



## Case Report

## Emphysematous Kidney Related to the Use of Empagliflozin in a Diabetic Woman

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## ABSTRACT

**Background/Objective:** Sodium-glucose cotransporter-2 (SGLT2) inhibitors are part of the treatment for hyperglycemia in patients with diabetes. These drugs have shown important benefits including cardiovascular and renal protection among people with diabetes.

**Case Report:** We report a case of a 60-year-old woman with diabetes who presented to the emergency department complaining of left flank pain radiating to the groin. The patient was on multiple antidiabetic medications, including a recently added empagliflozin, considering the difficulty in controlling hyperglycemia. She quickly developed severe sepsis with shock, and imaging studies of the abdomen revealed the presence of encapsulated gas in the left kidney compatible with emphysematous pyelonephritis (EPN). There was no presence of nephrolithiasis or other anatomical or structural abnormality that could have precipitated this focal renal infection.

Besides antimicrobials, fluid resuscitation, and vasopressor agents, an emergent surgical nephrectomy, as well as intensive care, was required until the patient fully recovered. *Escherichia coli* was isolated from the initial blood cultures, and ceftriaxone was administered. The patient was subsequently discharged home in stable condition. Two months later, the patient was readmitted with near-syncope and abdominal pain, which was found to be related to small bowel obstruction. The patient decompensated rapidly and had a cardiac arrest even before surgical evaluation. She was resuscitated and admitted to the intensive care unit but showed no signs of neurologic recovery after the anoxic event. She did not survive this hospitalization.

**Discussion:** The exposure of SGLT2 inhibitors in this patient seemed to have been the precipitating factor for development of complicated pyelonephritis with gas gangrene. EPN is a consequence of a severe renal parenchymal infection, which carries high mortality even with prompt treatment.

**Conclusion:** Use of SGLT2 inhibitors has expanded worldwide as there are clear clinical benefits, but we need to recognize their uncommon yet potentially fatal complications, such as EPN.

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## Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are known to cause severe urinary tract infections due to their mechanism of action by blocking SGLT-2 in the proximal renal

tubules, reducing reabsorption of filtered glucose, resulting in increased glucose excretion and lower plasma glucose concentration.<sup>1</sup> Emphysematous pyelonephritis (EPN) is a severe infection of the renal parenchyma linked to a high mortality. EPN presents more commonly among persons with diabetes, and it tends to cause severe illness and potential complications to other organs.<sup>2</sup>

We report a case of EPN in a woman with diabetes presumably precipitated by multifactorial causes, highlighting the use of empagliflozin as an important trigger, possibly secondary to its mechanism of action without any structural obstruction in the urinary tract. Given its rarity, the finding of this case provides

**Abbreviations:** EPN, emphysematous pyelonephritis; ICU, Intensive care unit; SGLT-2, Sodium-glucose cotransporter-2; UTI, urinary tract infection.

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guidance to health care providers to individualize the use of SGLT2 inhibitors, keeping in mind their adverse effects and potential complications, therefore, requiring close monitoring.

### Case Report

A 60-year-old woman presented to the emergency department (ED) with left flank pain radiating to the groin, vomiting, dizziness, and lightheadedness for 2 days, with absence of urinary symptoms or fever. Her medical history was relevant for coronary artery disease with prior angioplasty, and difficult-to-control type 2 diabetes mellitus managed with insulin glargine 30 units twice a day, insulin lispro 30 units thrice a day, dulaglutide 1.5 mg weekly injection, and empagliflozin 25 mg once daily. The latter had been introduced 4 months prior to this presentation. Her hypertension was managed with losartan 50 mg daily and her hypertriglyceridemia with icosapent ethyl 2 g twice a day. The patient was a former smoker and had quit smoking 7 years ago. She had strong family history for heart disease, hypertension, diabetes, and dyslipidemia. On physical examination, body mass index was 26 kg/m<sup>2</sup>. She had costovertebral tenderness, tachycardia, and hypotension that did not respond to crystalloids and subsequently required vasopressors.

