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# Diabetic Ketoacidosis Precipitated by Pembrolizumab: A Case Report on the Challenges of Long-term Management

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## CASE REPORT

# Diabetic Ketoacidosis Precipitated by Pembrolizumab: A Case Report on the Challenges of Long-Term Management

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**Introduction:** Pembrolizumab (Keytruda®) is a potent and selective humanized monoclonal immunoglobulin antibody that blocks programmed cell death-1 on T cells, augmenting the antitumor immune response. Pembrolizumab is an approved adjuvant therapy for treating metastatic melanoma.

**Clinical Findings:** A 75-year-old man with metastatic melanoma developed diabetic ketoacidosis before receiving a sixth cycle of pembrolizumab.

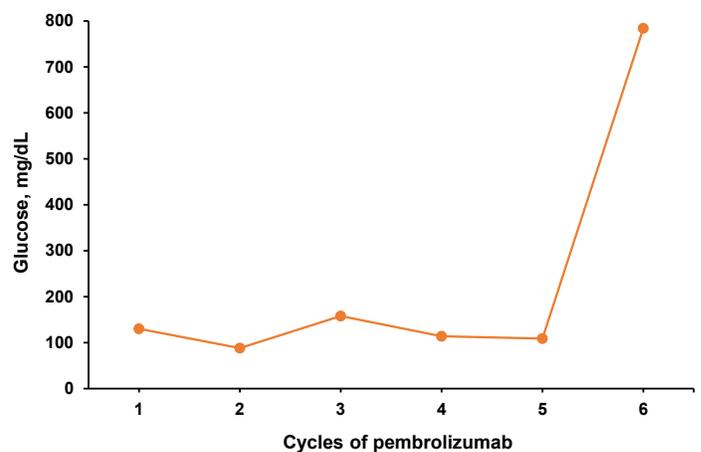
**Clinical Course:** He received intravenous insulin, fluids, and electrolyte repletion per the diabetic ketoacidosis protocol. He presented again to the emergency room with profound hyperglycemia 1 week after discharge. Following a second round of treatment, his home insulin regimen was titrated for better glycemic control, and pembrolizumab was discontinued.

**Conclusions:** As cases of diabetes associated with immune checkpoint inhibitor therapy are increasingly reported, challenges may include adequately managing diabetes long-term, preventing diabetic ketoacidosis, and discontinuing pembrolizumab due to immune-related adverse effects.

**Keywords:** autoimmune diabetes, immune checkpoint inhibitors, pembrolizumab

A 75-year-old man was diagnosed with stage IIIB malignant melanoma of the left upper arm. Following a local excision and a left axillary sentinel lymph node dissection, the man was given adjuvant therapy with 400 mg intravenous (IV) pembrolizumab every 6 weeks starting in June 2020. His past medical history included surveillance for low-grade prostate cancer, essential hypertension, and pre-diabetes.

When he presented to the cancer care center to receive the sixth cycle of pembrolizumab, his blood sugar was 784 mg/dL (Figure 1), and he complained of excessive thirst, urination, fatigue, and weakness developing in the last week. His physical exam showed that he was in significant distress with tachycardia, poor skin turgor, and epigastric tenderness. Based on further evaluation, he showed hyperglycemia, hyponatremia, and



**Figure 1.** Blood Glucose Level Before Each Cycle of Pembrolizumab

metabolic acidosis (Table 1). He also met the criteria for diabetic ketoacidosis (DKA). He started a DKA protocol with administration of IV insulin at 0.14 units/kg/hour based on his weight of 90.7 kg, IV fluids, and electrolyte repletion.

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**Table 1.** Laboratory Values During Each Emergency Room Admission and Hospitalization

	ER visit 1	ER visit 2	Reference
Sodium, mEq/L	127	128	136-145
Potassium, mEq/L	5.0	4.9	3.5-5.0
Chloride, mEq/L	88	92	95-105
Bicarbonate, mEq/L	17	24	22-28
Anion gap, mEq/L	22	12	3-10
BUN, mg/dL	51	31	7-18
Creatinine, mg/dL	1.57	1.34	0.6-1.2
Average estimated eGFR	42	51	75 (for ages 70+)
Glucose	784	562	<140 mg/dL (non-fasting)
pH blood	7.18	7.35	7.35-7.45
Urine glucose	>500	>500	None
Urine ketones	Present	Trace	None
pH urine	5.0	5.0	4.6-8.0

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ER, emergency room.

After the anion gap normalized, on the second day of hospitalization, he was given insulin on a sliding scale. His acute kidney injury secondary to DKA resolved with administration of IV fluids. He was discharged on day 4 of hospitalization with a new diagnosis of diabetes mellitus secondary to pembrolizumab, and he was advised to continue taking 15 units of insulin glargine at night and 500 mg twice daily of metformin. He was asked to follow up with his primary care physician, given a new referral for endocrinology, and taught to use and monitor his blood glucose levels.

