Refractory Diabetic Ketoacidosis Related to Enfortumab Vedotin Monotherapy for Metastatic Urothelial Carcinoma

B. Kwok, A. Bhatt, W. J. Wise, C. D. Gibson; Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, NYU Langone Health, New York, NY, United States.

Introduction: Enfortumab vedotin (EV) is a promising salvage therapy for patients with locally advanced or metastatic urothelial carcinoma (MUC). EV is an antibody–drug conjugate that delivers a microtubule-disrupting agent to cells expressing Nectin-4, which is overexpressed in most urothelial cancers. Although a favorable clinical response rate has been reported, the severity and characteristics of EV-related adverse effects are not well described. Here, we discuss a case of refractory diabetic ketoacidosis (DKA) related to EV administration. Case Report: A 75-year-old obese man with MUC presented with fatigue. He was diagnosed with MUC with metastatic hepatic lesions one year prior to presentation. He previously tolerated nivolumab and ipilimumab with mild gastrointestinal upset. However, his disease progressed and he was subsequently enrolled in a clinical trial for EV. Three days after his second infusion of EV, he developed profound fatigue and became increasingly disorientated. On physical exam, he was hypotensive, febrile, and lethargic with no other neurological findings. The remainder of his physical exam was within normal limits. Labs showed acute kidney injury (KDIGO stage 3), metabolic acidosis, and hyperglycemia with ketosis. Cross-sectional imaging and cultures did not reveal a nidus of infection. Work-up also revealed hemoglobin A1c 5.3%, C-peptide 34.2ng/mL (normal 0.8 - 3.5ng/mL) and negative/normal insulin, GAD65, and islet cell antibody titers. Broad-spectrum antibiotics, intravenous fluids, vasopressors, and insulin were administered for DKA and undifferentiated shock. However, he had refractory DKA despite receiving a total daily dose of at least 1000 units of intravenous insulin. Continuous renal replacement therapy was initiated but the patient continued to have progressive multisystem organ failure and expired on hospital day 3. Discussion: EV was granted FDA breakthrough therapy designation for patients with MUC who received prior platinum-based therapies and/or immune checkpoint inhibitors in March 2018. Hyperglycemia is a recognized side effect of EV, with 6% of patients in phase I and II studies developing at least grade 3 hyperglycemia (>250-500 mg/dL). To date, we are among the first to report a fatality secondary to intractable diabetic ketoacidosis despite intravenous insulin and renal replacement therapy. Further investigation to elucidate the mechanism of EV-related hyperglycemia is necessary. The elevated C-peptide level in our patient suggests that his DKA was driven by insulin resistance rather than loss of endogenous insulin production. This case report highlights the importance of recognizing rare and serious adverse events related to novel drugs.

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