Lactic acidosis was present (8.4 mmol/L), as well as leukocytosis (10 900) with left shift (segments 77% and bands 9%). Platelet count was 76 000. Glycosylated hemoglobin A1C was 14% despite multiple antidiabetic drugs but before empagliflozin was added. Kidney function was acutely compromised (creatinine 3.5, blood urea nitrogen 57 mg/dL) given shock, severe sepsis, and hypovolemia. Liver function tests were abnormal (aspartate aminotransaminase 81 U/L, alanine transaminase 79 U/L, alkaline phosphatase 160, and total bilirubin 1.6). Serum glucose was >500 mg/dL, and urine analysis showed a large amount of glucose, rare bacteria, and white blood cells <1/HPC. Imaging of the abdomen showed severe EPN of the left kidney involving 80% of the parenchyma and radiological signs of ischemic colitis with presence of portal venous gas and air within branches of the superior mesenteric vein. (Fig. 1 and 2).

Initial antibiotic treatment was with cefepime, vancomycin, and metronidazole. An emergent nephrectomy was necessary, and the bowel was found to be viable. Postoperative management in intensive care unit (ICU) was required, and she had a successful recovery. A pan-susceptible *Escherichia coli* was isolated; therefore, antibiotics were soon de-escalated.

After surgery and a short ICU stay, the patient recovered and was discharged home. She was instructed to take cefpodoxime 200 mg twice daily for 7 days (day 14 after nephrectomy), while empagliflozin was discontinued. Two months later, she was admitted to the hospital after a near-syncope episode at home and abdominal pain. She was found to have a small bowel obstruction and was decompensated quickly. Unfortunately, the patient experienced a cardiopulmonary arrest during which she had a massive emesis and aspiration of gastric contents. After full resuscitation and ICU stay, she did not recover and had evidence of anoxic brain injury. Due to critical condition following cardiopulmonary collapse, surgery was never performed. The patient's family decided to withdraw life support and the patient died.

### Discussion

SGLT2 inhibitors have been associated with cardiovascular, renal, and metabolic benefits. The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial demonstrated a significant reduction in death from cardiovascular causes.<sup>3</sup> Hospitalizations due to heart failure and death from any cause were seen in patients

### Highlights

- SGLT-2 inhibitors have positive impact on blood pressure and kidney function in patients with diabetes with or without heart failure.
- SGLT2 inhibitors decrease glucose reabsorption in the tubules, therefore increasing concentrations of glucose in the urine predisposing to UTI, including pyelonephritis.
- The medical community should be aware of potential and rare complications of SGLT2 inhibitors and advise patients how to recognize early symptoms and seek medical attention promptly.

### Clinical Relevance

This case describes the presence of rapid developing emphysematous pyelonephritis in the absence of an anatomical anomaly or obstruction of the urinary tract while diabetes was treated with empagliflozin.

with diabetes, who were treated with empagliflozin (10–25 mg daily) in addition to standard care compared with patients with no exposure to SGLT2 inhibitors.<sup>3</sup> Similar cardiovascular benefits were shown in the CANagliflozin cardioVascular Assessment Study (CANVAS) trial, although those patients treated with canagliflozin had significantly higher incidence of distal amputations.<sup>4</sup> Moreover, the Multicenter Trial to Evaluate the Effect of Dapagliflozin on



Fig 1. Computed tomography of the abdomen showing emphysematous left kidney (coronal plane).



**Fig. 2.** Computed tomography of the abdomen reveals presence of gas in the left renal parenchyma entirely encapsulated (axial plane).

