

CASE REPORT



Nivolumab-induced autoimmune diabetes mellitus and hypothyroidism in a patient with rectal neuroendocrine tumor

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ABSTRACT

We present a rare case of autoimmune diabetes mellitus and hypothyroidism in an elderly man initiated on nivolumab two months prior to admission for treatment of a high-grade neuroendocrine rectal tumor. This patient presented to a local community hospital with one-week history of severe nausea, thirst, and bilateral leg edema. Biochemical studies confirmed the diagnosis of diabetic ketoacidosis in the setting of autoimmune diabetes mellitus and primary hypothyroidism, likely due to nivolumab use. This case illustrates an acute complication due to secondary diabetes mellitus in the setting of a novel anticancer agent. There are three key takeaways for physicians managing patients on nivolumab. First, there should be a discussion of the benefits and risks of immunomodulatory therapy. Second, patients should be tested for immunological and other markers before being started on checkpoint inhibitors. Third, oncologists must be aware of the signs and symptoms of life-threatening hyperglycemia and severe hypothyroidism. Additional studies are needed to identify those patients at highest risk for autoimmune complications.

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Nivolumab; checkpoint inhibitors; autoimmune diabetes mellitus; hypothyroidism; endocrinopathy

1. Introduction

There have been important advancements in cancer therapy over the past few years, especially in the area of neuroendocrine tumors. Systemic chemotherapy is beginning to be replaced by therapeutics specifically targeted at molecular entities, which is having an impact on agent selection, patient management, and long-term outcomes [1].

Nivolumab-induced diabetes mellitus is a rare but serious and potentially life-threatening adverse effect of checkpoint inhibitors in the treatment of solid tumors, especially neuroendocrine tumors. While this adverse effect is not presently known to be reversible, oncologists need to be cognizant of signs and symptoms of hyperglycemic crisis when initiating a patient on nivolumab, a monoclonal antibody that blocks the programmed cell death 1 (PD-1) receptor.

2. Case report



A 78-year-old male patient presented to a community hospital with one-week history of severe nausea, thirst, and bilateral leg edema in January 2017. The patient was initiated on nivolumab two months before admission for treatment of a high-grade neuroendocrine rectal tumor associated with pelvic lymphadenopathy and perirectal soft tissue metastatic

lesions, diagnosed ten months prior to admission. His past medical history was significant for a remote history of prostate cancer, hypertension and gout. The patient had no history diabetes or thyroid disease. The patient was hypotensive (86/53 mm Hg). Physical exam was significant for somnolence, and negative for periorbital edema and thyromegaly. No acetone smell in the breath was noted.

Laboratory data revealed plasma blood glucose of 1298 mg/dL, pH < 7.096, bicarbonate < 4 mEq/L, beta-hydroxybutyrate > 50 ng/dL, anion gap of 41 mmol/L, TSH 33.66 m[IU]/mL, free T4 0.3 ng/dL, and hemoglobin A1c of 9.2%. Further studies found a glutamic acid decarboxylase-65 of 74 IU/L, C-peptide level <10 ng/mL, and thyroid peroxidase antibodies of 252.1 [IU]/mL.

Biochemical studies confirmed the diagnosis of diabetic ketoacidosis (DKA) in the setting of autoimmune diabetes mellitus and primary hypothyroidism, likely due to nivolumab use.

The patient was initiated on standard care for DKA, including fluid repletion, intravenous insulin administration, and correction of electrolyte imbalances. Oral levothyroxine therapy was initiated for hypothyroidism. The patient was discharged from the hospital nine days later on multiple daily basal insulin therapy in a stable condition with endocrinology follow up. Nivolumab therapy has been discontinued. After an extended battle with primary cancer, the patient died 18 months later.

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The authors have not published, posted, or submitted any related papers from the same study

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3. Discussion

This case illustrates an acute life-threatening complication due to secondary/autoimmune diabetes mellitus along with hypothyroidism in the setting of a novel anticancer agent. Endocrine toxicities such as diabetes mellitus may appear months or even years after initiation of therapy [2]. The proposed mechanism for induction involves T cell activation, leading to the death of pancreatic beta cells [3]. While thyroid dysfunction is not adequately understood in the setting of nivolumab therapy, the results of a large cohort study in Japan suggest that patients with pre-existing anti-thyroid antibodies and elevated TSH at baseline may face a higher risk [4]. Other endocrinopathies, including thyroid dysfunction, hypopituitarism, and adrenal insufficiency have also been associated with checkpoint inhibitors. For example, a recent case report described two elderly women presenting with transient thyrotoxicosis within two to four weeks of initiating nivolumab treatment, while thyroid dysfunction typically occurs around twelve weeks after initiation [5]. Thus, awareness of this medication's side effects is warranted given the potential for serious medical emergencies such as DKA and thyrotoxicosis.

There are three key takeaways from this case for oncologists and primary care physicians managing patients on nivolumab. First, there should be a discussion of the benefits and risks of immunomodulatory therapy. This should involve coordination between the oncologist and primary care physician involved in the patient's care. If the patient already has uncontrolled diabetes mellitus or thyroid dysfunction, an endocrinology referral may be warranted.

Second, patients should be tested for immunological and other markers before being started on checkpoint inhibitors. While no official screening guidelines are present, examples include testing for hemoglobin A1c, fasting blood glucose, thyroid panel, glutamic acid decarboxylase autoantibody, islet antigen 2 antibody, PD-1, and programmed death-ligand 1 antibody [6]. Given that this patient had a neuroendocrine tumor, other tests such as an adrenocorticotrophic hormone stimulation test for adrenal insufficiency should also be considered.

Third, oncologists should be aware of signs and symptoms of hyperglycemia and thyroid dysfunction (both hypo- and hyperthyroidism) and be ready to

provide appropriate patient education regarding this, as delay in treatment can lead to life-threatening complications. This can be facilitated through periodically checking the patient's hemoglobin A1c serum glucose level, and thyroid function [3].

In conclusion, there should be a heightened suspicion for checkpoint-inhibitor induced autoimmune diabetes and other endocrinopathies when initiating a patient on nivolumab.

As the approved indications for anti-PD1 therapy expand in the near future, the number of patients receiving these drugs will rapidly increase, as well as autoimmune adverse events.

Additional studies are needed to identify those patients at highest risk for autoimmune complications.

Disclosure statement

M.Z. reports consulting for Guidepoint, G.L.G. Other authors report no conflict of interest to disclose.

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