Pembrolizumab-Induced Type 1 Diabetes in a 95-Year-Old Veteran With Metastatic Melanoma

Damond B. Ng, MD, MPH[a]; Jane Weinreb, MD[a,b]; and Sara-Megumi Rumrill, MD[c,d]

Low C-peptide levels should prompt a high suspicion for immune checkpoint inhibitor-induced type 1 diabetes, and initiation of insulin therapy should be strongly considered.

Author affiliations can be found at the end of the article.
Correspondence:
Damond Ng
(dng@mednet.ucla.edu)

Immune checkpoint inhibitors (CPIs) have revolutionized cancer therapy and improved the prognosis for a variety of advanced solid tumors and Hodgkin lymphoma, but evidence is growing regarding severe endocrine disturbances.[1,2] CPIs block inhibitory molecules on activated T cells to increase tumor cell destruction but also can breach normal tolerance, resulting in a spectrum of immune-related adverse events (irAE).[1,2] Programmed cell death-1 (PD-1) inhibitors are one type of CPIs. Pembrolizumab is a humanized monoclonal antibody that targets the PD-1 checkpoint pathway and is approved for the treatment of malignant melanoma and non-small cell lung cancer.[3,4] When the PD-1 checkpoint pathway is inhibited, T cells targeting cancer are activated, as are autoreactive T cells, such as those regulating pancreatic islet cell survival, which can lead to type 1 diabetes mellitus (T1DM).[5]

CASE PRESENTATION

A 95-year-old male veteran with long-standing, stable prediabetes was treated with pembrolizumab for stage 4 melanoma. Four months after treatment initiation and 3 weeks after completion of his sixth treatment cycle of pembrolizumab (2 mg/kg every 3 weeks), he presented for surveillance positron emission tomography (PET) and was incidentally found to have a serum glucose of 423 mg/dL. Hypothesis-driven history taking revealed polyuria, polydipsia, and a 12-lb weight loss during the previous 3 months. The patient reported no abdominal pain, nausea, or vomiting. He showed no evidence of pancreatic metastases on recent imaging. His family history was notable for a daughter with T1DM diagnosed at a young age.

On examination, the patient's vital signs were normal aside from a blood pressure of 80/40 mm Hg. His body mass index was 30. He was alert and oriented with comfortable respirations and no Kussmaul breathing. He exhibited dry mucous membranes and poor skin turgor. Laboratory studies revealed 135 mmol/L sodium (reference, 135-145), 4.6 mmol/L potassium (reference, 3.6-5.2), 100 mmol/L chloride (reference, 99-106), bicarbonate of 26.5 mmol/L (reference, 23-29), serum blood urea nitrogen 27 mg/dL (reference, 6-24), 1.06 mg/dL creatinine (reference, 0.74-1.35), and 423 mg/dL glucose (reference, 70-100), with negative urine ketones. Further studies demonstrated 462 μmol/L fructosamine (reference, 190-270), correlating with hemoglobin A_{1c} (HbA$_{1c}$) close to 11.0% (HbA$_{1c}$ was drawn on admission but cancelled by the laboratory for unknown reasons).[6,7] Later, an inappropriately low C-peptide level of 0.56 ng/mL (reference, 0.8-3.85) and a negative antiglutamic acid decarboxylase (GAD) antibody titer resulted. The patient was given IV hydration and admitted to the hospital.

With input from endocrinology, the patient was started on 0.3 units per kg of body weight basal-prandial insulin therapy. Pembrolizumab was held. Six weeks after discharge, his HbA$_{1c}$ was 7.2%, and C-peptide improved to 1.95 ng/mL and plasma glucose 116 mg/dL. After shared decision making with his health care team, the patient decided against restarting pembrolizumab. The patient reported that his functional status was preserved, and he preferred to take fewer medications at his advanced age. He died comfortably 6 months after this presentation from complications of metastatic melanoma.

DISCUSSION

Immunotherapy is now an integral part of cancer treatment and can result in endocrine disturbances.[1,2] Life-threatening irAEs

are rare and may mimic more common conditions; thus, there is growing recognition of the need to educate health care professionals in appropriate screening and management of these conditions. CPI-induced T1DM is an uncommon but clinically significant event with an incidence of 0.4 to 1.27% and a median onset of 20 weeks after initiation of therapy (range, 1-228 weeks).[8-12] In case series from 3 academic centers, 59 to 81% of patients with CPI-induced T1DM presented with diabetic ketoacidosis (DKA), and only 40 to 71% of patients were autoantibody positive.[13-16] These patients are older than those presenting with classic T1DM, often require intensive care unit admission, and nearly invariably require exogenous insulin injections for metabolic control.[13-16]

Based on the later age of onset of cancers that may be treated with CPI, patients with CPI-induced T1DM may be misdiagnosed with T2DM or hyperglycemia from other causes, such as medications or acute illness in the outpatient setting, risking suboptimal treatment.

