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CHALLENGES IN THE DIAGNOSIS OF EUGLYCEMIC DIABETIC KETOACIDOSIS IN A PATIENT WITH MULTIPLE SCLEROSIS TAKING A SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR

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☐ **Abstract—Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been reported to cause euglycemic diabetic ketoacidosis (eDKA), a diagnosis that may be challenging to establish in the emergency department (ED). Case Report: This is a case report of missed eDKA in a 47-year-old male taking empagliflozin (a SGLT2 inhibitor) that presented to the ED with generalized weakness. His past medical history included multiple sclerosis (MS) diagnosed 4 years ago and type 2 diabetes mellitus. The patient attributed his weakness to MS. His neurologist was consulted and agreed with the plan to discharge the patient with diagnoses of asthenia and dehydration and a prescription of prednisone. The patient returned to the ED the next day with similar symptoms and was admitted to the hospital for treatment of eDKA. He was eventually treated per the hospital diabetic ketoacidosis (DKA) protocol and discharged home with instructions to discontinue empagliflozin. Why Should an Emergency Physician Be Aware of This?: The increasing utilization of SGLT2 inhibitor in patients with type 2 diabetes mellitus will inevitably lead to more cases of eDKA seen in the ED. Emergency physicians need to consider this diagnosis in patients taking these medications that present with symptoms including weakness, nausea, vomiting, abdominal pain, and dehydration. Patients taking these medications should be warned about these symptoms, especially because they may be falsely reassured by relatively low plasma glucose levels on home glucometer readings.**

☐ **Keywords—empagliflozin; euglycemic diabetic ketoacidosis; multiple sclerosis; SGLT2 inhibitors**

INTRODUCTION

Diabetic ketoacidosis (DKA) is a disease that is well known to emergency physicians (EPs) and is traditionally defined as a triad of hyperglycemia (>250 mg/dL), elevated anion gap metabolic acidosis, and ketosis (1). Less frequently encountered and perhaps underrecognized is euglycemic diabetic ketoacidosis (eDKA), defined as DKA without marked hyperglycemia (plasma glucose <250 mg/dL) (2). The mechanism of eDKA has not been fully elucidated but is thought to be facilitated by factors such as partial treatment of DKA, food restriction, alcohol intake, and inhibition of gluconeogenesis (1). SGLT2 inhibitors work by increasing urinary glucose excretion and were approved by the U.S. Food and Drug Administration (FDA) in 2013 for the treatment of type 2 diabetes mellitus. In 2015, the FDA released a safety announcement warning that SGLT2 inhibitors may lead to ketoacidosis (3). In the announcement, the FDA mentioned 20 cases from the FDA Adverse Event Reporting System database of acidosis reported as DKA, ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to June 2014. These cases

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were atypical for DKA because most of the patients had type 2 diabetes mellitus and their reported blood glucose levels "were only slightly increased compared with typical cases of DKA" (3).

CASE REPORT

A 47-year-old man presented to the emergency department (ED) with a chief complaint of generalized weakness for the past 3 days. His medical history included multiple sclerosis (MS) diagnosed 4 years ago and type 2 diabetes mellitus. His medications included teriflunomide for the treatment of MS, subcutaneous regular insulin taken with meals, metformin, and empagliflozin. He denied any recent medication changes or additions. He endorsed compliance with his medications and a diabetic diet. He stated that the generalized weakness was consistent with previous flares of MS. He specifically denied fever, nausea, vomiting, visual changes, and headache.

Triage vital signs were a temperature of 97.1°F, a pulse of 115 beats/min, blood pressure 134/86 mm Hg, respirations 18 breaths/min, and oxygen saturation of 99% on room air. On examination, the patient was well-appearing; pertinent findings were tachycardia and dry mucous membranes of the oropharynx. His neurologic examination did not demonstrate any focal deficits. A complete blood cell count was significant for hemoglobin 18.4 g/dL and hematocrit 59.8%. A basic metabolic panel demonstrated glucose 216 mg/dL, blood urea nitrogen 16 mg/dL, creatinine 1.3 mg/dL, sodium 135 mEq/L, potassium 4.4 mEq/L, chloride 101 mmol/L, and bicarbonate 10 mmol/L. The anion gap was 24. Urinalysis demonstrated 4+ ketones and 3+ glucose. A blood gas was not collected. A computed tomography scan of the head without contrast demonstrated findings consistent with multiple sclerosis but no acute intracranial event. The patient was treated with 1 L of Ringer's lactate and reported mild symptomatic improvement. The patient's neurologist was consulted and he agreed with the plan for discharge and recommended prescribing prednisone in case the patient's symptoms were related to an MS flare. His discharge diagnoses were asthenia and dehydration. The patient was given strict return precautions before discharge.

