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The Coexistence of Glycemic Diabetic Ketoacidosis, Recurrent Genital Abscess and Proximal Renal Tubular Acidosis in the Presence of a Concurrent SGLT-2 Inhibitor is Not Merely an Association, but Rather a Significant Correlation

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Abstract

SGLT2 inhibitors, such as Empagliflozin, are a type of antidiabetic drugs that offer significant advantages to diabetic individuals by decreasing renal tubular glucose re-absorption, leading to a rapid rise in urinary glucose excretion and subsequently lowering overall serum blood glucose levels. Despite these benefits, the use of these medications has been linked to the emergence of complications like euglycemic Diabetic Ketoacidosis (eDKA), a rare and serious metabolic disorder. Additionally, other complications such as recurrent genital abscesses and renal tubular acidosis have been associated with this drug class, although they have been less frequently reported and studied. The case of a woman who experienced life-threatening eDKA, recurrent genital abscesses and proximal renal tubular acidosis within just two months of starting Empagliflozin serves as an example of the potential risks associated with SGLT2 inhibitors.

Keywords: Covalent organic framework • Titanium dioxide • Optimization • Methylene blue • Tetracycline

Introduction

Euglycemic Diabetic Ketoacidosis (eDKA) is an infrequent but potentially life-threatening metabolic complication that can occur in individuals with Diabetes Mellitus (DM) who are undergoing treatment with Sodium-Glucose Co-Transporter Inhibitors (SGLT-2i) [1]. Although the association between SGLT-2i and eDKA has been extensively studied and reported, the occurrence of recurrent genital abscesses in patients concurrently taking these medications remains a less explored phenomenon. The reported incidence of SGLT-2i-induced DKA is estimated to be between 0.16 and 0.76 events per 1000 patients-years [2]. Furthermore, the development of proximal Renal Tubular Acidosis (RTA) as a result of SGLT2-i usage is considered to be relatively uncommon and lacks comprehensive documentation. In this particular case, we present an extraordinary occurrence where all of these complications manifested simultaneously following the recent initiation of SGLT-2i treatment.

Case Presentation

A 44-year-old female patient, who has a medical history of non-insulin-dependent diabetes and is unable to tolerate metformin, was prescribed Empagliflozin two months ago. She presented to the emergency department with symptoms of redness, swelling and pain in the right vulvar area, accompanied by nausea, one episode of vomiting, fever, chills and loss of appetite. The patient denied experiencing any diarrhea. Upon admission, the physical examination revealed severe sepsis, characterized by a rapid heart rate of 120 beats per minute, increased respiratory rate of 26 breaths per minute and a mild fever of 100.4°F. The entire right lower abdominal quadrant was tender upon light palpation. The right vulvar region showed evident erythema, swelling and tenderness extending to the mons pubis area, measuring approximately 7.0 × 7.0 × 7.0 cm, with some extension into the right lower abdominal quadrant. No purulent discharge or fluctuant mass was observed during the examination. Laboratory tests confirmed the diagnosis of sepsis, as indicated by a leukocytosis count of 14,000/mm (normal range: 5000/

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mm-10,000/mm). Further laboratory investigations revealed a high anion gap metabolic acidosis with compensatory respiratory alkalosis, with an anion gap of 24 mEq/L (normal range: 8-12 mEq/L), pH level of 7.07 (normal range: 7.35-7.45) and bicarbonate level of 15 mEq/L (normal range: 21-36 mEq/L). Arterial pCO_2 and HCO_3 levels were measured at 11 mmHg and 10.6 mEq/L, respectively (normal range: 35 to 45 mmHg and 22-26 mEq/L) (Table 1). The lactic acid level in the patient's blood was within the normal range at 1.0 mmol/L (normal range: <2 mmol/L) upon arrival. Additionally, the patient's plasma glucose level was measured at 222 mg/dL. Urinalysis revealed the presence of 80 mg/dl of ketones, 100 mg/dl of protein and >500 mg/dl of glucose (Table 2). Beta-hydroxybutyrate levels were measured at 60.8 mg/dl (reference range <3 mg/dL), confirming the diagnosis of euglycemic diabetic ketoacidosis (Table 3). The patient's Hemoglobin A1C (HbA1C) upon admission was 8.7%. Subsequent imaging *via* Computerized Tomography (CT) of the abdomen and pelvis revealed significant edema in the right groin and right vulva, along with a 1.2 cm early abscess. The patient also reported a previous perianal abscess occurrence following the initiation of Empagliflozin. The initial episode was described as a large pustule in the left medial thigh, which was closely monitored by the primary care provider for two months without progression to abscess formation or necessitating hospitalization. The pustule eventually resolved with daily warm compresses. The patient noted that the current presentation was notably more painful, red and swollen compared to the first occurrence.