the Incidence of Cardiovascular Events (DECLARE-TIMI58) trial did not show an increase or decrease of major adverse cardiovascular events in patients taking dapagliflozin; however, it showed to be beneficial in lowering cardiovascular deaths as well as hospitalizations related to heart failure.<sup>5</sup> Furthermore, the positive effects of such drugs on cardiovascular health are thought to be by promoting weight loss, reducing blood pressure, and decreasing vascular resistance as well as lowering serum uric acid levels.<sup>6–12</sup> Other clinical benefits from SGLT2 inhibitors include slowing the progress of nephropathy among patients with diabetes and high cardiovascular risk (12.7%) when compared to patients in the placebo group (18.8%).<sup>13</sup> These benefits are linked to the renovascular protection associated with decrease in hyperfiltration once the higher concentration of sodium activates the tubuloglomerular feedback in the macula densa, leading to afferent vasomodulation.<sup>12,14</sup> Nevertheless, SGLT2 inhibitors have been associated with high incidence of urinary tract infection (UTI), including severe pyelonephritis and severe cases of Fournier's gangrene.<sup>15</sup> Patients with diabetes treated with SGLT2 inhibitors have a 3–5-fold increased risk for genital infections.<sup>16</sup> A meta-analysis of 12 randomized placebo-controlled trials on patients with uncontrolled diabetes (highest glycohemoglobin 12%) evaluating dapagliflozin vs placebo was able to determine an incidence of UTI between 3.6% and 5.7% in the studied group.<sup>17</sup> Only 1<sup>4</sup> of all 3 landmark studies on SGLT2 and cardiovascular outcomes<sup>3–5</sup> showed an association of these drugs with increased urinary frequency, and mycotic UTI was the most common in all 3 trials. EPN is a potentially life-threatening condition if not suspected, promptly diagnosed, and properly treated. Over the last 2 decades, its mortality has been reduced to nearly 13% due to rapid recognition and appropriate treatment.<sup>18</sup> Septic shock is the most common fatal complication among these patients,<sup>19</sup> and available guidelines have shown to decrease sepsis-related mortality<sup>20</sup> by implementing and quickly executing a checklist that would guide clinicians toward the best decisions for patients. There is strong evidence supporting that EPN occurs almost entirely in people with diabetes, with women being affected in most cases.<sup>2,18</sup> Pathogenesis seems to play an important role in

the appearance of EPN in these 2 populations, but it is not well defined yet. High levels of glucose within the tissue, presence of gas-forming pathogens, impaired vascular blood supply, and host immunity are predisposing factors in the development of EPN under persistent hyperglycemia.<sup>21</sup>

Acute EPN results mostly from bacterial invasion of the renal parenchyma.<sup>18</sup> Once the microorganisms start to proliferate and ascend the urinary tract, the culprit bacteria produce gas from anaerobic metabolism, especially fermentation of glucose.<sup>21</sup> Furthermore, the renal parenchyma shows features of abscess formation, vascular thrombosis, and necrotizing tissue.<sup>19</sup> All these microscopic characteristics may explain the severity of the kidney anatomical disruption and overall clinical presentation. Currently, the gold standard therapy is surgical resection of the affected kidney, although there is literature supporting a less invasive approach such as percutaneous drainage or even antibiotics alone.<sup>18,20,22,23</sup>

A specific relationship between SGLT2 inhibitors and EPN has not been strongly established. In fact, there are a few cases reported that correlate SGLT2 inhibitors with EPN, each one in a particular context and some differences distinguishing one from the other. A case report linked the management with empagliflozin to EPN but in a patient with immunosuppression and vesicoureteral reflux, and the isolated pathogen was *Candida glabrata*.<sup>24</sup> Another report highlights the relationship of canagliflozin with EPN, although the clinical presentation is relevant for the presence of nephrolithiasis, which by itself can precipitate a severe form of pyelonephritis.<sup>25</sup> A recent case of a patient with diabetes and a fungal mass associated with empagliflozin has been reported.<sup>26</sup>

In this case, the glucose plasma concentration and the elevated glycosylated hemoglobin A1C demonstrate a challenging case that most clinicians often encounter, but not only the fact of the unusual diabetes presentation is unforeseen, but also signs of ischemic colitis with presence of portal venous gas and air within branches of the superior mesenteric vein are reported probably secondary to the intra-abdominal disseminated infection. These rare radiological findings associated with EPN are uncommon based on the limited documented evidence and much less in a patient with diabetes and recent introduction of empagliflozin. Certainly, this drug could have correlated with the severity of the disease, especially in a female patient with difficult-to-control hyperglycemia, both of which are the most common risk factors associated with EPN.

## Conclusion

This rare case features the severity of EPN in a patient at high risk given her sex and uncontrolled diabetes, despite being treated with several antidiabetics including empagliflozin. SGLT2 inhibitors could potentially precipitate a severe form of UTI in patients with the aforementioned risk factors; however, further evidence and research are warranted. Education and awareness regarding newer drugs and potential adverse reactions are needed among patients and providers; emphasizing the risk of UTI in patients with diabetes, regardless of the use of antidiabetics. This case has been previously presented in a scientific meeting in an abstract format.<sup>27</sup>

## Disclosure

The authors have no multiplicity of interest to disclose.

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Consent was obtained from the patient's spouse. Previously published as an abstract.

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