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New Onset, Refractory Hyperglycemia with Diabetic Ketoacidosis After Enfortumab Vedotin Treatment: A Case Report

Authors

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CASE REPORT

New Onset, Refractory Hyperglycemia with Diabetic Ketoacidosis After Enfortumab Vedotin Treatment: A Case Report

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Introduction: A patient with no prior diagnosis of diabetes presented with diabetic ketoacidosis (DKA) and severe insulin resistance after being treated with enfortumab vedotin (EV). EV-associated DKA is uncommon—described in only a few case reports—and has unknown pathophysiology. This case characterizes the unique features of DKA in this patient and an unusual amount of insulin resistance not typically seen in patients with diabetes.

Clinical Findings: A 71-year-old male presented with fatigue, xerostomia, and increased thirst. He had a history of obesity, hypertension, and invasive, high-grade papillary urothelial carcinoma. His laboratory results were consistent with DKA.

Clinical Course: The patient was admitted to the hospital and treated using a standardized protocol to correct the hyperosmolality, hypovolemia, metabolic acidosis, and hyperglycemia associated with DKA. After the DKA resolved, the patient needed substantial daily doses of insulin, up to 1000 units per day, for multiple days before being transitioned to an oral antihyperglycemic regimen. His workup included negative results for autoantibodies associated with type 1 diabetes and an elevated C-peptide level, suggesting preserved endogenous production of insulin with severe insulin resistance.

Conclusions: EV has a clear role in treating urothelial carcinoma, showing improved survival in certain clinical contexts. Hyperglycemia is a common (14% of patients) side effect, with DKA being a rare and potentially fatal consequence. Patients with known risk factors, such as obesity or elevated hemoglobin A1c, should be closely monitored for hyperglycemia and DKA during EV treatment.

Keywords: transitional cell carcinoma, hyperglycemia, diabetic ketoacidosis, insulin resistance, immunoconjugate

A 71-year-old male presented to the emergency department with fatigue, xerostomia, and increased thirst. He had a past medical history of gout, hypertension, obesity (body mass index of 32), and invasive, high-grade papillary urothelial carcinoma (with metastasis to regional lymph nodes). Despite no previous diagnosis of diabetes, he had diabetic ketoacidosis (DKA) with a blood glucose of 800 mg/dL (reference range: 70-99 mg/dL), an anion gap of

17, and a positive test result for serum ketones. He had an accompanying acute kidney injury with his creatinine elevated to 1.41 mg/dL (reference range: 0.5-1.3 mg/dL) from his baseline of 1.0 mg/dL. All previously acquired random tests for blood glucose levels in this patient were less than 200 mg/dL, and he had no prior diagnosis of diabetes.

The patient started cycle one of enfortumab vedotin (EV) as a treatment for urothelial carcinoma 16 days before this presentation. A standard cycle includes treatments on days 1, 8, and 15.¹ He received his third treatment (at the standard dose of 1.25 mg/kg) 1 day before presentation. This EV treatment was being used because the patient did not tolerate the

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first-line regimen of cisplatin and gemcitabine due to thrombocytopenia, and his disease progressed with the second-line regimen pembrolizumab.

The DKA-associated hyperosmolality, hypovolemia, metabolic acidosis, and hyperglycemia were corrected using a standardized protocol involving isotonic saline infusion, electrolyte repletion, and intravenous insulin infusion. His anion gap normalized, and his creatinine returned to baseline within 24 hours. After his blood glucose normalized and fluid resuscitation was complete, he continued to need large total daily doses of insulin to maintain euglycemia. During days 1 through 5, after the DKA resolved, the patient needed between 800 and 1000 units of insulin each day (Figure 1). Over the next 4 days, his insulin needed steadily decreased. He was then transitioned to glipizide at 2.5 mg given by mouth daily, with adequate glycemic control.

Further workup indicated he had a hemoglobin A1c of 7.4% (reference range: 4.5%-5.6%) and a C-peptide level of 18.7 ng/mL (reference range: 1.1-4.4 ng/mL) on admission. Test results were negative for autoantibodies against glutamic acid

decarboxylase-65, islet cell, insulin, and zinc transporter 8. One year after presentation, the patient's hemoglobin A1c normalized to 5.4%. At that time, he discontinued glipizide and was not continued on EV.

DISCUSSION

EV is an antibody-drug conjugate that targets the cell adhesion molecule nectin-4, which is highly expressed in urothelial carcinoma.² EV comprises nectin-4 conjugated to the microtubule-disrupting agent monomethyl auristatin E, which becomes internalized and disrupts the cellular microtubule network, leading to cell-cycle arrest and apoptosis.² EV can be used for locally advanced or metastatic urothelial cancer as a third-line agent if patients do not tolerate or relapse on platinum-based chemotherapy (cisplatin-based or carboplatin-based) and/or immunotherapy with a programmed cell death-1 inhibitor.³ EV therapy is limited to a small population but has improved survival and progression-free survival more than other standard chemotherapy agents indicated in this context.⁴

