

## CASE REPORT

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# When hyperglycemia is not type 2 diabetes: A case report of diagnostic challenges in immune checkpoint inhibitor-associated diabetes

Lisa L Bethea

## ABSTRACT

**Introduction:** Immune checkpoint inhibitors (ICIs) have improved outcomes across multiple malignancies but are associated with immune-related adverse events affecting diverse organ systems. Immune checkpoint inhibitor-induced diabetes mellitus is a rare endocrine toxicity characterized by abrupt pancreatic  $\beta$ -cell destruction and rapid onset insulin deficiency. Because the presentation may mimic new-onset type 2 diabetes, delayed recognition may occur, particularly outside oncology settings.

**Case Report:** A 48-year-old female with T2N0M0 triple-negative breast cancer has undergone chemoimmunotherapy with Pembrolizumab every three weeks and Paclitaxel/Carboplatin weekly for 12 weeks. Two weeks later, she presented for her second phase of chemoimmunotherapy with Pembrolizumab, Doxorubicin, and Cyclophosphamide to be administered every three weeks. Pre-infusion laboratory testing revealed severe hyperglycemia with serum glucose of 489 mg/dL. Urinalysis demonstrated marked glucosuria and ketonuria. The patient was referred to the emergency department for evaluation and treatment. She received intravenous (IV) fluids and insulin, resulting in a significant reduction in blood glucose to 203. The patient was discharged with metformin therapy and outpatient follow-up. Subsequent evaluation revealed hemoglobin A1C of 10%, increased from 5.9% two months earlier, and a markedly suppressed C-peptide level of 0.1 ng/mL, indicating severe insulin deficiency. The patient was

referred to endocrinology for lifelong insulin management. Follow-up HbA1C three months later improved from 10 to 7.6. The patient was maintained on long-acting insulin Glargine, short-acting insulin for meals, and Metformin. The rapid transition from normoglycemia to severe hyperglycemia, presence of ketosis, and profound insulin deficiency were consistent with immune checkpoint inhibitor-associated diabetes. Initial management focused on treatment of hyperglycemia rather than recognition of immune-mediated  $\beta$ -cell destruction. This case illustrates the diagnostic challenges that may arise when patients receiving immunotherapy present in non-oncology clinical environments.

**Conclusion:** Immune checkpoint inhibitor-associated diabetes is an uncommon but potentially life-threatening complication of programmed cell death protein-1 (PD-1) blockade therapy. Increased awareness and structured evaluation of hyperglycemia in patients receiving immunotherapy may facilitate earlier diagnosis and appropriate management.

**Keywords:** Autoimmune diabetes, Hyperglycemia, Immune checkpoint inhibitors, Pembrolizumab

### How to cite this article

Bethea LL. When hyperglycemia is not type 2 diabetes: A case report of diagnostic challenges in immune checkpoint inhibitor-associated diabetes. *J Case Rep Images Oncology* 2026;12(1):17–21.

Article ID: 100156Z10LB2026

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doi: 10.5348/100156Z10LB2026CR

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Received: 12 March 2026

Accepted: 30 May 2026

Published: 30 June 2026

## INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed the treatment of multiple malignancies

by enhancing antitumor immune responses. Agents targeting the programmed cell death protein-1 (PD-1) pathway, including pembrolizumab, are widely used in the treatment of melanoma, lung cancer, and triple-negative breast cancer [1, 2]. Although these therapies have demonstrated substantial improvements in survival outcomes, they are associated with a distinct spectrum of immune-related adverse events (irAEs) resulting from dysregulated immune activation.

Endocrine toxicities represent an important subset of immune-related adverse events and include thyroid dysfunction, hypophysitis, adrenal insufficiency, and autoimmune diabetes mellitus [3, 4]. Immune checkpoint inhibitor-associated diabetes is a rare but clinically significant complication characterized by abrupt pancreatic  $\beta$ -cell destruction and rapid onset of insulin deficiency [5, 6].

Because patients receiving ICIs are frequently evaluated across multiple clinical environments, including oncology clinics, infusion centers, emergency departments, and primary care settings, recognition of immune-mediated endocrinopathies may be delayed. This is a case of severe hyperglycemia occurring during pembrolizumab therapy that was ultimately diagnosed as immune checkpoint inhibitor-associated diabetes mellitus.

## CASE REPORT

A 48-year-old female with a history of T2NoMo triple-negative breast cancer undergoing neoadjuvant treatment with combination chemotherapy and immune checkpoint inhibitor therapy presented to an oncology infusion center for routine treatment. Past medical history was significant for hyperlipidemia but no other cardiovascular disease, diabetes, or pulmonary conditions. The patient had recently completed four cycles of pembrolizumab in combination with paclitaxel and carboplatin over a 12-week period as part of the initial phase of therapy. Two weeks later, the patient presented for initiation of the second phase of treatment, consisting of doxorubicin (Adriamycin), cyclophosphamide, and pembrolizumab. Vital signs were within normal limits, and weight was stable. Review of systems was unremarkable.

