Acute hypophysitis secondary to nivolumab immunotherapy in a patient with metastatic melanoma

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ABSTRACT

The treatment for melanoma is challenging because of its nature of being refractory particularly in metastatic stages. Treatment options include surgical resection of the lesion, radiation therapy, chemotherapy, and immunotherapy. Immunotherapy such as anti-cytotoxic T-lymphocyte antigen-4 and anti-programmed cell death protein 1 (PD-1) are increasingly being used in the treatment of metastatic malignant melanoma. Nivolumab is a PD-1 inhibitor used for the treatment of malignant melanoma. In our case, an 83-year-old patient presented with enlarged inguinal lymphadenopathy 2 years after curative surgical resection of her toes secondary to melanoma. She was started on nivolumab therapy after positron emission tomography (PET)–computed tomography scan and biopsy confirmed metastatic melanoma. She was responding well to the treatment as evidenced by repeated PET scan. Unfortunately thereafter, she was hospitalized with severe lethargy and generalized weakness attributed to immune-related adverse effects of thyroiditis and hypophysitis. Therefore, nivolumab was discontinued, and she was treated with high dose steroids and thyroid supplementation. The most common side effects of nivolumab therapy are immune-mediated colitis, immune-mediated hypothyroidism, immune-mediated hyperthyroidism, and immune-mediated adrenal insufficiency. It is important for clinicians to monitor patients closely with appropriate laboratories and regular follow-ups to identify side effects early so that they can be treated appropriately.

Key Words: Hypophysitis, melanoma, nivolumab

INTRODUCTION

Cancer cells evade detection and destruction by the immune system through up-regulation of specific receptors that would disguise them as normal cells.[¹] This mechanism allows the malignant cells to proliferate and grow without being detected by the immune system. The novel therapies target these cancer cells specifically and block a specific receptor, thus exposing them to the immune T-cells.[¹,²] One of the novel drugs, programmed cell death protein 1 inhibitor (PD-1), revolutionized cancer treatment. Nivolumab is a monoclonal antibody that works by binding to the PD-1 receptor thereby inhibiting the interaction of programmed death receptor-1 ligand (PD-L1) and PD-L2 ligands. This allows the immune cells to detect the cancer cells and mount a response. Nivolumab is currently being used in treatment for metastatic melanoma, nonsmall cell lung cancer (NSCLC), and renal cell cancer.[²⁻⁴] An important side effect of this medication is identified as immune-related adverse events (irAEs) which include pneumonitis, colitis, hepatitis, nephritis, hyperthyroidism, hypothyroidism, and adrenal insufficiency.[⁵] Primary hypophysitis is a rare inflammatory, autoimmune disorder of the pituitary gland where the immune cells (predominantly leukocytes) infiltrate the gland.[⁴,⁵] This produces a mass effect[⁵] which can lead to hormonal...
since 3–4. Many costimulatory and inhibitory pathways for the blockade. PD-1 is upregulated on T cells in response to persistent antigen exposure, usually in response to the immune synapse formed between antigen-presenting cells and T-cells and these processes, interactions drive the immune escape of the tumor. The role of the immune-checkpoint axis is to essentially maintain self-tolerance and prevent autoimmunity. Many costimulatory and inhibitory interactions drive the immune synapse formed between antigen-presenting cells and T-cells and these processes, in turn, regulate the intensity and duration of T-cell response. Cancer and/or noncancer cells from the surrounding microenvironment commonly overexpress inhibitory proteins which are responsible for the downregulating T-cell-effector functions, such as cytotoxic T-lymphocyte-associated-protein 4 (CTLA-4) and PD-1, leading to the immune escape of the tumor. Since this major discovery, the treatment and management of several solid tumors have dramatically changed since it now revolves around targeting the CTLA-4 and PD-1 pathways for the blockade. PD-1 is upregulated on T cells after persistent antigen exposure, usually in response to the immune synapse formed between antigen-presenting cells and T-cells and these processes, interactions drive the immune escape of the tumor.

The patient was then started on anti-PD1 therapy with nivolumab to treat metastatic melanoma. She clinically responded well to the treatment with minimal side effects. After 5 cycles of nivolumab therapy, a repeat PET scan was obtained. The results showed a decrease in metabolic activity of the lesion at the anterior aspect of the right leg with a resolution of the other hypermetabolic foci at the ankle. Decreased size of the metabolic activity of the right inguinal lymph node and decreased metabolic activity of the lesion at the aortic bifurcation. On the other hand, the lymph nodes within the mediastinum had persistent hypermetabolism and a new hypermetabolic lymph node at the bilateral hilar regions. There was the resolution of the focus hypermetabolism at the right thyroid lobe, but a new diffuse hypermetabolism which indicates thyroiditis. No treatment was initiated at this time because she was asymptomatic with normal thyroid-stimulating hormone (TSH) levels.

About 5 months later, she presented to the hospital complaining of fatigue, forgetfulness and symptomatic bradycardia. Chest X-ray was normal. CT scan and magnetic resonance imaging of the head were unremarkable. At this time, further laboratory investigations revealed a TSH was 36.4 mU/L (normal 0.5–4.7) with free T4 of 0.25 (normal 0.73–2). The thyroid peroxidase antibody levels were >600 was diagnosed with acute autoimmune thyroiditis. The patient was started on levothyroxine supplementation which resulting in dramatic clinical improvement.

