A case report of sodium glucose co-transporter 2 inhibitor associated euglycemic diabetic ketoacidosis: a diagnostic challenge

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European Journal of Medical Case Reports
Volume 6(1):11–16
https://doi.org/10.24911/ejmcr/173-1622061632

ABSTRACT

Background: Type 2 diabetes (T2DM) is becoming more prevalent worldwide and sodium-glucose co-transporter-2 (SGLT2) inhibitors are being increasingly used in its management. However, they have been associated with the serious complication of euglycemic diabetic ketoacidosis (EDKA).

Case Presentation: A 51-year-old female on canagliflozin for T2DM presented with a 2-week history of vomiting and abdominal pain. With a blood glucose of 9.0 mmol/l, a diagnosis of diabetic ketoacidosis was at first overlooked and the patient was initially managed for pyelonephritis. However, a diagnosis of EDKA was subsequently reached on day 3 after a blood gas revealed a high anion gap metabolic acidosis with ketones of 3.9 mmol/l.

Conclusion: This case demonstrates the diagnostic challenge posed by the atypical presentation of SGLT2 inhibitor associated EDKA. Furthermore, it underlines the need for patient education concerning stopping these medications during illness and highlights how their association with urinary tract infections may further increase the risk of EDKA.

Keywords: Case report; diabetes; SGLT2 inhibitors; euglycemic diabetic ketoacidosis; medication related complication.

Received: 26 May 2021 **Accepted:** 08 September 2021 **Type of Article:** CASE REPORT **Specialty:** Diabetology

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Background

The prevalence of diabetes is increasing with latest figures estimating almost 500 million people are currently living with the condition worldwide, of which the majority have type 2 diabetes (T2DM) [1]. As reported by Saeedi et al. [1], this figure is projected to continue to rise meaning the management of diabetes and its associated complications will be an increasing burden on future medical practice.

Over recent decades several new oral hypoglycemic medications have been developed to help manage the mounting number of patients with T2DM [2]. The most recently approved of these novel agents are the sodium-glucose co-transporter-2 (SGLT2) inhibitors, which include canagliflozin, dapagliflozin, and empagliflozin [2]. They primarily work through reducing glucose reabsorption at the proximal renal tubule and have grown in popularity due to their cardiovascular and renal benefits [3] as well as their ability to promote weight loss and lower blood pressure [4]. However, SGLT2 inhibitors have been linked with causing diabetic ketoacidosis (DKA) with both the European Medicines Agency [5] and US Food and Drug Administration [6] issuing warnings to this effect.

DKA is a well-established medical emergency, more commonly seen in patients with type 1 diabetes (T1DM), that is defined as a biochemical triad of; metabolic acidosis (HCO^{3-} <15.0 mmol/l and/or venous pH <7.3), ketosis (ketonemia 3.0 mmol/l or significant ketonuria more than 2 + on standard urine sticks) and hyperglycemia (blood glucose >11.0 mmol/l) [7]. However, when associated with SGLT2 inhibitors, the presentation of DKA can differ with the development of euglycemic diabetic ketoacidosis (EDKA), where the blood glucose levels can be normal or only mildly raised (<13.9 mmol/l) [8].

We, therefore, present the following case to illustrate how this atypical presentation can be a diagnostic challenge for clinicians before discussing the key learning points.

Case Presentation

A 51-year-old female presented to the acute medical unit with a 2-week history of vomiting, abdominal pain, and progressive lethargy. She had a history of poorly controlled T2DM, with an HbA1c of 120 mmol/mol, that was managed with metformin 1g BD, gliclazide 80 mg BD and canagliflozin, which had recently been increased to the maximum dose of 300 mg OD. Prior to her admission, she had been treated in the community with oral antibiotics

for a presumed urinary tract infection (UTI) following a positive urine culture, but her symptoms had failed to resolve. On arrival she was tachycardic at 120 beats per minute and tachypneic at 28 breaths per minute but normotensive, afebrile and with normal oxygen saturations on room air. Initial blood results demonstrated a c-reactive protein (CRP) of 110 mg/l with a white cell count (WCC) of 12.7 × 10^9/l but were otherwise unremarkable with a blood glucose level of 9.0 mmol/l and with both unimpressive renal and liver function tests including a normal serum amylase (Table 1). She was started on broad-spectrum IV antibiotics for possible intra-abdominal sepsis and a CT scan of the abdomen and pelvis was arranged. This showed mild hydronephrosis of the left kidney secondary to a possible pelviureteric junction obstruction with minimal perinephric stranding (Figure 1) and so she was continued on IV antibiotics for a presumptive diagnosis of pyelonephritis.