Upon admission to the intensive care unit, the patient was diagnosed with eDKA and received treatment with IV fluids, insulin bolus, drip and potassium replacement until resolution of the eDKA. Surgical incision and drainage were performed as the patient was found to have a right suprapubic abscess and a left gluteal abscess. Empirical antibiotic therapy with Piperacillin-Tazobactam, Clindamycin and Vancomycin was initiated to cover potential necrotizing infections. Subsequent wound cultures from the abscesses grew Methicillin sensitive *Staphylococcus aureus*, leading to a transition to Nafcillin based on culture sensitivities. Following resolution of the eDKA, the patient developed refractory hypokalemia ranging between 2-3 mEq/L (reference range 3.5-5.2 mEq/L) associated with persistent non-anion gap acidosis and bicarbonate levels ranging between 10–12 mmol/L. Further investigations revealed a urine pH<5.5 (reference range 4.5 to 7.8), persistent hyperchloremia ranging 110-115 mEq/L (reference range 96-106 mEq/L) and an elevated urine anion gap of 16 mEq/L (reference range <10 mEq/L), all indicative of proximal Renal Tubular Acidosis (RTA). The patient received bicarbonate supplementation along with potassium replacement therapy with improvement in her electrolyte derangements. The patient was discharged with bicarbonate 650 mg once per day along with potassium supplementation, Cephalexin 500 mg four times per day for 14 days with continuation of probiotics and discontinuation of Empagliflozin and initiation of insulin NPH-Regular 70/30 and clear instructions for dressing changes. On 6-month follow-up, the patient reported no recurrence of abscesses or pustules and denied any recent hospitalization related to RTA and/or eDKA.

	Our patients' laboratory values	Reference range
WBC (cells/mm^3)	14,300	4,000-10,500
Hemoglobin (g/dl)	13.8	11.2-15.7
Hematocrit (%)	40.2	34.1-44.9
Platelets count (cells/mm^3)	1,98,000	150-400
Sodium (mEq/L)	136	136-145
Potassium (mEq/L)	3.2	3.5-5.1
Chloride (mEq/L)	100	96-106
Carbon dioxide (mmol/L)	15	21-32
Anion gap	24.2	<10
BUN (mg/dL)	8	07-18
Creatinine (mg/dL)	0.78	0.6-1.3
Estimated GFR (mL/min)	>60	>60
Glucose (mg/dL)	222	74-110
Beta-hydroxybutyrate (mg/dL)	60.8	<3
Lactic acid (mmol/L)	1	<2

Note: cells/mm^3=cells per cubic millimeter, g/dl=grams per deciliter, %=percentage of RBC in blood, mEq/L=milliequivalents per liter, mmol/L=millimoles per liter, mg/dL=milligrams per deciliter, ml/min=milliliters per minute

Table 1. Serum laboratory findings.

	Our patient's urinalysis values	Reference range
Urine color	Yellow	Yellow
Urine appearance	Clear	Clear
Urine pH	5.0	05-09
Urine specific gravity	1.023	1.005-1.030
Urine protein	100 mg/dL	Negative
Urine glucose	>500 mg/dL	Negative
Urine ketones	80 mg/dL	Negative
Urine blood	Negative	Negative
Urine nitrite	Negative	Negative
Urine bilirubin	Negative	Negative
Urine urobilinogen	Negative	Negative
Urine leukocyte esterase	Negative	Negative
Urine RBC	0-5 RBC/HPF	0-5
Urine WBC	0-5 WBC/hpf	0-5
Urine squamous epithelium	0-5 epi/HPF	0-5
Urine bacteria	Rare	None seen
Urine mucus	Rare	Rare

Note: mg/dL=milligrams per deciliter, RBC/HPF=Red Blood Cell per High Power Field, Wbc/HPF=White Blood Cell per High Power Field, epi/HPF=squamous epithelial cells per High Power Field

Table 2. Urine laboratory studies.