Given the infrequent incidence and lack of controlled trials, screening and treatment recommendations for CPI-induced T1DM are based on principles derived from case series and expert opinion. Development of polyuria, polydipsia, weight loss, nausea, and/or vomiting should prompt investigation for possible development or worsening of hyperglycemia, suggestive of development of T1DM.[17] American Society of Clinical Oncology (ASCO) guidelines recommend that serum glucose be assessed at baseline and with each treatment cycle during induction for 12 weeks, then every 3 to 6 weeks thereafter.[17] There is no reported association between the number of CPI treatments and the development of DM.[8,9] Following our patient's fifth pembrolizumab cycle, a random glucose reading was noted to be 186 mg/dL (Figure 1). Under the ASCO guidelines, ideally the patient would have received close clinical follow-up given the striking increase

FIGURE 1 Glycemic Markers During Pembrolizumab Treatment[a]
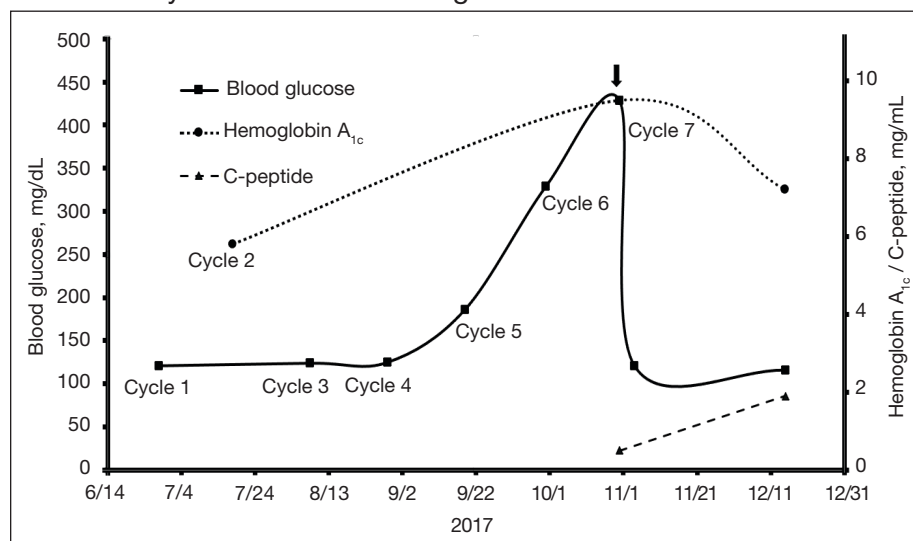
Checkpoint inhibitor (CPI) therapy was discontinued after the diagnosis of CPI-induced type 1 diabetes and the patient was started on insulin therapy.
[a]Hemoglobin A_{1c} at diagnosis estimated to be 11.0% from fructosamine of 42 umol/L.

in plasma glucose compared with prior baseline lower values and perhaps been further evaluated with an anti-GAD antibody titer to screen for T1DM.[17]

This patient's case adds to the published reports of CPI-induced T1DM without DKA and represents the oldest patient experiencing this irAE in the literature.[13-16] The degree of elevation of his initial fructosamine, which is comparable to an average plasma glucose of approximately 270 mg/dL, belied the rapid rate of rise of his recent plasma glucose. Given the trajectory of glycemic markers and symptoms, one could certainly be concerned about imminent decompensation to DKA. However, fortuitous point-of-care glucose reading prior to surveillance PET resulted in a new critical diagnosis and initiation of treatment.