However, 7 days after discharge, our patient called his primary care physician's office, reporting a blood glucose level of 525 mg/dL. He presented to the emergency room again with fatigue and reported a 20-pound weight loss in the last 3 months (Table 2). He received IV fluids, 10 units of IV insulin, and electrolyte repletion in the emergency room. The next day, he was discharged with the following insulin regimen: 18 units of insulin glargine at bedtime and 4 units of insulin lispro pre-meal.

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**Table 2.** Characteristics During Second Hospitalization

	Labs	Reference
Weight, kg	90.7	-
C-peptide, ng/mL	<0.1 (L)	0.5-2.7
Lipase level, IU/L	90 (H)	15-55
Insulin antibody	Negative	Negative
Glutamic acid decarboxylase antibody	Negative	Negative
IA-2 autoantibody	Negative	Negative
TSH, $\mu$ U/mL	1.64	0.5-5.0
Cortisol, $\mu$ g/dL*	10.4	10-20
ACTH, pg/mL*	25.2	7.2-63.3

Abbreviations: ACTH, adrenocorticotrophic hormone; IA-2, islet tyrosine phosphatase 2; TSH, thyroid-stimulating hormone.

\*Measured between 6 AM and 8 AM.

Two days after the second hospitalization, our patient presented to his oncologist, where pembrolizumab adjuvant therapy was discontinued and a new PET/CT (positron emission tomography/computed tomography) scan was scheduled. The next day, he presented for his first appointment with an endocrinologist. Based on his recent blood glucose levels, his insulin regimen was titrated to increase insulin glargine to 24 units every morning and increase insulin aspart to 10 units with breakfast and lunch and 6 units with dinner.

## DISCUSSION

Pembrolizumab (Keytruda®) is a potent and selective humanized monoclonal immunoglobulin antibody that blocks programmed death receptor-1 on T cells, thereby augmenting the antitumor immune response.<sup>1,2</sup> Clinical trials showed that pembrolizumab significantly increased progression-free survival in non-small-cell lung cancer, overall survival in refractory melanoma, and overall response rates to treatments for advanced melanoma.<sup>3-5</sup> In December 2015, the Food and Drug Administration approved pembrolizumab as adjuvant therapy for treating unresectable or metastatic melanoma.<sup>6,7</sup> Studies estimated that 0.2% of people undergoing treatment with pembrolizumab develop diabetes.<sup>8,9</sup> A number of case reports highlighted DKA as the first clinical presentation of autoimmune diabetes among patients undergoing treatment

with pembrolizumab.<sup>10-24</sup> Of note, one case of DKA induced by autoimmune diabetes occurred within 3 weeks after a single dose of pembrolizumab.<sup>25</sup> In a review of 71 cases of diabetes induced by an immune checkpoint inhibitor (ICI), the mean age of onset was 61.7 years, 55% of cases were men, and melanoma was the most frequent type of cancer.<sup>26</sup> Furthermore, in all these case reports, permanent exogenous insulin was the mainstay of treatment for long-term management, and significant hyperglycemia occurred in a short time.<sup>26</sup> In a separate review of 90 case reports of diabetes mellitus caused by ICI therapy, 71% of cases presented with DKA as the first sign of diabetes.<sup>27</sup>

The mechanism by which ICIs cause autoimmune diabetes is not fully understood. One possible mechanism may be the destruction of pancreatic beta islet cells by host T cells, which are no longer inhibited due to the immunotherapy agents.<sup>28</sup> Specifically, immune-related adverse events may be due to reduced self-tolerance mediated by T cells, B cells, autoantibodies, and cytokines. In addition, emerging studies are investigating the role of epigenetics, environmental factors, immune status, and intestinal microbiota in the propensity to develop immune-related adverse effects associated with ICI therapy.

In the case of our patient, his ultimate insulin regimen exceeded his insulin requirement while he was hospitalized. This finding supports past evidence that patients with ICI-induced diabetes have varying levels of insulin sensitivity.<sup>29</sup> In addition, our patient's C-peptide level was undetectable and islet autoantibodies were negative. In their review, deFilette et al. reported that 53% of patients with ICI-induced diabetes had positive islet autoantibodies.<sup>27</sup> This positivity may pose a challenge to clinicians who cannot predict the development of insulin-deficient diabetes by monitoring islet antibodies, which has been used in cases of type 1 diabetes.<sup>30</sup>

Clinical challenges remain in the long-term management of new onset diabetes secondary to pembrolizumab. These challenges include uncovering its clear etiology, adequate glycemic control to prevent DKA, and lack of a clear protocol for discontinuing ICI therapy.

**Conflicts of interest:** None

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