CLINICAL VIGNETTE

Diabetic Ketoacidosis Associated with Use of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor: A Spotlight on Ketosis Prone Diabetes Subtypes

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Case Presentation

A 51-year-old female presented to the emergency department with left flank pain, dysuria, and urinary urgency. The urgency and dysuria started four days prior with the onset of flank pain the night before presentation. She reported mild nausea without vomiting and denied fevers or chills. Her past medical history included type 2 diabetes, Hashimoto's thyroiditis, and chronic constipation. Her only surgery was a hysterectomy. Medications included dulaglutide 0.75 mg once a week daily, empagliflozin 25 mg, metformin 1000 mg BID, and daily levothyroxine 50mcg. She had no known drug allergies and family history was noncontributory. She was a lifetime non-smoker, drank 1 glass of alcohol daily, did not use recreational drugs, and ate a strictly plant-based diet with little carbohydrates or processed foods. She exercised several hours every day.

Upon examination in the emergency department, she had a temperature of 36.2 degrees Celsius, blood pressure of 125/76 mmHg, pulse of 83 beats per minute, respirations of 20 per minute, and a BMI of 19.1. She was non-toxic appearing with a normal head and neck, cardiovascular, lung, and skin exam. Her abdominal exam revealed a flat, soft abdomen without distension, mild suprapubic tenderness without rebound or guarding, and left costovertebral angle tenderness. A urinalysis showed 3+ blood, 4+ glucose, 1+ protein, 1+ leukocyte esterase, and 1+ ketones. Microscopic analysis showed >1000 red blood cells per uL, 173 white blood cells per uL, and 3 squamous epithelial cells per uL. Her chemistry panel showed normal electrolytes, a mild acute kidney injury with serum creatinine of 1.01 mg/dL (baseline of 0.85 mg/dL), glucose of 154 mg/dL, and an anion gap of 23 mmol/L (normal range 8-19 mmol/L). A computed tomography (CT) of the kidney, ureter, and bladder without intravenous or oral contrast showed no evidence of renal stones or hydronephrosis but was limited on the evaluation of pyelonephritis given lack of intravenous contrast. There were no other findings to explain her flank pain. She was treated for presumed complicated urinary tract infection with ciprofloxacin 500mg twice daily for seven days.

The patient was discharged to the outpatient setting where she followed up with her primary care physician and endocrinologist. The next day, a repeat urinalysis showed a completely normal urinalysis with resolution of all abnormal indices the day before, except remaining 4+ glucose and 1+ ketones. A comprehensive metabolic panel that day showed a glucose of 136 mg/dL and normalization of the anion gap to 16 mmol/L. Review of the available data raised concern for an episode of normoglycemic diabetic ketoacidosis (DKA) in setting of the sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin. This medication was subsequently discontinued (also due to concern for recurrent urinary tract infections). Given the rarity of diabetic ketoacidosis in a patient with type 2 diabetes, as well as need for multiple diabetic medications despite excellent diet and exercise, the patient's diagnosis was re-evaluated. Glutamic acid decarboxylase and islet cell antibodies were both negative and she was found to have a C-peptide of 1.1ng/mL (normal range 0.5-2.0 ng/mL). She was continued on dulaglutide and metformin at that time, but ultimately over the course of the year her C-peptide levels fell, and she required insulin therapy to manage her diabetes. Ultimately, her diabetes was re-classified as "provoked" Ketosis Prone Diabetes (KPD).

Discussion

Patients with diabetes are generally classified as autoimmune type 1 diabetes (T1D), with presence of autoantibodies and lack of pancreatic beta cell secretion of insulin, or type 2 diabetes (T2D) where inefficient insulin activity (or insulin resistance) predominates. However, there are several less common forms of diabetes in which patients lack these classic phenotypes. Patients who lack typical T1D antibodies but have episodes of diabetic ketoacidosis, much as our patient did, have a variant form of diabetes classified as Ketosis Prone Diabetes (KPD). Such patients have been classified by presence or absence of classical autoantibodies (glutamic acid decarboxylase [GAD65Ab], zinc transporter T8 [ZnT8Ab], or islet antigen-2 [IA2Ab]) and by beta cell function (fasting and glucagon-stimulated C-peptide levels). This classification identifies 4 subgroups of KPD which each appear to have distinct natural histories. The subtypes are classified according to antibody presence/absence(A-/+) and beta cell function /absence(B+/).[1] A further differentiator between these subtypes is the presence of lack thereof of an identifiable stressor ("provoked KPD") as these patients are hypothesized to have islet autoimmunity manifested as T cell reactivity to islet autoantigens.[2]

Ketosis Prone Diabetes is more common in Africa, though it also occurs in the Caribbean, Latin America, parts of Asia

(including Japan) and in Native Americans. It is reportedly rare in Caucasians.[3] In the United States, it is estimated that approximately half of American diabetics with African heritage diagnosed with ketoacidosis in fact have KPD.[3] KPD has a male to female ratio of approximately 3:1 and patients often have typical risk factors associated with T2D (abdominal obesity, hypertension, dyslipidemia, excess body mass), though the onset of their KPD often mimics T1D with acute development of hyperglycemia associated with weight loss, polyphagia, and polyuria with ketosis.[3]

The genetics of KPD is not fully elucidated, though it seems to be more prevalent in certain human leukocyte antigen haplotypes (HLA-DR3 and HLA-DR4) and less common in others (HLA class II alleles (DQA*03 and DQB1*02)).[3] On the presentation of diabetic ketoacidosis, KPD patients will often have acute loss of pancreatic beta cell function. However, patients classified as A-B+, as our patient was, will have recovery of beta cell function in 50% of cases, while the other 50% may have some period of insulin independence and subsequently develop a decline in beta cell function.[2,3] Treatment for KPD is aimed at achieving euglycemia through lifestyle interventions as well as medications. For those requiring insulin therapy, long-acting insulin can help establish normoglycemia and decrease gluco-lipo-toxicity thereby restoring residual β cell function and reducing apoptosis.[4,5] In patients with KPD, caution should be taken when choosing medications given their propensity towards ketosis via acute provoked insulinopenia.[3]

DKA associated with the use of SGLT2 inhibitors in patients classified as type 2 diabetics ranges from 0.16 to 0.76 events per 1000 patient-years.[6] The underlying mechanism of euglycemic DKA (EDKA) is due to a carbohydrate deficit which results in a decreased insulin secretion and excess counter-regulatory hormones like glucagon, epinephrine, and cortisol. Patients taking SGLT2 inhibitors should have these medications discontinued as soon as the diagnosis is recognized and held at least until recovery from the acute illness. Patients presenting with EDKA from SLGT2 inhibitors should also raise an index of suspicion for alternate diagnoses, including KPD.

In the case presented, our patient had a first episode of EDKA triggered by an SGLT2 inhibitor and with her subsequent gradual worsening glycemia, ultimately was reclassified as having “provoked” A-β+ Ketosis Prone Diabetes. This was a unique case in that patients with KPD often have classic T2D risk factors, including central adiposity, however, her reported Latin/Hispanic heritage may have been a risk factor. While her beta cell function appeared initially stable, this case also highlights the need to observe beta cell recovery from an episode of EDKA to ensure beta cell insufficiency does not follow, as it did in our patients. Finally, this case highlights the lesser-known types of diabetes and when to have an index of suspicion to investigate further.

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