As part of routine pre-infusion laboratory evaluation, serum glucose was measured at 489 mg/dL. Repeat testing confirmed persistent severe hyperglycemia with a glucose level of 408 mg/dL. Urinalysis obtained at the infusion center demonstrated marked glucosuria (>1000 mg/dL) and positive ketones. Due to concern for possible diabetic ketoacidosis, the patient was referred to the emergency department for further evaluation.

At the emergency department triage, point-of-care glucose measurement was 378 mg/dL. Vital signs were within normal limits except for sinus tachycardia noted on the electrocardiogram. The patient denied increased thirst, frequent urination, and increased hunger. She did note occasional fatigue but contributed it to the cancer and chemotherapy. Approximately 1 h later, the patient

was placed in an examination room, laboratory testing was obtained, and 1 L of normal saline was administered intravenously. At that time, serum glucose was 390 mg/dL.

Following intravenous fluid administration, glucose decreased to 278 mg/dL. The patient subsequently received 5 units of insulin, resulting in further reduction of serum glucose to 203 mg/dL. The patient was discharged with metformin 500 mg twice daily and instructions to follow up with primary care.

At outpatient follow-up, hemoglobin A1C was measured at 10%, representing a marked increase from 5.9% obtained two months earlier. Basal insulin therapy was initiated at 10 units daily, and a continuous glucose monitoring device was prescribed.

Given the rapid onset of severe hyperglycemia in a patient undergoing immunotherapy, further evaluation was performed to assess endogenous insulin production. Laboratory testing revealed a C-peptide level of 0.1 ng/mL (reference range 0.8–5.2 ng/mL), consistent with profound insulin deficiency.

Basal insulin dosing was titrated to maintain blood glucose levels below 180 mg/dL, ultimately reaching 18 units daily. Prandial insulin therapy was subsequently initiated to address postprandial hyperglycemia. The patient was referred to endocrinology for lifelong management. Follow-up HbA1C three months later improved from 10 to 7.6. The patient was maintained on long-acting insulin Glargine, short-acting insulin for meals, and Metformin.

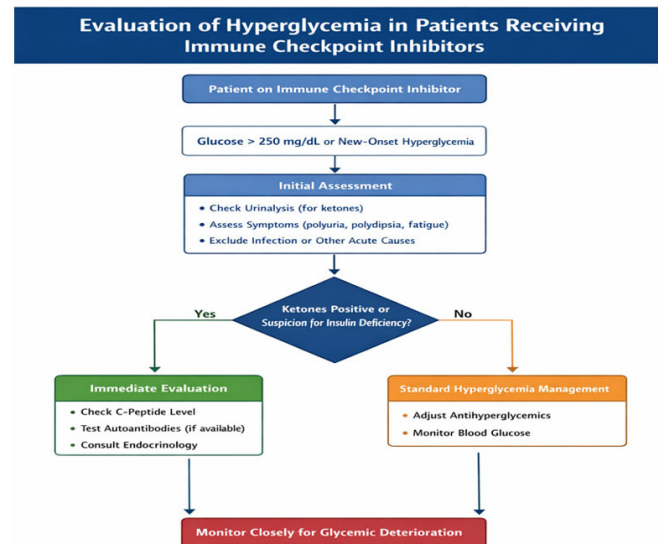


Figure 1: Proposed evaluation pathway for hyperglycemia in patients receiving immune checkpoint inhibitors [5, 6, 13, 14]. Patients receiving immune checkpoint inhibitor therapy who develop new-onset hyperglycemia or glucose levels greater than 250 mg/dL should undergo initial assessment including evaluation for ketosis and symptoms of hyperglycemia. If ketones are present or insulin deficiency is suspected, further evaluation with C-peptide testing and endocrinology consultation should be considered. Patients without evidence of insulin deficiency may undergo standard hyperglycemia management with close glucose monitoring. The algorithm is intended to facilitate early recognition of immune checkpoint inhibitor-associated diabetes and guide appropriate diagnostic evaluation.

## DISCUSSION

Immune checkpoint inhibitor-associated diabetes mellitus is an uncommon but increasingly recognized immune-related adverse event. The condition has been reported most frequently with PD-1 pathway inhibitors such as pembrolizumab and nivolumab [5, 7].