On day 3 of her admission, there had been limited progress in her condition and a blood gas was performed revealing a high anion gap metabolic acidosis; pH 7.13, pCO^2 1.0kPa, HCO^{3-} 2.7 mmol/l, Na^+ 129 mmol/l, K^+ 3.9 mmol/l, Cl- 104 mmol/l, base excess -23.8 mmol/l and lactate 0.9 mmol/l (Table 2). Blood ketones were found to be 3.9 mmol/l and given her comparatively normal blood glucose level a diagnosis of EDKA was reached, thought to be secondary to her SGLT2 inhibitor canagliflozin. She was subsequently transferred to the medical high dependency unit where she made a full recovery following additional treatment with IV insulin and fluids. Before discharge her gliclazide and canagliflozin were stopped, her metformin was continued, and she started on a basal-bolus insulin regime. In light of this admission with EDKA and her prior history of poor glycemic control, anti-GAD and anti-IA2 antibody tests were sent looking for possible latent autoimmune diabetes in adults

Table 1. *Summary of admission blood results.*

TEST	VALUE	REFERENCE RANGE	TEST	VALUE	REFERENCE RANGE
Hb (g/l)	118	120-150	Sodium (mmol/l)	131	133-146
MCV (fl)	80.8	83.0-101.0	Potassium (mmol/l)	4.2	3.5-5.3
WCC (×10^9/l)	12.7	4.0-10.0	Urea (mmol/l)	4.5	2.5-7.8
Neutrophils (×10^9/l)	9.0	2.0-7.0	Creatinine (µmol/l)	54	44-71
Platelets (×10^9/l)	800	150-410	eGFR	>90	>90
Bilirubin (µmol/l)	4	<21	Adjusted Calcium (mmol/l)	2.38	2.20-2.60
ALP (U/l)	171	30-130	Amylase (U/l)	29	<100
ALT (U/l)	8	10-49	CRP (mg/l)	110	<10
Albumin (g/l)	48	35-50	Glucose (mmol/l)	9.0	3.8-11.0

Hb, haemoglobin; MCV, mean corpuscular volume; WCC, white cell count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; CRP, c-reactive protein.

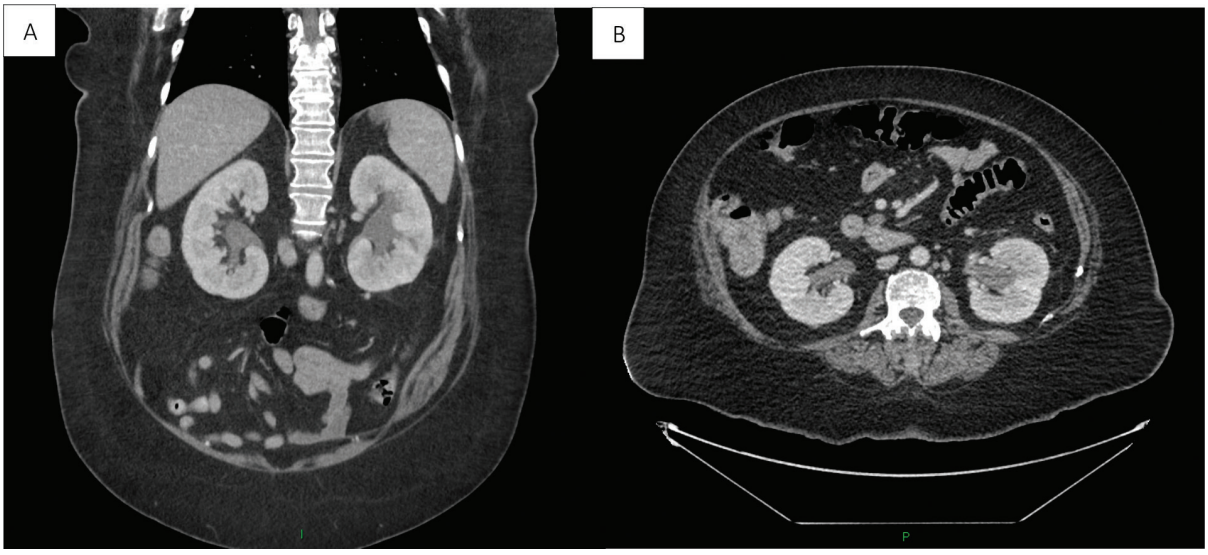

Figure 1. *CT images in both the coronal (A) and axial (B) planes demonstrating mild hydronephrosis of the left kidney secondary to a possible pelviureteric junction obstruction with minimal perinephric stranding suggesting possible pyelonephritis.*

