IMMUNE CHECKPOINT INHIBITOR-INDUCED THYROID STORM AND FATAL CARDIOGENIC SHOCK IN A PATIENT WITH METASTATIC MELANOMA

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ABSTRACT

Background: Immune checkpoint inhibitors significantly improve mortality in advanced melanoma. However, these agents, particularly as combination therapy, have significant adverse effects that often manifest as autoimmune presentations. In this case, we describe immune checkpoint inhibitor-induced thyroid storm and fatal cardiogenic shock in a patient with metastatic melanoma.

Case: 65-year-old gentleman with metastatic melanoma presented with syncope. He was started on nivolumab and ipilimumab 11 days prior to admission, with pre-initiation thyroid tests in normal range. Workup revealed new thyrotoxicosis, complete heart block, rhabdomyolysis, troponin 2.76, and LVEF 60% on echocardiogram. Management was initiated with methimazole. Additionally, a dual chamber pacemaker was placed because although complete heart block is a known complication of hyperthyroidism, reversal of thyrotoxicosis does not guarantee heart block resolution. A subsequent asystolic episode was attributed to lead capture failure, and repeat studies showed thyroid storm, troponin >50, and LVEF 20%. The patient deteriorated into cardiogenic shock requiring emergent IABP. Ultimately, family opted for comfort measures.

Conclusions: This is the first reported case of immune checkpoint inhibitor-induced thyrotoxicosis complicated by complete heart block, with subsequent thyroid storm leading to terminal cardiogenic shock in a patient with metastatic melanoma.

KEYWORD

cardiogenic shock, thyroid storm, nivolumab, ipilimumab, melanoma

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INTRODUCTION

Nivolumab (BRAND: Opdivo) and ipilimumab (BRAND: Yervoy) are immune checkpoint inhibitors that have revolutionized the management of metastatic melanoma having shown significant improvement in mortality as monotherapy, with further benefit as combined therapy (1,2). Since these agents are essentially antibodies that function via modulation and regulation of the immune system, it is not surprising that associations have been identified between immune checkpoint inhibitors and immune-mediated adverse effects, including endocrinopathies, hepatitis, and in rare isolated cases, rhabdomyolysis and myocarditis (3-6). Importantly, treatment-related adverse events of high severity were significantly increased in the combined immune checkpoint inhibitor treatment group compared to monotherapy (1,2). In this report, we present a case of metastatic melanoma in which combined immune checkpoint inhibitor therapy toxicity manifested as new complete heart

block likely secondary to acute thyrotoxicosis, which devolved into florid thyroid storm and rapid decompensation into cardiogenic shock and ultimately death.

Case Presentation

A 65-year-old gentleman with metastatic melanoma experienced a syncopal episode associated with profound generalized weakness upon regaining consciousness. On EMS arrival, he was found to have a heart rate ranging 20-30 beats per minute and was rushed to the hospital. Workup revealed new thyrotoxicosis (TSH 0.08, free T4 3.7), complete heart block on EKG, rhabdomyolysis, troponin level of 2.76, and a left ventricular ejection fraction (LVEF) of 60% on transthoracic echocardiogram.

His medical history consisted of metastatic melanoma, well-controlled hypertension and type II diabetes. The melanoma was initially diagnosed from a right-sided neck mass, with subsequent PET scan positive for right neck lymph node and rectoanal activity. Following mass excision and an unremarkable colonoscopy, he was deemed to be a candidate for combined nivolumab and ipilimumab therapy, which was started 11 days prior to admission. Thyroid function tests completed prior to immunotherapy were in the normal range (TSH 1.81, free T4 1.46). In the interval leading up to hospital admission, the patient described intermittent nausea and fatigue that he had attributed to the new immunotherapy.

Since hyperthyroidism in similar immunotherapy-related cases manifested as autoimmune thyroiditis, management was initiated with 20 milligrams of methimazole daily for a presumed autoimmune, drug-induced thyrotoxicosis. Additionally, a dual chamber pacemaker was placed because although complete heart block is a known, albeit uncommon complication of hyperthyroidism, reversal of thyrotoxicosis would not guarantee resolution of the heart block.

The patient's clinical status was stable with the management in place. However, on the third day of the hospital course, the patient was found unresponsive; telemetry displayed an asystolic episode. Urgently rushed to the electrophysiology laboratory, pacemaker functionality was found to be intact, and the presumed cause of asystole was lead capture failure. One lead was revised as a precautionary measure.

