CLINICAL VIGNETTE

Severe Hypothyroidism Associated with Pembrolizumab

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Case

A 45-year-old female with recurrent anaplastic astrocytoma presented to the emergency department with worsening lethargy.

The patient's astrocytoma had been diagnosed eighteen months prior. Following her diagnosis, she started radiotherapy and temozolomide and underwent ventriculoperitoneal shunt placement for hydrocephalus. She had three subsequent recurrences treated with more temozolomide as well as bevacizumab and lomustine. Her fourth recurrence was identified six weeks prior to presentation, and pembrolizumab and carboplatin were added to bevacizumab therapy.

The patient deteriorated clinically, with worsening diplopia, right-sided weakness, hypersomnolence, severe dysarthria, and anorexia. Prior to starting pembrolizumab she had ambulated with the assistance of a walker and slept about 70 percent of the day. Three weeks after pembrolizumab was started, the patient's family noted poor oral intake for which a percutaneous endoscopic gastrostomy tube was placed. A TSH obtained prior to initiation of pembrolizumab was 4.1 mcIU/mL (reference 0.3-4.7 mcIU/mL). Five and a half weeks after pembrolizumab was started, the patient's TSH was rechecked and had risen to 44.5 mcIU/mL, with a free T4 of 0.4 ng/dL (reference 0.8-1.7 ng/dL). At this time, the family reported that the patient was sleeping 90 percent of the day and was unable to ambulate without falling due to lethargy and weakness. Her TSH was rechecked at 105.9 mcIU/mL, with a free T4 of 0.1 ng/dL. Given the patient's increasing lethargy and severely elevated TSH, she was directed to the emergency department for evaluation of possible myxedema coma.

Review of systems was notable for weight loss over the preceding months, attributed to decreased intake, chronic cold intolerance, and the neurologic changes mentioned above, including increased somnolence. There were no hair, skin, or nail changes. Following the initiation of enteral alimentation she had been started on stool softeners, but there was no overt constipation. The patient had no prior history of thyroid disease. Her father had a remote history of thyroid lobectomy, with thyroid hormone replacement for post-surgical hypothyroidism. The patient had no recent sick contacts or viral illnesses.

On presentation, the patient's vitals included temperature 37.2 C, pulse 96, blood pressure 135/98, oxygen saturation 96% on room air, and weight 66.7 kg, with a BMI of 26.89 kg/m^2. On exam, the patient was awake and following commands but was very lethargic. There were bilateral periorbital ecchymoses and mild swelling present related to a ground level fall several days prior to presentation. On neck palpation, there was no thyroid fullness, thyroid nodules/masses, lymphadenopathy, or tenderness. Cardiopulmonary and abdominal exams were unremarkable. All four extremities were cooler to touch, with intact and symmetric peripheral pulses, and without edema. There was right upper extremity weakness, particularly with fingergrip, and the patient's speech was unintelligible. Brachial, biceps, patellar, and ankle tendon reflexes were diminished.

Laboratory evaluation revealed a normal complete blood cell count, normal basic metabolic panel with a glucose of 150 mg/dL, bland urinalysis, normal lactate, and negative blood cultures. Thyroid studies were notable for a TSH of 145 mcIU/mL, with a free T4 that was below the detectable limit; thyroglobulin antibody level of 1183 IU/mL (reference <4.0 IU/mL); and thyroid peroxidase antibody level of 316 IU/mL (reference ≤20 IU/mL). Imaging studies, including a facial x-ray to assess for periorbital fractures, a CT brain to assess for acute bleeding, and an x-ray series to evaluate ventriculoperitoneal shunt function, were all unremarkable.

Because of the degree of hypothyroidism and the patient's altered mental status, myxedema coma was initially a concern. However, due to the patient's normal vital signs and a relatively intact sensorium, the diagnosis was more consistent with severe hypothyroidism than myxedema coma.

The patient was treated with intravenous levothyroxine 100 mcg daily (dosing based on 1.6 mcg/kg/day). On hospital day 2, while still lethargic, she answered more yes/no questions, participated more actively in examinations, and shrugged when asked if she felt cold. She demonstrated greater expression than was elicited prior to admission. On hospital day 3, the patient was discharged home, with instructions to take levothyroxine 112 mcg daily through her percutaneous endoscopic gastrostomy tube 1-2 hours before bolus feeds were administered. The patient's TSH normalized to 1.9 mcIU/mL two weeks after the initiation of levothyroxine.

Discussion

Programmed cell death-1 protein (PD-1) binds to Programmed death-1 ligand 1 (PD-L1) in an interaction important for maintaining peripheral immune tolerance. This interaction is also exploited by cancer cells, which aberrantly express PD-1 on their cell surfaces to avoid induction of apoptosis by natural killer (NK) cells and others.[1-3] Immune checkpoint inhibitors, including the PD-1 inhibitor pembrolizumab, have proven effective in treating many solid organ malignancies.[1,2] Among other adverse effects, however, thyroid disease has been reported in literature[2-7] with some estimates involving up to 10-15% of patients.[2-5,8]

In general, the clinical course of thyroid disease associated with immune checkpoint inhibitors begins with hyperthyroidism, indicated by decreased TSH and elevated free T4 values, with subsequent progression to hypothyroidism.[2-4] The hyperthyroidism stage is most commonly asymptomatic, beginning three to six weeks following initiation of immune checkpoint inhibitors and lasting a median of six weeks.[2-4] Progression to hypothyroidism, if it occurs, will usually develop by ten weeks after starting immune checkpoint inhibitors.[2-4] Of note, there is a spectrum of clinical thyroid dysfunction, with some developing isolated hypothyroidism without thyrotoxicosis and some developing antibody-negative hypothyroidism.[3,5] Interestingly, one patient developed biochemically euthyroid Graves' ophthalmopathy rather than the more commonly reported clinical presentation of a destructive thyroiditis.[7]

The mechanism of the thyroid dysfunction is not completely understood, but is thought to be distinct from a simple unmasking phenomenon of thyroid cells to the immune system.[5,8] A recent study demonstrated that immune checkpoint inhibitor-induced hypothyroidism was associated with alterations in the relative number of circulating NK cells as well as a decrease in immunosuppressive monocytes, indicating that an immune lineage alteration is likely responsible in part for increased autoimmunity in these conditions.[8]

The management of thyroid disease associated with novel checkpoint inhibitors is similar to the management of other cases of hypothyroidism. Thyroid hormone replacement with levothyroxine is started at a dose of roughly 1.2-1.6 mcg/kg daily,[9] although some recommend starting at a lower dose of levothyroxine 50 mcg daily.[10] The levo-thyroxine dose is titrated to normalization of thyroid function tests.[2,3] In one study, all patients started on levothyroxine therapy required continued thyroid hormone replacement at 14 months to maintain a euthyroid state.[3] Our patient's severe hypothyroidism was fortunately diagnosed prior to progression to myxedema coma, which has high mortality and would be treated with intravenous levothyroxine and intravenous liothyronine. Scoring systems have been developed to diagnose patients with myxedema coma as well as to identify those at risk of developing myxedema coma.[11,12]

We report a case of severe hypothyroidism associated with the PD-1 inhibitor pembrolizumab in a patient without baseline thyroid disease. The patient developed severe biochemical and clinical hypothyroidism, with profoundly elevated thyroid autoantibody titers, only three weeks after the initiation of pembrolizumab. Measurement of baseline thyroid function tests prior to starting therapy with immune checkpoint inhibitors, as well as routine thyroid function test monitoring while on therapy, should be considered.

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Submitted November 21, 2018