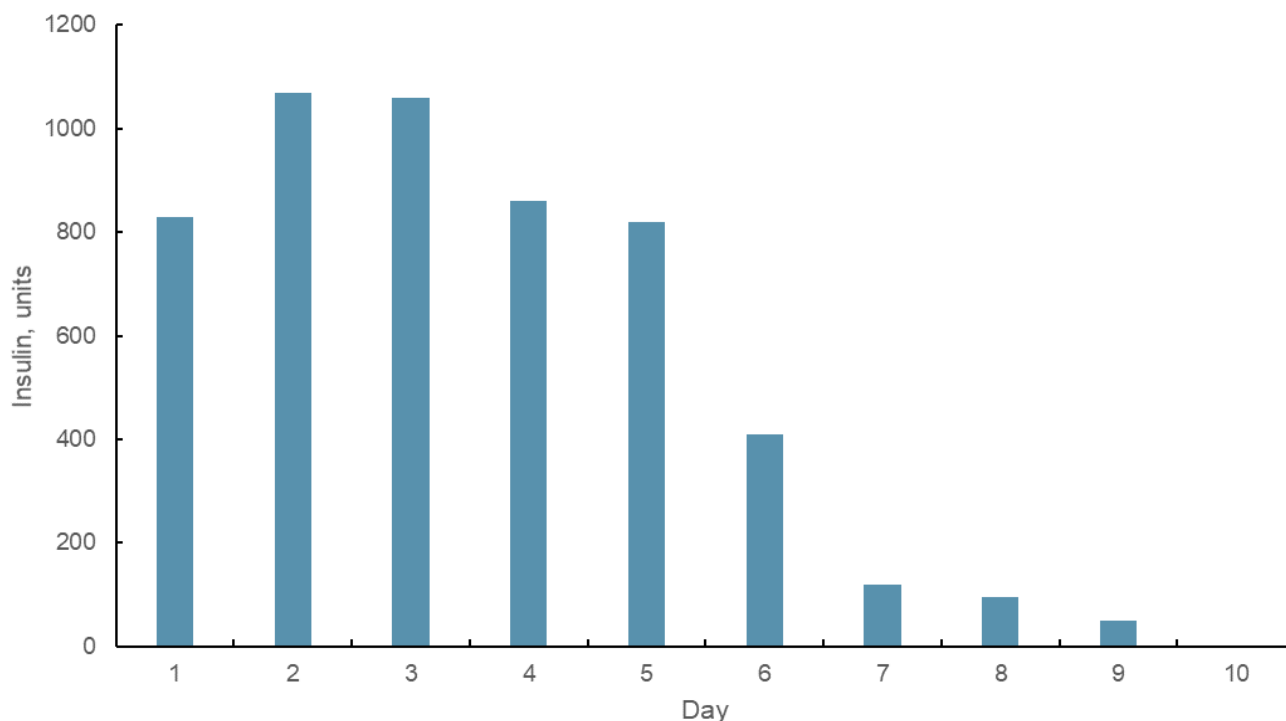


Figure 1. Daily Insulin Dose Needed for Patient Who Presented With Diabetic Ketoacidosis Associated With Entfortumab Vedotin. The quantities recorded represent the amounts of insulin administered after DKA resolved and exclude amounts used to acutely manage DKA.

Given the recent addition of EV therapy to the market and its increasing use in the clinical setting, adverse effects are still being discovered and characterized.^{5,6} A frequent and well-known adverse effect of EV is hyperglycemia, which occurs in 14% of patients, with a median time to onset of 2 to 3 weeks.⁶ In clinical trials, 5% of patients treated with EV needed initiation of insulin. Risk factors for this adverse effect have unsurprisingly included obesity and elevated hemoglobin A1c before treatment. However, hyperglycemia has also developed in patients without these pre-existing conditions.^{1,7} The manufacturer recommends close blood-glucose monitoring in patients at risk and temporarily holding further EV treatments if blood glucose becomes greater than 250 mg/dL.

This patient presented with a case of EV-associated hyperglycemia and DKA. The elevated C-peptide level suggested that he did not have reduced endogenous insulin production, but rather he experienced insulin resistance leading to blood glucose levels greater than 800 mg/dL. He also likely had a relative insulin deficiency with the inability to suppress lipolysis and ketogenesis, leading to DKA. Both hyperglycemia and DKA are often seen in patients who have a form of diabetes and encounter a significant physiological stressor. This case is atypical given that the patient had no prior history of diabetes and onset of DKA after receiving EV. Thankfully, the DKA responded to standard therapies.⁸ The patient improved with fluid resuscitation and insulin, but he needed insulin doses approximately 5 to 10 times higher than needed in typical patients with diabetes.

The mechanism by which DKA occurs is unknown. One hypothesis is that EV directly blocks the insulin receptor. This mechanism would explain both the insulin resistance and DKA seen in this case. EV has a half-life elimination of 3.6 days, and in this case, higher therapeutic levels of EV correlated with insulin resistance. Other important hormones involved in metabolism, such as glucagon, catecholamines, cortisol, and adipokines, have not been studied in EV-associated DKA cases. Also, the effect of EV on beta-cell function, both during treatment and long term, has not been characterized.⁶

The medical literature that represents EV-associated DKA is limited to a few case reports, making it difficult to understand and manage without conjecture.⁸ The frequency of DKA or duration of insulin resistance is not defined. This case provided unique data on the severity and duration of insulin resistance along with the associated clinical presentation of DKA without being confounded by preexisting insulin resistance or endogenous insulin deficiency.

The mechanism by which EV-associated hyperglycemia and DKA occurs has yet to be understood. However, further characterization with more case reports and research focused on preventive strategies could support safer treatment with EV, which is typically given to patients with notable morbidity.

Conflicts of Interest: None

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