The patient's clinical status continued to worsen, and repeat studies at this point showed fulminant thyroid storm (TSH 0.02, free T4 8.5), worsening rhabdomyolysis, troponin >50, and LVEF 20% (Table 1). Management was intensified to include 200 milligrams propylthiouracil every four hours in place of methimazole, as well as 100 mg intravenous hydrocortisone every eight hours and Lugol's iodine solution. On the fourth day of admission, the patient developed sustained ventricular tachycardia, which eventually converted to sinus with lidocaine. The patient deteriorated into cardiogenic shock and multiorgan failure including acute renal compromise and severe hepatic dysfunction. He required intubation, emergent placement of an intra-aortic balloon pump, and bedside dialysis. The possibility of ECMO was discussed; however, with the rapid decline in the patient's clinical status, the family opted to focus on comfort measures.

DISCUSSION

The rapid deterioration of this patient in the interval of less than five days was profound. We suspect that this case was primarily propelled forward by rapid thyroid storm eventually leading to cardiogenic shock and death. However, the precise interplay between this thyroid dysfunction, rhabdomyolysis, heart block, and cardiogenic shock remains unclear.

Given the limited literature on immune-mediated adverse effects related to nivolumab and ipilimumab, it is difficult to clearly elucidate whether one agent in particular was the underlying trigger leading to this patient's devastating hospital course. Nivolumab may have been the primary agent since the constellation of symptoms in this case, namely thyroid dysfunction, rhabdomyolysis, hepatic dysfunction, persistent hyperglycemia, and cardiogenic shock, have each been reported as side effects of nivolumab in isolated case reports, though never manifesting together in one patient. However, without conclusive evidence supporting this notion, and with combined therapy known to worsen adverse effects approximately 2-3 fold (1,2), we surmise that the rapid deterioration described was the synergistic effect of nivolumab and ipilimumab combined immunotherapy.

Endocrinopathies are estimated to occur in up to 10% of patients treated with immune checkpoint inhibitors, with the thyroid gland among the most frequently affected (7). In these cases, hyperthyroidism generally manifests as a transient process similar to Graves disease with elevated TSH receptor antibodies (8); however, antibodies eventually resulted negative in this case, making thyroiditis the more likely etiology. A nuclear scan for further clarification was deferred due to acuity of clinical status.

Complete heart block as a complication of hyperthyroidism has been documented in numerous case reports over the last several decades (9). The pathogenesis is unclear, with the leading hypothesis suggesting myocardial inflammation surrounding the AV node in repeated inflammatory states could eventually result in cumulative damage to cardiomyocytes. Of note, cardiac conduction abnormalities are not a known adverse effect of immune checkpoint inhibitors. Therefore, we suspect that in this case, immunotherapy led to thyrotoxicosis complicated by complete heart block. It is also possible that the underlying worsening rhabdomyolysis may have affected the cardiac tissue, contributing to heart block and subsequent lead capture failure.

To our knowledge, this is the first reported case of immune checkpoint inhibitor-induced thyrotoxicosis complicated by complete heart block, with subsequent thyroid storm leading to cardiogenic shock and death in a patient with metastatic melanoma. Novel therapeutic agents such as the immune checkpoint inhibitors nivolumab and ipilimumab are undoubtedly highly efficacious and offer significant mortality benefit to the vast majority of patients suffering with metastatic melanoma. The importance of this case report is to increase awareness and highlight that implementing these agents are not without considerable risk and can even be fatal.

Table

Table 1. Critical laboratory values and trends during the hospital course

	Day 1	Day 2	Day 3	Day 4	Day 5
TSH	0.08	-	0.02	0.02	0.02
Free T4	3.7	-	8.1	8.5	8.0
CK	4088	6848	7676	7643	9020
Troponin	2.76	2.56	-	>50.00	>50.00
LVEF	-	60%	-	20%	-

The table displays the laboratory trends of multiple values over the hospital course. TSH decreased as free T4 increased as thyroid storm evolved. CK continued to rise throughout the admission, suggestive of ongoing and worsening rhabdomyolysis. Troponin levels peaked as the patient deteriorated into cardiogenic shock. The LVEF dropped significantly in only 48 hours, temporally correlating with worsening thyroid storm and cardiogenic shock. TSH = thyroid stimulating hormone. CK = creatine kinase. LVEF = left ventricular ejection fraction.

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