Kidney Medicine

Diabetic Ketoacidosis and Acute Kidney Injury Associated With Enfortumab Vedotin for Urothelial Carcinoma: A Case Report

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Enfortumab vedotin is a novel breakthrough therapy that received accelerated US Food and Drug Administration approval in 2019 for the treatment of metastatic urothelial carcinoma in patients who have failed other lines of treatment. The characteristics of its adverse effects are not well understood. Diabetic ketoacidosis has been reported in 2 postmarketing reports presented as abstracts at the 2020 American Thoracic Society Conference and the 2021 American Society of Nephrology Conference. Both cases progressed rapidly and expired in <3 days. We present a similar case of a man in his late 50s with no history of diabetes who was diagnosed with urothelial carcinoma 2 years prior. Despite several lines of treatment, including platinum-based chemotherapy and immune checkpoint inhibitors, he developed metastasis and was started on enfortumab vedotin. After his second dose of enfortumab vedotin, he was admitted to the intensive care unit for diabetic ketoacidosis with an initial A1C level of 7.7%. He was intubated for airway protection, started on pressors, and developed oliguric acute kidney injury requiring continuous venovenous hemodialysis. Despite aggressive treatment, the patient died on hospital day 2. The lethality of this aggressive diabetic ketoacidosis despite therapy suggests some other effect of enfortumab vedotin on glucose metabolism in addition to insulin resistance and the need for prior diabetes screening.

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INTRODUCTION

Enfortumab vedotin is a fully human monoclonal antibody that was granted breakthrough therapy designation in 2018 and accelerated approval by the US Food and Drug Administration in December 2019 for the treatment of patients with advanced or metastatic urothelial carcinoma who had previously received treatment with a platinum agent and/or immune checkpoint inhibitors.[1,2] Enfortumab vedotin resulted in an objective response in more than 40% of patients with advanced urothelial carcinoma who demonstrated progression after previous treatment, and the trial was stopped early because of the superior overall survival benefit observed at the planned interim analysis.[3] Although a favorable clinical response rate has been reported, the severity and characteristics of its related adverse effects are not well described.

The most common (≥20%) all-grade adverse effects were fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus, and dry skin. Hyperglycemia, peripheral neuropathy, ocular disorders, skin reactions, infusion site extravasations, and embryo-fetal toxicity are labeled as warnings and precautions for enfortumab vedotin.[1-4] In the safety trial, diabetic ketoacidosis was recorded as the cause of death in 1 of the 5 deaths related to treatment. The other causes of death were as follows: (i) multiple organ dysfunction syndrome (due to suspected drug-induced hemolytic anemia), (ii) respiratory failure, (iii) urinary tract obstruction, and (iv) metabolic acidosis.[5]

To date, there are only 2 postmarketing reports presented as abstracts. The first, reported the case of a 75-year-old man who developed diabetic ketoacidosis 3 days after receiving his second infusion of enfortumab vedotin; he died on hospital day 3.[6] The second patient was a 69-year-old man who developed diabetic ketoacidosis after starting enfortumab vedotin and also died despite interventions.[7]

We present a similar case of a man in his late 50s with metastatic urothelial carcinoma whose disease progressed despite receiving platinum-based chemotherapy followed by immune checkpoint inhibitors. He was started on enfortumab vedotin, developed diabetic ketoacidosis 2 weeks later, and died despite interventions.

CASE REPORT

An obese man in his late 50s (weight, 112 kg and body mass index, 35 kg/m^2) with no history of diabetes and significant past history of hypertension, hyperlipidemia, pulmonary embolism on apixaban, and metastatic urothelial carcinoma presented to the emergency department because of fatigue and shortness of breath.

Two years prior, the patient presented with gross hematuria and had a transurethral bladder resection of a bladder tumor for which the pathology revealed a high-grade invasive papillary urothelial carcinoma. He received a 6-week course of intravesical bacilli Calmette-Guerin for a total of 6 doses. A repeat cystoscopy a few weeks after treatment showed recurrence of the urothelial carcinoma. The patient deferred cystectomy, so he received a full dose of intravesical gemcitabine/docetaxel. Computed tomography scan and positron emission tomography–computed tomography performed 4 months