Assessing the need for inpatient evaluation includes obtaining urine ketones and acid-base status as screening for DKA.[17] Antibodies and C-peptide can be sent to support diagnosis of new onset T1DM, although the initiation of therapy should not be delayed for these results.[17] As noted before, many of these patients also are antibody negative.[13-16] Low C-peptide levels should prompt a high suspicion for CPI-induced T1DM, and initiation of insulin therapy should be strongly considered.[17] In a case series of 27 patients, 85% exhibited a rapid loss of β-cell function, evidenced by

FIGURE 2 Letter

We are starting our mutual patient on a new medication for their malignancy. There can be rare but clinically significant endocrine AEs with this medication that may present first in primary care. We would like you to be aware so we can enhance our shared knowledge, care coordination, and monitoring for any AEs together. Please alert us as soon as possible if you suspect an adverse reaction. We will also continue to follow the patient closely in Oncology.

Cancer type/indication for therapy: metastatic melanoma
Drug name: pembrolizumab
Drug class: Programmed cell death-1 inhibitor, a type of immune checkpoint inhibitor

Endocrine irAE that may present first in primary care and recommendation for initial workup and endocrine consultation:
• Hypothyroidism (8.5% incidence; 95% CI, 7.5-9.7%): TSH, free thyroxine;
• Hyperthyroidism (3.7% incidence; 95% CI, 2.8-4.7%): TSH, free thyroxine, TSH receptor antibodies;
• Hypophysitis (1.1% incidence; 95% CI, 0.5-2.6%): basic metabolic panel, TSH, free thyroxine, morning ACTH and cortisol levels;
• Primary adrenal insufficiency (0.8% incidence; 95% CI, 0.3-2.0%): basic metabolic panel, morning ACTH and cortisol levels; and
• Diabetes mellitus/hyperglycemia (0.4% incidence; 95% CI, 0.2-1.3%): finger stick glucose, hemoglobin A_{1c}.

Additional irAEs include colitis, hepatitis, myocarditis, nephritis, and pneumonitis and would require further evaluation and management as well. Do not hesitate to contact us if you are concerned for any of these AEs. For more information, we recommend the following 2 review articles:
1. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385
2. de Filette J, Andreescu C, Cools F, Bravenboer B, Velkeniers B. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. *Horm Metab Res.* 2019;51(03):145-156. doi:10.1055/a-0843-3366

Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse event; irAE, immune-related AE; TSH, thyroid-stimulating hormone.
Example letter can be used to alert a primary care clinician of a mutual patient started on immune checkpoint inhibitor therapy and can be saved as a template in the electronic health record.

the acute progression to hyperglycemia and low or undetectable levels of C-peptide at diagnosis.[9] Likewise, our patient had a low C-peptide level and negative anti-GAD antibody titer but was treated before these results were available. Inpatient admission for close glycemic monitoring may be reasonable; several cases reported prompt diagnosis and avoidance of DKA in this setting.[17]

In contrast to other irAEs, there is no available evidence that high-dose corticosteroids alter the course of pembrolizumab-induced T2DM.[18] Depending on the degree of hyperglycemia, endocrinology consultation and insulin treatment are appropriate where the diagnosis of T1DM is suspected even without evidence of DKA.[17] For patients with T2DM, there may be a positive synergistic effect of metformin in combination with CPIs in tumor control.[19] Our patient's C-peptide improved with insulin treatment, consistent with correction of glucose toxicity and a honeymoon period in his course. However, in patients reported with pembrolizumab-induced T1DM, insulin requirement for treatment generally persists despite cessation of pembrolizumab therapy.[13-16]

CONCLUSIONS

Pembrolizumab-induced T1DM is a rare, but potentially life-threatening irAE. The acute risk of DKA requires early recognition and prompt treatment of patients taking CPIs. More than 90% of primary care physicians (PCPs) fulfill general medical care roles for patients with cancer; therefore, they play an essential role in evaluating symptoms during therapy.[20] Further studies evaluating the role of PCPs and outcomes when PCPs are involved in oncologic care should be conducted.

With increased index of suspicion, this clinical scenario presents an opportunity for PCPs that may help reduce irAE-associated morbidity and mortality of patients on CPIs, like pembrolizumab. Figure 2 illustrates an example addendum that can be used to

alert and tag a PCP of a mutual patient after initiation of CPI therapy. Determining the optimal interface between PCPs, oncologists, and endocrinologists in delivering and coordinating high-quality cancer care in the setting of immunotherapy is an important area for ongoing quality improvement.

Author affiliations
[a]Department of Medicine, David Geffen School of Medicine, Los Angeles, California
[b]Veterans Affairs Greater Los Angeles Healthcare System, California
[c]San Francisco Veterans Affairs Medical Center, California
[d]Department of Medicine, University of California, San Francisco

Author disclosures
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