Table 2. *Summary of blood gas results.*

TEST	VALUE	REFERENCE RANGE
pH	7.13	7.35-7.45
pCO_2 (kPa)	1.0	4.6-6.4
pO_2 (kPa)	18.3	11.0-14.4
Na^+ (mmol/l)	129	136-145
K^+ (mmol/l)	3.9	3.4-4.5
Cl^- (mmol/l)	104	98-107
Ca^{2+} (mmol/l)	1.39	1.15-1.27
Lactate (mmol/l)	0.9	0.0-1.3
HCO^{3-} (mmol/l)	2.7	22.0-28.0
Base excess (mmol/l)	-23.8	

pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; Na^+, sodium; K^+, potassium; Cl^-, chloride; Ca^{2+}, calcium; HCO^{3-}, bicarbonate.

but were subsequently found to be negative. By 4 months post-discharge her HbA1c had significantly improved to 56 mmol/mol.

Discussion

Munro et al. [9] first coined the term EDKA in 1973 when they observed 37 cases of severe ketoacidosis (HCO^{3-} <10 mmol/l) without significant hyperglycemia (blood glucose <300 mg/dl or 16.7 mmol/l) in a series of 211 patients with T1DM. As with DKA, these cases of EDKA occurred in the context of a precipitating trigger including acute illness, pregnancy and medication compliance related issues. Although interestingly, it was proposed that preceding periods of reduced carbohydrate intake were the reason for the unusual state of euglycemia found in each case at the time [9]. However, other etiologies for EDKA are now recognized including a ketogenic diet, chronic alcohol use, liver disease, and the use of SGLT2 inhibitors [10]. While the patient in the presented case also had a precipitating illness with pyelonephritis, she differs from these original cases reported by Munro et al. [9] as she had T2DM and was on an SGLT2 inhibitor. The use of this medication and the concurrent pyelonephritis therefore likely both contributed to the etiology of EDKA in her case. Although the risk of EDKA with SGLT2 inhibitors may be relatively low, estimated to occur in approximately 1 in 1,000 patients with T2DM receiving this treatment, it is a medication related complication that clinicians should be mindful of given its potential severity [11].

SGLT2 inhibitors work through blocking the SGLT2 protein in the proximal renal tubule, reducing glucose reabsorption and promoting increased glycosuria [8]. While this has the therapeutic effect of reducing blood glucose levels, it is one of the proposed mechanisms through which SGLT2 inhibitors are linked to causing EDKA. In DKA, absolute insulin deficiency or insulin resistance results in reduced glucose utilization. Subsequently there is a switch to lipolysis, via an increase in the action of counter-regulatory hormones (CRH) such as catecholamines, cortisol, and glucagon [7]. This allows for the metabolism of free fatty acids (FFA) as an alternative energy source, but also results in the production of ketones and a predisposition to ketoacidosis [10]. In addition, the CRH also stimulate gluconeogenesis and glycogenolysis as part of a stress response, causing the hyperglycemia typically seen in DKA [7].

Conversely, in EDKA associated with SGLT2 inhibitors, the increase in glycosuria as a consequence of this medication lowers blood glucose levels, preventing hyperglycemia, and therefore contributing to the development of EDKA. This reduction in blood glucose levels also further stimulates the CRH, promoting lipolysis, FFA metabolism and the production of ketones [12]. Furthermore, it has been shown that SGLT2 inhibitors act to cause EDKA via two other mechanisms; firstly by a direct stimulatory effect on pancreatic alpha-cells leading to increased glucagon release, and secondly through impairing renal excretion of ketones [8]. These differing mechanisms combine to leave patients taking SGLT2 inhibitors more vulnerable to developing EDKA, especially in the presence of other triggers or physiological stressors.

With this pathophysiology, the atypical presentation of EDKA can pose a diagnostic challenge to clinicians. It is well established that patients in DKA typically present with symptoms including abdominal pain, nausea, vomiting, breathlessness, and dehydration although, this collection of symptoms has a wide list of other differentials [7]. EDKA also presents in a similar fashion as illustrated in the presented case and previous case reports [13,14]. However, the absence of significant hyperglycemia associated with EDKA is the main reason for its diagnostic challenge and delay in recognition. In our case, the patients blood glucose level was only 9.0 mmol/l on admission, which is lower than would be expected in DKA or for a patient with an HbA1c of 120 mmol/mol. This corresponds well with a previous case series of 13 patients with

EDKA on canagliflozin where initial blood glucose levels were normal or only mildly elevated, with the highest being 12.9 mmol/l [13]. In these cases, the diagnosis of EDKA was initially overlooked and only reached on discovering that the patients had a high anion gap metabolic acidosis with ketosis, as was also the case with our patient [13]. This, therefore, highlights how an initial normal or lower than expected blood glucose reading may be misleading and falsely reassuring if clinicians are unaware of the potential for EDKA with SGLT2 inhibitors. Exclusion of a diagnosis of DKA based on blood glucose readings alone could therefore be perilous, delaying the recognition and management of this potentially life-threatening condition [14]. In order to avoid this pitfall, it is recommended that blood gases and ketone levels are checked and that clinicians have a high level of clinical suspicion [8,10].