Table 1. Laboratory Values

	Day of Second Dose EV (Day 8 of Treatment)	Initial Laboratories in ED	Laboratories on Day 1 of Admission (ICU)	Laboratories on Day of Expiration
Sodium (mEq/L)	136	138	136	143
Potassium (mEq/L)	4.2	5.8	5.9 (hemolyzed)	5.7
Chloride (mEq/L)	108	106	115	116
Serum bicarbonate (mEq/L)	18	12	6	<6
Blood urea nitrogen (mg/dL)	10	10	9	10
Creatinine (mg/dL)	0.73	1.52	1.64	3.45
Random glucose (mg/dL)	170	450	391	124
Lactate (mmol/L)		2.4	1.5	>16
Alanine aminotransferase (U/L)	70	76	57	86
Aspartate aminotransferase (U/L)	82	48	52	136
Total calcium (mg/dL)	7.8	7.5	6.9	7.1
Ionized calcium (mg/dL)			3.4	3.6
Albumin (g/dL)	3.2	2.5	2.5	2.1
Phosphorus (mg/dL)		1.5	0.8	10.2
Hemoglobin A1C (%)			7.7	
C-peptide (ng/mL)			5.05	
GAD65 antibodies (IU/mL)			<5	
Ethylene glycol (mg/L)			<10	
Blood acetone level			Positive 1:8	Negative
Blood gas				
Ph		7.22 (VBG)	7.27 (ABG)	<6.8 (ABG)
Partial pressure Carbon dioxide (PCO_2)		20 (VBG)	<19 (ABG)	Incalculable
Partial pressure oxygen (PO_2)		49 (VBG)	139 (ABG)	135 (ABG)
Bicarbonate		8 (VBG)	Incalculable (ABG)	Incalculable
Complete blood count				
White blood cells ($x10^3/mm^3$)	9.12	1.5	0.72	1.09
Hemoglobin (g/dL)	12.5	12.7	11.2	12.3
Platelet count ($x10^3/mm^3$)	162	136	102	52
Urinalysis				
Ph		6.0	6.0	
Glucose (mg/dL)		>1000	100	
Ketones (mg/dL)		80	50	

Abbreviations: ABG, arterial blood gas; EV, enfortumab vedotin; g/dL, grams/deciliter; ICU, intensive care unit; IU/ml, international units/milliliter; mEq/L, milliequivalent/liter; mg/dL, milligrams/deciliter; mg/L, milligrams/liter; mm^3, millimeters cube; mmol/L, millimoles/liter; ng/mL, nanograms/milliliter; U/L, units/liter; VBG, venous blood gas.

after completion of gemcitabine/docetaxel demonstrated metastases to the liver and retroperitoneal lymph nodes, with liver biopsy confirming metastatic urothelial carcinoma. The patient received another round of chemotherapy with gemcitabine and carboplatin (6 cycles) and then maintenance treatment with avelumab. Despite these interventions, the patient's cancer progressed, so a decision was made by the oncologist to start the patient on enfortumab vedotin at a dose of 1.25 mg/kg intravenous (IV) piggyback to run >30 minutes on days 1, 8, and 15 and every 28-day cycle with blood draws before treatment. The patient also received premedication with 20 mg dexamethasone IV, 1 mg granisetron IV, 50 mg diphenhydramine IV, and 650 mg acetaminophen orally.

Six days after the second dose of enfortumab vedotin (day 14 of treatment), the patient developed generalized weakness, pruritic rash, and shortness of breath. He was advised to go to the closest emergency department for management. At the emergency department, he was noted to be ill-appearing, diaphoretic, tachypneic, and tachycardic. His blood pressure was 116/53 mm Hg with 98% oxygen saturation in room air. Initial laboratory test results are shown in Table 1. He was started on an insulin drip for diabetic ketoacidosis and admitted to the intensive care unit. He also received 8 g of calcium gluconate, 45 mmol/L of sodium phosphate, and empiric antibiotics with cefepime. His initial hemoglobin A1C level was 7.7%. His urine output, which was initially 50-100 mL/h, dropped to 10 mL/h.

An urgent nephrology consult was called for oliguric acute kidney injury and refractory acidosis due to diabetic ketoacidosis and other electrolyte abnormalities. The patient was intubated for airway protection and worsening tachypnea. He was started on propofol and dexmedetomidine for sedation and became hypotensive, requiring norepinephrine and vasopressin. Due to

hemodynamic instability with refractory acidosis and acute kidney injury, a decision was made to start the patient on continuous venovenous hemodialysis (CVVHD) at a blood flow rate of 200 mL/minute and dialysate flow rate of 2.4 L/hour (22 cc/kg/h) with zero net ultrafiltration. CVVHD was started approximately 22 hours following admission.