The next day, the patient returned to the ED complaining of worsening weakness despite taking a dose of prednisone at home. At that visit, the patient was documented to have decreased strength in his lower extremities compared with the initial physical examination. The EPs also noticed the elevated anion gap and other laboratory value abnormalities from the initial encounter. A repeat basic metabolic panel in the ED again demonstrated an elevated anion gap. The patient was then admitted to the hospital with a presumptive diagnosis of eDKA caused by the use of empagliflozin. The admitting team initially attempted to manage the patient with subcutaneous insulin; however, a repeat basic metabolic panel demonstrated widening of the anion gap and the patient was transferred to the intensive care unit. The bloodwork at the time of admission was also significant for moderate acetone. Once begun on the hospital's DKA protocol (intravenous [IV] insulin infusion and IV fluids), the anion gap closed and the patient experienced symptomatic relief. The patient's neurologist evaluated the patient while he was admitted and suggested that his weakness was more likely caused by the metabolic disturbance and less likely related to an MS exacerbation. Upon discharge, he was given a prescription for insulin glargine and instructed to permanently discontinue taking empagliflozin.

DISCUSSION

An association of eDKA with the use of SGLT2 inhibitors is becoming increasingly recognized in the literature (1–9). This case adds to the collection of literature and, given the bounce-back nature of the case, also uniquely emphasizes that this is a diagnosis that can easily be missed. All 13 patients in the first case series of eDKA with use of SGLT-2 inhibitors were taking canagliflozin (the first SGLT2 inhibitor to the market) (1). This case adds to the relatively fewer cases of eDKA in patients taking empagliflozin and strengthens the evidence that eDKA is not only caused by canagliflozin but rather is a class effect of the SGLT2 inhibitors (4,6,8).

This patient had a plasma glucose <250 mg/dL, elevated anion gap, and 4+ ketones in his urine—all findings that are consistent with a diagnosis of eDKA. A weakness of this case report is that a blood gas was not collected and therefore the patient's actual serum pH, although presumably acidotic, is not definitively known. An arterial or venous blood gas is not part of the standard workup for generalized weakness and the patient's glucose level of 216 mg/dL did not trigger additional evaluation for acidosis. Other causes of elevated anion gap metabolic acidosis, including alcoholic ketoacidosis, starvation ketosis, and toxic alcohol ingestion, were considered; however, the patient denied alcohol or drug use and endorsed compliance with his diabetic diet, making these differential diagnoses less likely.

Multiple EPs physically saw this patient and reviewed his work-up before the patient was discharged. His reassuring examination combined with his plasma glucose of 216 mg/dL likely contributed to a false impression of well-being. The false impression of clinical stability seen in eDKA caused by only mildly elevated glucose levels is emphasized by multiple sources (1–3,5,7). The patient also self-attributed his weakness to previous flares

of MS and denied other symptoms typical of DKA (e.g., vomiting, abdominal pain, and polydipsia), further clouding the true diagnosis (4,7,10). The patient's attribution of his symptoms to MS was, in this case, misleading and serves as a reminder to EPs to maintain broad differentials and to avoid cognitive biases such as premature closure, anchoring, information and availability biases, and confirmation bias (11). All of these factors combined with the challenges inherent to working in a busy ED likely contributed to the EPs overlooking the decreased serum bicarbonate level, elevated anion gap, and ketonuria.

Once recognized, the treatment of eDKA is similar to that of DKA. Treatment consists of IV hydration with isotonic IV fluid, IV dextrose (to prevent iatrogenic hypoglycemia), insulin infusion (0.1 units/kg/hr), and potassium as needed (10). The importance of the insulin infusion is highlighted in this case. The patient was initially managed by the admitting team with subcutaneous insulin, but his anion gap failed to close with this therapy. After being started on the insulin infusion the anion gap normalized and his symptoms improved.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

This is a case report of a patient with eDKA in a patient taking a SGLT2 inhibitor that was initially missed in the ED. The increasing utilization of SGLT2 inhibitor in patients with type 2 diabetes mellitus will inevitably lead to more cases of eDKA seen in the ED. EPs need to consider this diagnosis in patients who are taking these medications that present with symptoms including weakness, nausea, vomiting, abdominal pain, and dehydration (5). Patients taking these medications should be warned about these symptoms, especially because they may be falsely reassured by relatively low plasma glucose levels on home glucometer readings. Finally, the case serves as a reminder to always provide patients with good return precautions. Fortunately, this patient listened to the EP's return precautions and came back for the appropriate diagnosis and treatment.

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