A challenging case of new-onset paroxysmal atrial fibrillation with rapid ventricular response secondary to autoimmune thyroiditis after a single dose of nivolumab-ipilimumab

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A 61-year-old man with moderately differentiated distal esophageal adenocarcinoma, HER-2 2+ by IHC, HER-2 negative by FISH, metastatic to liver, left adrenal gland, and lymph nodes, was randomized to nivolumab 1 mg/kg (93 mg) and ipilimumab 3 mg/kg (280 mg) intravenously every 21 days. He was admitted to the hospital 19 days after initiation of therapy secondary to worsening dysphagia, inability to tolerate oral intake, early satiety, nausea, and vomiting. He underwent placement of a percutaneous gastrostomy tube the following day for nutritional needs. The next morning, 21 days after his first dose of the immune checkpoint inhibitors, he developed near syncope, lightheadedness, and diaphoresis after shaving his face. His heart rate exceeded 170 and was irregularly irregular (see Figure). This required vagal maneuvers, intravenous doses of metoprolol, digoxin, and initiation of a diltiazem intravenous drip for 24 hours, to achieve rate control and hemodynamic stability. The patient had no additional symptomatology, including no headaches, no visual disturbances, no polyuria, and no polydipsia. He has no history of hypertension, diabetes mellitus, or coronary arteriosclerosis.

An extensive work-up ensued, including serial cardiac enzymes, and EKGs that demonstrated no evidence of an acute coronary syndrome. A transthoracic echocardiogram showed a normal left ventricular ejection fraction (LVEF) of 70%, with no regional wall motion abnormalities. A computed tomography angiography of the chest demonstrated no evidence of pulmonary embolism. Laboratory tests revealed normal electrolytes, including serum sodium and potassium, normal glycemia, and normal renal function tests. Additionally, we confirmed no evidence of hypophysitis or adrenalitis, with normal LH at 8.1 mIU/mL, normal FSH at 4.6 mIU/mL, normal IGF-1 at 35 ng/mL, as well as an intact adrenal cortical axis with normal ACTH at 9 pg/mL, normal morning cortisol levels at 16.5 mcg/dL, normal renin activity and aldosterone levels. Fractionated metanephrines were normal also.

His thyroid function tests were markedly abnormal, with a very elevated free T4 at greater than 7.77 ng/dL, very elevated total T3 at 360 ng/dL, a markedly reduced TSH at less than 0.01 mcunit/mL. This in contrast to his baseline thyroid function tests, measured the day prior to initiation of therapy, with a TSH at 2.44 mcunit/mL, and a free T4 at 1.25 ng/dL (see Table). Additional tests measured the day of the event included the Thyroid Peroxidase Antibody (TPO), elevated at 574 IU/mL, as well as the Thyrotropin Receptor Antibody (TRAb), elevated at 2.20 IU/L. The Thyroid Stimulant Immunoglobulin (TSI), was low at less than 1.0 TSI Index, and the Interleukin-6 levels were low at less than 5 pg/mL.

The patient was successfully managed with beta-blockers; his cardiac rhythm returned to normal sinus. No corticosteroids were necessary.

Following the hyperthyroid phase, the patient became euthyroid and then hypothyroid, requiring thyroid-replacement therapy.

The use of immune-checkpoint blocking antibodies anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD1), alone or in combination, have demonstrated objective antitumor responses in multiple tumor types, including melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The investigational use of these agents is being increasingly applied to other tumor types.

CTLA-4 and PD-1 are two co-inhibitory receptors that are expressed on activated T-cells against which therapeutic blocking antibodies have reached routine clinical use. Immune checkpoint blockade can induce inflammatory adverse effects, termed immune-related adverse events (IRAEs), which resemble autoimmune disease.

This case is that of a middle-aged gentleman who developed a sudden but significant episode of atrial fibrillation with rapid ventricular response 21 days after his initial dose of nivolumab-ipilimumab. The patient lacked the risk factors and comorbidities that commonly co-exist with atrial fibrillation, such as advanced age, alcohol consumption, family history of atrial fibrillation, hypertension, sleep apnea, and heart disease. He was found to have acute autoimmune thyroiditis, suggesting exposure to the immune checkpoint inhibitors nivolumab-ipilimumab as the causative agent.

In clinical trials, it has been determined an increased susceptibility to hypophysitis in those treated with CTLA4-targeted immunotherapy, and PD-1-targeted treatment have been predominantly linked with primary thyroid dysfunction. Additionally, the combination of nivolumab and ipilimumab has greater incidences of thyroiditis than monotherapy. These data suggest that additive effects of the two therapies might contribute to certain IRAEs.

References

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Conclusions

In immunotherapy-related thyroiditis, hyperthyroidism is thought to be as a consequence of destruction of follicular thyroid cells with consequent liberation of thyroid hormones, but the exact mechanism is still under investigation.

Table. Thyroid function tests at baseline (i.e., the day prior to initiation of nivolumab-ipilimumab), the day of the atrial fibrillation with rapid ventricular response event (Day 0), and at 2 days, 4 days, 10 days, 13 days and 40 days following the event.

Test (units)	Baseline	Day 0	2 days post-event	4 days post-event	10 days post-event	13 days post-event	40 days post-event
TSH (mcunit/mL)	2.44	< 0.01			0.09	1.19	33.91
Free T4 (ng/dL)	1.25	> 7.77	4.8	2.69	1.04	0.76	0.58
Total T3 (ng/dL)	360	239	176				

Figure. EKG the day of the atrial fibrillation with rapid ventricular response event.