CLINICAL VIGNETTE

Euglycemic Diabetic Ketoacidosis: Challenge is in the Diagnosis

Patrick Bui, MD and Amar C. Nawathe, MD

A 63-year-old woman presented to the emergency department with nausea and abdominal pain. She was dieting but noted anorexia and unintentional weight loss for several weeks. Her past medical history was significant for gastric bypass surgery and type 2 diabetes mellitus. Her diabetes regimen included metformin, glipizide and canagliflozin. CT scan revealed edema in the gastric wall. Labs were remarkable for acidosis: sodium of 136 mmol/L, potassium 4.3 mmol/L, bicarbonate 19 mmol/L, chloride 103 mmol/L with anion gap of 14 and corrected anion gap of 17.5 due to serum albumin of 2.6. Blood glucose level was 113 mg/dL. She was also anemic with low ferritin. Additional CT imaging revealed retroperitoneal lymphadenopathy and lesions in the lung suspicious for metastatic disease and she was admitted to the hospital. Due to poor oral intake, she was maintained on D5-NS intravenous fluids. On hospital day 2, upper endoscopic evaluation performed but was limited as it could not reach the gastric remnant from prior bypass surgery and did not reveal any significant findings. Her serum bicarbonate level was again 19 mmol/L with glucose level of 123 mg/dL. On hospital day 3, her acidosis worsened to serum bicarbonate of 15 mmol/L. Anion gap was 13. Serum albumin decreased to 2.3 g/dL. Lactic acid level was within normal limits at 0.9 mmol/L. Serum ketones were positive. Arterial blood gas revealed pH 7.29, pCO2 29 mm Hg, HCO3 13.9 mEq/L. She was transferred to the intensive care unit and was started on intravenous insulin infusions and fluids with rapid correction of the anion gap and metabolic acidosis by the end of the day.

Discussion

Poor oral intake and ketonemia in our patient was initially believed to be from starvation ketoacidosis. Dextrose infusion failed to correct the problem and further worsened the acidosis. There was no alcohol or drug use. A patient with type 2 diabetes without hyperglycemia created a diagnostic dilemma initially in the hospital stay and delayed the diagnosis and necessary management of euglycemic diabetic ketoacidosis (EKDA).

In 1973, Munro et al first described EDKA in 17 young patients with type 1 diabetes mellitus. These patients all presented with a common symptom of vomiting, with reduction in carbohydrate intake and continued insulin use. It was proposed that the latter prevented gluconeogenesis and utilization of limited amount of glucose by the cells, leading to lipolysis and release of free fatty acids and ketone production. Resultant insulin resistance prevented further use of glucose by the cells thus preventing hypoglycemia.[1] EDKA has been described in diabetes patients with pancreatitis, prolonged fasting, cocaine use, depression, systemic infections and during pregnancy.[2]

EDKA is not restricted to type 1 diabetes patients. With the use of sodium glucose cotransporter-2 inhibitors [SGLT2i] in the treatment of diabetes mellitus type 2, several cases of this class of drugs' association with EDKA have been reported. SGLT2i reversibly inhibit the sodium dependent glucose transporter protein channel [SGLT2] in the proximal tubule of the glomerulus, promoting glycosuria and controlling blood glucose levels. It is believed that SGLT2i reduces the threshold for the development of EDKA in the presence of stressors such as infections, surgical stress, poor oral intake, lack of insulin. The pathophysiologic mechanisms by which SLGT2i promotes ketoacidosis include reduction in insulin glucagon ratio and dehydration. Glycosuria lowers blood glucose levels, which leads to less glucose mediated insulin secretion. Decreased paracrine inhibition by insulin and decreased SGLT2 medicated glucose transport into the alpha cells results in elevated glucagon levels. Diuresis caused by SGLT2i may promote dehydration and elevations of counter-regulatory hormones such as glucagon, cortisol and epinephrine that further drive lipolysis and ketone body formation and insulin resistance.[3]

In our patient, the delta delta ratio was less than one, meaning that the change in anion gap was less than change in serum bicarbonate. This suggested a mixed high anion gap acidosis and non-anion gap acidosis. This is typically seen in EDKA in contrast to diabetic ketoacidosis where the delta delta ratio is close to one suggesting pure anion gap metabolic acidosis. Na+/H+ exchanger 3 receptor (NHE3) is co-expressed with SGLT2 in the early proximal tubule where it is responsible for about 30% of sodium and important for bicarbonate absorption. SGLT2i by its action on SGLT2, also inhibits NHE3 thereby preventing urinary bicarbonate resorption and increased urine anion gap. Prior work on mice models has shown that exposure to SGLT2i has resulted in modest reduction in blood pH and bicarbonate concentration.[4]

With diagnosis of EDKA, our patient was correctly treated with prompt resolution of the acidosis. Throughout her hospitalization, her blood glucose levels were less than 200 g/dL. Poor appetite and oral intake, SGLT2i canagliflozin use, and dehydration likely contributed. Unfortunately, she was found to have metastatic gastric cancer arising from the gastric pouch remnant from the prior gastric bypass surgery. This was

diagnosed on the interventional radiology biopsy. She was discharged home and later entered hospice.

The Center for Disease Control and Prevention estimates that 30.3 million people or 9.4 percent of the U.S. population has diabetes mellitus.[5] In 2010, diabetes mellitus was either a primary or a secondary diagnosis for 5.3 million hospital discharges.[6] Over the years, the burden of the diabetes continues to increase. Euglycemia inherent in the diagnosis of EDKA masquerades the diagnosis and requires a high level of suspicion in cases with metabolic acidosis. Failure to diagnose can be potentially fatal.

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