the most common endocrinopathy of mAbs, felt to be due to development of antibodies against the pituitary gland.[1-5] The incidence of hypophysitis due to Anti-CTLA4-mAbs is 0-17%, and this incidence rate may be underreported as many institutions are not routinely monitoring pituitary function.[1,2,4,6] Pituitary damage is usually independent of type of malignancy and has been reported in kidney, prostate, pancreatic, lung, melanoma, and lymphoma.[1] Male gender and older age are reported risk factors for hypophysitis.[1-2,4-6] The dosage of anti-CTLA4 drug appears to influence the rate of hypophysitis.[1] Ipilimumab has been FDA approved for metastatic melanoma at a dose of 3mg/kg intravenously every 3 weeks for a total of 4 doses.[1,3] In smaller studies of patients treated with lower doses of ipilimumab of 3mg/kg, incidence of hypophysitis was low at 1.8-3.3%.[1,3,4] With higher doses, the incidence of hypophysitis is more frequent. In a trial of patients receiving 3-9mg/kg of the drug, 4.9-17% experienced hypophysitis.[1-3]

Interestingly, combination therapy with ipilimumab and nivolumab, an anti-PD 1 antibody, has also been associated with hypophysitis with an incidence of 9%.[6] This incidence does not appear to be greater in combination therapy when compared to monotherapy with ipilimumab alone.[5] In fact, hypophysitis from monotherapy with an anti-PD 1 agent alone is rare with only 5 cases reported in the literature.[5]

Pituitary-thyroid and pituitary-adrenal axes are affected most commonly.[1] Hypogonadotrophic hypogonadism is seen in 83-87% of males.[1] Low prolactin levels are a common finding and tend to indicate permanent pituitary dysfunction.[4] Rarely, the posterior pituitary is affected with diabetes insipidus or SIADH.[1,5] Presentation of hypophysitis includes nonspecific symptoms of headaches, fatigue, weakness, confusion, and erectile dysfunction.[1,4] Symptoms occurred at median time of 11 weeks after initiation of therapy with ipilimumab (after the third infusion) but have been reported as early as 4 weeks from first infusion.[1,4]

Monitoring includes routine evaluation of pituitary function through early morning blood draws, especially if patient is symptomatic. Laboratory testing of cortisol, ACTH, TSH, and free T4 should be done at baseline and repeated at the start of each infusion cycle.[2] Imaging should be performed in patients with pituitary dysfunction to evaluate for the possibility of pituitary metastasis and a biopsy may be required with imaging of abnormalities.[1,4] MRI of hypophysitis often demonstrates pituitary swelling with occasional thickening of the stalk but may be normal in up to 50% of patients.[1-3]

Replacement therapy as used in all etiologies of panhypopituitarism. In these patients, ipilimumab should be held and steroids started immediately.[2,7] Physiologic steroids should be used, and patients should be educated on sick day dosing. Higher doses of corticosteroids (1-2mg/kg of prednisone or equivalent) may be used if visual disturbances such as diplopia are present due to pituitary enlargement.[2] Thyroid replacement with levothyroxine should be delayed until cortisol deficiency is treated to avoid precipitating an adrenal crisis.[2,7] Androgen replacement can be deferred initially as function of the pituitary-gonadal axis recover in 57% of males.[1-5] Growth hormone replacement should be avoided due to the contraindication of active malignancy.[4] Ipilimumab may be continued once patient has been stabilized and treated for pituitary deficiencies.[7] Counseling about the chronicity of the disease is important as persistent hypopituitarism was reported in up to 76% of patients. In fact, hypophysitis may be the only irreversible adverse effect cause by mAb.[1]

Because mAbs are being used more commonly to target a wide range malignancies and the presence of IRAEs signify a more favorable response to the treatment, hypophysitis may become a more frequent occurrence.[1,4,5] It is important to promptly recognize the possibility of panhypopituitarism in these patients given that adrenal and thyroid insufficiency are potentially life-threatening events.[3]

Tables

Table 1. Laboratory Evaluation.

	Reference Range	12/24/13	4/1/15
			Baseline
Sodium	135-146mmol/L	142	
TSH	0.3-4.7mcIU/mL		1.3
Free T4 Automated	0.8-1.6ng/dL		
ACTH	6-59pg/mL		
Cortisol			
Testosterone	47-244 pg/mL		

	Reference Range	5/13/15	6/6/15	6/27/15	9/1/15
		On Pembrolizumab Therapy			After 3rd infusion of combination therapy
Sodium	135-146mmol/L				134
TSH	0.3-4.7mcIU/mL	0.69	1.6	2.5	0.15
Free T4 Automated	0.8-1.6ng/dL		0.9	0.8	0.48
ACTH	6-59pg/mL	15			<5
Cortisol		34 (midday draw)			0.3ug/dL (am draw)
Testosterone	47-244 pg/mL				<1

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