The patient's clinical condition worsened with worsening acidosis, hypocalcemia, and shock despite the use of 4 different pressors. On day 2 of admission, after receiving 12 hours of continuous kidney replacement therapy, he experienced cardiac arrest and died.

DISCUSSION

Enfortumab vedotin is an antibody-drug conjugatedirected against tumor cells containing the nectin-4 transmembrane protein, which is highly expressed in urothelial carcinoma and implicated in cell–cell adhesion.[8] Nectin-facilitated adhesion supports several biologic processes, such as immune modulation, host–pathogen interactions, and immune evasion. Enfortumab vedotin delivers a microtubule-disrupting agent, monomethyl auristatin E, to cells that express nectin-4, disrupting microtubule networks and resulting in apoptotic death.[1] During the pivotal trial of enfortumab vedotin, patients with an A1C level of ≥8% or A1C level of 7%-8% with associated diabetes symptoms were excluded because patients with baseline hyperglycemia or uncontrolled diabetes (A1C > 7%) were at greater risk of developing worsened hyperglycemia, but the precise mechanism remains unidentified.[3] Is it possible that the internalization of the antibody-drug conjugate-nectin-4 complex and proteolytic cleavage of the conjugated monomethyl auristatin E play roles in the metabolism of glucose? Or does it trigger other biochemical reactions, leading to worsening acidosis? It is important to understand the mechanism of onset to be able to prevent or quickly recognize and treat because it is proving to be very lethal.

Our patient was never diagnosed with diabetes mellitus in the past, so the development of a hyperglycemic emergency would not have been expected before starting the medication. This raises concerns regarding patients who might have underlying diabetes but have had no prior testing. The cases of diabetic ketoacidosis due to enfortumab vedotin reported to date, including our case, all died in <3 days following diagnosis, despite aggressive management in the intensive care unit. Therefore, this might suggest a need to measure A1C levels in all patients before starting enfortumab vedotin and to have a black box warning advising against starting enfortumab vedotin in patients with an A1C level of >7.0%.

As noted above, the precise mechanism of developing hyperglycemia or diabetic ketoacidosis is unidentified. The case presented in the abstract of the 2020 American Thoracic Society International Conference in Philadelphia, PA had an elevated C-peptide level of 34.2 ng/mL and was negative for GAD65 antibodies.[6] Our case also had a mildly elevated levels of C-peptide and negative GAD65 antibodies, suggesting that hyperglycemia might be related to insulin resistance rather than deficiency. Despite this fact, there is usually a precipitating factor for patients with diabetes to develop diabetic ketoacidosis; however, the exact mechanism is currently unknown. Could this be some other effect of the drug on glucose metabolism in addition to insulin resistance? The nearly universal lethality of this aggressive diabetic ketoacidosis despite therapy would suggest something different from the insulin resistance we see in type II diabetes mellitus. Will screening for diabetes mellitus even necessarily be a useful preventative measure if this represents a different pathophysiology?

Pasquel et al[9,10] have reported that the mortality rate due to diabetic ketoacidosis alone is less than the mortality rate for patients in a hyperosmolar hyperglycemic state. The greatest mortality was noted in patients with combined hyperosmolar hyperglycemic state and diabetic ketoacidosis.[9,10] Severe hypokalemia and hypoglycemia were noted to be associated with higher mortality. Our patient did not experience hypokalemia or hypoglycemia during treatment or a very rapid progression of acidosis despite receiving insulin IV and CVVHD. This also strengthens the theory that it could be due to some other effect of the drug on glucose metabolism and unlikely simply due to a severe form of drug-induced diabetes mellitus.

Metastatic urothelial carcinomas are very aggressive and progress very rapidly. The discovery of enfortumab vedotin and its approval by the Food and Drug Administration for use in the management of metastatic urothelial carcinomas that have failed other lines of treatments, provides a huge breakthrough in the management of such an aggressive disease. The mechanism of development of hyperglycemia remains unknown, and to date, patients diagnosed with diabetic ketoacidosis progress very rapidly to death. We suggest, therefore, that A1C should be assessed in every patient before starting enfortumab vedotin, and caution should be exercised when using this medication in patients with diabetes mellitus, especially those with A1C level of >7.0%.

ARTICLE INFORMATION

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