Three weeks later, she was again admitted to the hospital after she was discovered to be hypersomnolent and severely lethargic. Her laboratory work showed a TSH level of 1.92 μU/L, free T4 0.87. Cortisol level was drawn, and it was <0.5 μg/dl and thyroid peroxidase antibody levels >600. Insulin-like growth factor-1 and prolactin levels were normal. She was diagnosed with acute severe autoimmune adrenal insufficiency and acute autoimmune thyroiditis related to Nivolumab therapy. The adrenocorticotropic hormone (ACTH) level was <0.01 pg/mL confirming a central cause for the adrenal insufficiency of the patient and a possible diagnosis of Nivolumab associated hypophysitis. She was treated with intravenous (IV) hydrocortisone 100 mg every 8 h and IV levothyroxine 75 mcg daily supplementation. Nivolumab had to be stopped due to the immune-mediated side effects. After 2 days of therapy, the patient clinically improved and she became more arousable. She underwent aggressive physical therapy and was subsequently discharged to a rehabilitation center for further care.

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to chronic infections or cancers. PD-L1 and PD-L2, the ligands for PD-1, can be expressed by tumor cells, as well as several other hematopoietic and nonhematopoietic cell types. There are several inflammatory biomarkers and cytokines that stimulate the expression of PD-L1 and PD-L2. Oncogenic signaling pathways in cancer cells can also contribute to the upregulation of PD-L1 expression. When PD-1 binds its ligand, the T cell receives an inhibitory signal. Expression of PD-1 ligands is a mechanism for cancer cells to escape detection and antitumor immune responses. Immune checkpoint inhibitor, a monoclonal antibody similar to Nivolumab and it works on cytotoxic T-lymphocyte antigen-4 (CTLA-4). Nivolumab is now approved by the FDA to treat metastatic melanoma, NSCLC, renal cell carcinoma, Hodgkin’s Lymphoma, Head and Neck Cancer and Urothelial Carcinoma. Combining Nivolumab with Ipilimumab therapy has also proven to be of therapeutic and survival benefit secondary to the complimentary action on the immune system.

The most common side effects from this treatment are rash (21%), pruritus (19%), cough (17%), upper respiratory tract infection (11%), and peripheral edema (10%). IrAEs are not a common finding of nivolumab treatment, nevertheless, when it occurs, it can be severe. According to an article published in the American Health and Drug Benefits, about 21% of the patients developed immune-mediated colitis, 8% developed hypothyroidism, <1% developed pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis, 1.1% developed autoimmune hepatitis, 0.9% immune-mediated pneumonitis, and 0.7% immune-mediated nephritis. Patients on Nivolumab should be followed up regularly and screened for these potential outcomes.

In our case, the patient developed endocrinopathies of thyroiditis and hypophysitis. Symptoms of hypophysitis include fatigue and headache. The diagnosis was confirmed by obtaining ACTH, TSH, follicle-stimulating hormone, luteinizing hormone, growth hormone, and prolactin levels, which are expected to be low in this clinical condition. Other potential causes of hypophysitis must be ruled out before attributing it to the drug therapy to prevent unnecessary discontinuation of nivolumab. Most commonly, hypophysitis is observed in patients treated with 3 mg/kg and 10 mg/kg dose of Nivolumab. When toxicity occurs, patients should be managed by administering high-dose corticosteroids (1 mg/kg of prednisone daily) in an acute setting. In general, after the acute phase patient needs to be on a long-term hormone replacement therapy, especially with the history of secondary hypothyroidism or hypoadrenalism. Nonetheless, some patients can be weaned off over a period.

Isolated hypothyroidism or hyperthyroidism can also occur with nivolumab treatment, mostly mild grade 1 or 2. Therefore, patients should be screened before starting the treatment and during the treatment with measuring TSH levels. Studies show a median time frame of 2.5 months for the onset of symptoms that are unrelated to any specific dosage of nivolumab. A grade 1-2 hypo or hyperthyroidism does not indicate a dose adjustment. These patients can be managed with thyroid hormone replacement and can be continued with the treatment. There is no indication to discontinue nivolumab therapy either knowing the patient will be followed up with TSH level on a regular basis. In acute thyroiditis, however, high dose of prednisone (1 mg/kg of prednisone) is indicated. The clinical response after treatment is good. If the patient develops grade 3-4 immune-mediated hypothyroidism, then the nivolumab should be discontinued.

CONCLUSION

Nivolumab is an optimal treatment option for metastatic malignant melanoma. It works by specifically blocking human PD-L1 found on many cancer cells, attaching to the human programmed death receptor-1 (PD-1) found on the surface of activated T cells. The binding of PD-1 to its ligand results in the inactivation of the T-cell. Antibodies that block this interaction allow the immune system to attack the cancer cell. Upregulation of the immune cells helps to target the therapy to eradicate the cancer cells. The same mechanism also causes immune-mediated adverse effects which can be managed if caution is taken from the start of the treatment. Therefore, it is important to follow these patients with regular laboratory diagnostic tests and have a high clinical suspicion of the index for these well-recognized immune-mediated adverse effects. Mostly, Grade 1-2 toxicities can be managed without discontinuing the current treatment and grade 3-4 toxicity requires termination of the therapy. In general, a high dosage of corticosteroid helps to dampen the immune system and decreases the immune-mediated attack. More research needs to be done to identify any potential predictors of the adverse events. Maybe regular monitoring of endocrine function, i.e., thyroid function tests, cortisol levels in addition to gonadal function may need to be regularly monitored to screen for any potential immune-mediated endocrinopathy while on PD-1 inhibitor therapy.

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Conflicts of interest
There are no conflicts of interest.
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