### Pathophysiology

The PD-1 pathway plays a central role in maintaining immune tolerance. Engagement of PD-1 receptors on activated T lymphocytes with their ligands suppresses immune responses and protects normal tissues from autoimmune injury. Pembrolizumab blocks this inhibitory interaction, thereby enhancing cytotoxic T-cell-mediated tumor destruction [8, 9].

However, disruption of this regulatory pathway can permit autoreactive immune responses directed against normal tissues. Pancreatic islet cells may express PD-L1, suggesting that the PD-1/PD-L1 axis contributes to immune protection of  $\beta$ -cells. Inhibition of PD-1 signaling may therefore allow cytotoxic T cells to target pancreatic  $\beta$ -cells, resulting in rapid insulin deficiency [8].

Genetic susceptibility may also contribute to disease development. Certain human leukocyte antigen (HLA) haplotypes associated with autoimmune diabetes appear more frequently among patients who develop checkpoint inhibitor-associated diabetes [5].

### Epidemiology

The reported incidence of immune checkpoint inhibitor-associated diabetes is relatively low, estimated between 0.2% and 1% of treated patients [5, 10]. The PD-1 inhibitors appear to confer the highest risk. Because pembrolizumab is widely used across numerous malignancies, many reported cases of checkpoint inhibitor-associated diabetes have occurred during treatment with this agent [11, 12].

The median time to onset is typically 7–20 weeks after initiation of therapy, although substantial variability has been reported [5]. In this case, the patient completed 12 weeks of treatment before clinical presentation.

### Clinical Presentation

Checkpoint inhibitor-associated diabetes typically presents with abrupt and severe hyperglycemia. Blood glucose levels frequently exceed 300–500 mg/dL, and many patients present with diabetic ketoacidosis [5, 13].

Symptoms commonly include polyuria, polydipsia, fatigue, and weight loss. However, some patients are asymptomatic and identified through routine laboratory monitoring prior to infusion therapy [14].

A notable feature of this condition is the rapid deterioration in glycemic control, often occurring over weeks. Consequently, hemoglobin A1C values may underestimate the acuity of the underlying metabolic disturbance [6].

## Laboratory Findings

Laboratory evaluation typically demonstrates profound insulin deficiency, with markedly reduced or undetectable C-peptide levels [6]. Autoantibodies associated with autoimmune diabetes are detected in approximately half of cases but are not required for diagnosis [15].

## Management

Patients presenting with diabetic ketoacidosis should receive standard treatment including intravenous fluids, insulin therapy, and electrolyte correction. Long-term management generally requires lifelong insulin therapy due to irreversible  $\beta$ -cell destruction [6].

Unlike other immune-related adverse events, corticosteroids do not reverse checkpoint inhibitor-associated diabetes because pancreatic  $\beta$ -cell destruction is typically permanent [4]. Continuous glucose monitoring may assist with long-term glycemic control.

In many cases, immunotherapy can be continued after stabilization because  $\beta$ -cell destruction is usually complete by the time diabetes becomes clinically apparent [3].

## Diagnostic Considerations

This case illustrates several diagnostic challenges associated with checkpoint inhibitor-related endocrinopathies. Clinicians outside oncology settings may be unfamiliar with rare immune-mediated toxicities. Additionally, patients receiving immunotherapy often receive care across multiple clinical environments, which may limit awareness of treatment-related complications.

The rapid progression from normal glycemic control to severe hyperglycemia further complicates diagnosis. In such cases, early evaluation for ketosis and measurement of C-peptide levels can assist in distinguishing immune-mediated insulin deficiency from more common forms of diabetes (Figure 1) [5, 6, 13, 14].

## CONCLUSION

Immune checkpoint inhibitor-associated diabetes is an uncommon but serious complication of PD-1 blockade therapy. Patients receiving pembrolizumab may develop abrupt insulin deficiency resulting from immune-mediated pancreatic  $\beta$ -cell destruction. Early recognition is essential because delayed diagnosis may lead to life-threatening metabolic complications such as diabetic ketoacidosis. Clinicians should maintain a high index of suspicion for immune checkpoint inhibitor-associated diabetes when patients receiving immunotherapy develop sudden severe hyperglycemia. Prompt evaluation for ketosis and assessment of endogenous insulin production can facilitate accurate diagnosis and timely initiation of insulin therapy.

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**Acknowledgments****Artificial intelligence (AI) use in the article:**

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process.

During the preparation of this work, the author used Grammarly, Microsoft Copilot, and ChatGPT to outline/organize the manuscript and improve clarity and readability. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

**Author Contributions**

Lisa L Bethea – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

**Guarantor of Submission**

The corresponding author is the guarantor of submission.

**Source of Support**

None.

**Consent Statement**

Written informed consent was obtained from the patient for publication of this article.

**Conflict of Interest**

Author declares no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

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