In our case, the history of a UTI and pyelonephritis raises a further issue regarding the use of SGLT2 inhibitors. As previously shown, there is an established link between SGLT2 inhibitors and the development of EDKA. However, given their mechanism of action and the resulting increased glycosuria, it is also recognized that patients on these medications are more prone to developing UTIs as common side effects [15]. In addition, there have been case reports demonstrating UTIs as precipitants for EDKA [16,17]. It is, therefore, conceivable that the use of an SGLT2 inhibitor in this case contributed to the development of EDKA in two separate ways. First, as a risk factor for developing a UTI and subsequent pyelonephritis which acted as a trigger for EDKA, and second through the direct actions of the SGLT2 inhibitor predisposing the patient to developing ketoacidosis.

An additional learning point highlighted in this case relates to use of SGLT2 inhibitors during illness. The concept of the "Sick Day" rules is well established with patients advised to stop certain nephrotoxic medications when they feel unwell. Commonly included medications in this situation include the "DAMN" drugs; diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, metformin, and non-steroidal anti-inflammatory drugs. However, given the link between SGTL2 inhibitors and EDKA in the context of an acute illness, clinicians should also advise patients on these medications of the same "Sick Day" rules in order to prevent this complication [8]. The Medicines and Healthcare products Regulatory Agency issued a drug safety update in 2020 similarly recommending the withholding of SGLT2 inhibitors in patients admitted for major surgical procedures or acute medical illnesses and that blood ketone levels should be monitored [18]. Furthermore, patient education around EDKA and the potential for blood glucose readings to be normal or only mildly elevated is also important, as patients who are expecting to find significant hyperglycemia with home glucose monitoring may also be falsely reassured and delay seeking medical attention as a result [10,13].

Conclusion

This case further adds to the body of literature supporting the link between SGLT2 inhibitors and the serious complication of EDKA. It has demonstrated how this atypical presentation offers up a significant diagnostic challenge and one that clinicians must be vigilant of when seeing patients on this class of oral hypoglycemic medication. Furthermore, it has highlighted the need for checking blood ketones and blood gases when assessing patients on SGLT2 inhibitors as well as emphasized the importance of educating patients of the "Sick Day" rules prior to starting this therapy. Overall, while SGLT2 inhibitors have numerous advantages, this case report reminds us of their potential complications including the development of EDKA and an increased risk of UTIs which, as demonstrated, can be a harmful combination.

What is new?

EDKA is a recognized complication of SGLT2 inhibitors, and this case report further adds to the literature supporting this. It demonstrates the diagnostic challenge of its atypical presentation and highlights the importance of patient education regarding stopping these medications during a concurrent illness. Furthermore, in our case, we show how UTIs, another side effect of SGLT2 inhibitors, can also contribute to the development of EDKA in conjunction with SGLT2 inhibitors.

Key Learning Points

- Clinicians should have an awareness of the link between SGLT2 inhibitors and EDKA as well as the need for a high level of clinical suspicion given its atypical presentation with the absence of significant hyperglycemia.
- When assessing patients on SGLT2 inhibitors it is important to check ketones and blood gases regardless of blood glucose levels as a diagnosis of DKA cannot be excluded based on blood glucose levels alone.
- Prior to starting SGLT2 inhibitors patients should be educated about the risk of EDKA and the "Sick Day" rules with advise to stop these medications during a concurrent illness such as UTIs which are also a common side effect of these medications.

List of Abbreviations

CRH	Counter Regulatory Hormones
CRP	C-reactive Protein
DKA	Diabetic Ketoacidosis
EDKA	Euglycaemic Diabetic Ketoacidosis
FFA	Free Fatty Acids
SGLT2	Sodium Glucose Co-Transporter 2

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UTI	Urinary Tract Infection
WCC	White Cell Count

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this case report.

Funding

No funding was sought or obtained.

Consent for publication

Informed consent has been obtained and a signed patient consent form is attached with this manuscript.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	51 year old female
2	**Final diagnosis**	SGLT2 inhibitor associated euglycaemic DKA on the background of an acute illness with pyelonephritis
3	**Symptoms**	Abdominal pain, vomiting, progressive lethargy
4	**Medications**	Canagliflozin and gliclazide stopped, metformin continued, Insulin started
5	**Clinical procedure**	n/a
6	**Specialty**	Acute medicine/diabetes and endocrine