	Our patients ABG values	Reference range
ABG pH	7.31	(7.35-7.45)
ABG pCO_2 (mmHg)	21	(35-48)
ABG pO_2 (mmHg)	81.5	(83-108)
ABG pO_2/FiO_2 ratio (mmHg)	388.1	(>200)
ABG HCO_3 (mmol/L)	10.6	(21-28)
ABG O_2 saturation (%)	95.2	(94-98)
ABG base excess (mmol/L)	-13.4	(-2-3)
O_2 delivery	Room air	

Note: mmHg=millimeter of Mercury, mmol/L=millimoles per liter.

Table 3. Arterial blood gas results.

Discussion

The case emphasizes the significance of promptly recognizing and managing complications in these patients. Additionally, it underscores the necessity of adopting a comprehensive approach to address multiple concurrent issues, including sepsis, eDKA, vulvar abscess and proximal RTA.

The emergence of persistent hypokalemia with non-anion gap acidosis in this particular case raises concerns regarding the potential occurrence of significant complications, such as RTA. Proximal RTA is a form of renal tubular acidosis characterized by impaired bicarbonate reabsorption in the proximal tubules of the kidneys, resulting in metabolic acidosis [3]. Our patient's urine anion gap exceeded the reference range at 16 mEq/L (reference range <10 mEq/L), confirming our diagnosis. The common triggers for non-anion gap acidosis, such as diarrhea, recent use of Topiramate or diuretics and administration of normal saline, were absent from our patient's medical history and management. Throughout her hospitalization, our patient exclusively received lactated ringers. These findings narrowed down the diagnosis to a potential association between the use of an SGLT2 inhibitor and the development of non-anion gap

acidosis related to RTA. Consequently, the SGLT2 inhibitor emerges as the primary candidate for diagnosis. The precise mechanism by which SGLT2 inhibitors can cause Renal Tubular Acidosis (RTA) remains unclear, although there are several theories regarding their mode of action. SGLT2 inhibitors target the SGLT2 cotransporters located on the apical membrane of the proximal convoluted tubule, inhibiting the reabsorption of glucose [4]. According to Onishi, Akira, et al.[5], it has been proposed that the activities of SGLT2 and Na^+-H^+ Exchanger 3 (NHE3) are interconnected. Consequently, the suppression of NHE3 may contribute to the natriuretic response observed with SGLT2 inhibitors. This leads to increased urinary excretion of Sodium (Na^+) and bicarbonate, resulting in an elevated urinary pH in wild-type mice and ultimately causing serum metabolic acidosis. The study conducted by Onishi et al. focused on the SGLT2 inhibitor empagliflozin. However, further research is necessary to fully comprehend these mechanisms.

The development of euglycemic Diabetic Ketoacidosis (eDKA) with SGLT-2 inhibitors is believed to involve increased ketogenesis, reduced insulin secretion and decreased insulin activity [6-10].

It is important to note that SGLT-2 inhibitors may have certain potential side effects, including an increased risk of genital bacterial and/or mycotic infections in both men and women. Additionally, individuals with Diabetes Mellitus (DM) are generally more susceptible to developing abscesses, including genital abscesses. In this particular case, the occurrence of recurrent abscesses after initiating SGLT-2 inhibitor treatment strongly suggests a possible association with the medication, prompting consideration of discontinuing its use. After discontinuing empagliflozin for six months, the patient reported no recurrence of eDKA and denied any recurrent abscesses, confirming that the initiation of empagliflozin likely triggered these life threatening outcomes. Further research is needed to fully understand the potential risks and benefits of SGLT-2 inhibitors in different patient populations.

Conclusion

SGLT-2i is generally a safe and beneficial medication for reducing blood sugar in diabetic patients. However, like many other medications, adverse effects are risks that need to be considered in this patient population. Although eDKA in the setting of well-controlled diabetes by SGLT-2i is uncommon, this case serves as a reminder that it should be on the differential diagnosis in patients presenting with similar symptoms. It is also important to strongly consider RTA when assessing metabolic abnormalities and consider genital bacterial/mycotic infections in patients presenting with sepsis in the setting of newly initiated SGLT-2i.

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