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COMPLICATIONS SECONDARY TO THE USE OF SGLT2 INHIBITORS IN ONCOLOGICAL PATIENTS: A SERIES OF 5 CASES

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ABSTRACT

Sodium-glucose cotransporter-2 (iSGLT2) inhibitors, which include dapagliflozin, canagliflozin and empagliflozin, are a class of drugs initially used in the oral treatment of diabetes, heart failure and renal failure. They target the reabsorption of glucose in the kidney. Although they bring benefit to patients with these conditions and in general produce few adverse effects, in some cases, iSGLT2 can cause serious adverse effects such as metabolic acidosis, and fungal or bacterial urinary infections. Oncology patients, who in general have a weak immune system and are usually treated with chemotherapy and/or immunotherapy, are more susceptible to this type of adverse events than other patients. For this reason, it is necessary to adequately select the patients eligible to receive this type of drug and evaluate the potential benefits for them. In this series of five cases, we present two cases of metabolic acidosis, two cases of bacterial urinary sepsis, and one case of fungal urinary sepsis that occurred in patients admitted to the Medical Oncology Department of the University Hospital of Salamanca in 2023.

KEYWORDS

iSGLT2, cancer, metabolic acidosis, sepsis

LEARNING POINTS

- Adverse events associated with iSGLT2 can lead to serious complications in immunocompromised patients. There have been cases of prolonged admissions with high morbidity and mortality due to bacterial or fungal infections and metabolic acidosis, all of which are side effects derived from their use.
- In oncology patients, an adequate evaluation of the risk-benefit balance must be conducted before the introduction of new drugs.
- Studies should be conducted to assess the risk of serious adverse effects in oncology patients undergoing treatment with chemotherapy or immunotherapy.

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INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, which include dapagliflozin, canagliflozin and empagliflozin, are a class of drugs initially used in the oral treatment of diabetes, and that target the reabsorption of glucose in the kidney. Their effects include increased osmotic diuresis, natriuresis and glycosuria. They cause afferent arteriolar vasoconstriction by reducing glomerular pressure and proteinuria, promote hypercatabolic metabolism, which involves increased lipolysis and ketosis. Furthermore, they reduce systolic and diastolic blood pressures, modulate hyperactivation of the sympathetic nervous system, and provide reduced cardiac preload and afterload. Apart from being indicated as an oral antidiabetic, some SGLT2 inhibitors such as empagliflozin and dapagliflozin have been shown to have cardiovascular benefits in patients with heart failure (HF) by reducing mortality and hospitalization. These drugs are currently indicated as first-line treatment in patients with heart failure with reduced ejection fraction (HFrEF). In addition, the afferent arteriolar vasoconstriction in the kidneys related to the renin-angiotensin system blockade benefits patients with chronic kidney failure (CKD), regardless of their diabetes status[1,2].

We present a series of five cases of patients with active cancer who were admitted to the Department of Medical Oncology of the University Hospital of Salamanca (Spain) due to complications derived from the use of SGLT2 inhibitors.

CASE REPORT 1

The patient was an approximately 60-year-old woman with a medical history of arterial hypertension (AHT), hyperparathyroidism, and type 2 diabetes mellitus (T2D), with no toxic habits. Her usual medication included candesartan/hydrochlorothiazide, metformin, atorvastatin, dulaglutide, insulin glargine and empagliflozin.

In 2019, she had been diagnosed with a low-grade neuroendocrine tumour of the lung (stage IV) and she was treated with everolimus.

In July 2023, she was admitted to the emergency department with intense abdominal pain in the left hypochondriac region. An emergency analysis revealed lipase 437 U/l, LDH 437 U/l, glucose 215 mg/dl, C-reactive protein (CRP) 14.19 mg/dl, pH 7.12, bicarbonate 8.4 mmol/l, lactate 1.4 mmol/l *(Table 1)*. The urine analysis showed glycosuria of approximately 100 mg/dl. An abdominal CT scan revealed splenic infarction. She was hospitalized for pain management and close monitoring. Oral antidiabetics were suspended, and insulin was administered based on glucose levels. Treatment was initiated with bicarbonate and intravenous (IV) rehydration combined with 24-hour fasting due to the pancreatic reaction associated with the splenic infarction. The analytical alterations were resolved 72 hours after the suspension of SLGT2 inhibitors, and the patient was discharged.

CASE REPORT 2

The patient was a 70-year-old man with a medical history of AHT, T2D and asthma. He had been a smoker of over 60 cigarettes per day for 45 years and a light drinker.

He regularly received medication that included eplerenone, acetylsalicylic acid, bisoprolol, sacubitril/valsartan, levothyroxine, dapagliflozin and domiciliary oxygen therapy.

In May 2022, he was diagnosed with clear cell renal cell carcinoma (stage IV) with mediastinal, lung and right acetabular involvement. He received radiotherapy for the acetabular involvement and started systemic treatment with pembrolizumab and axitinib, which were still part of his treatment at the time of admission.

In October 2023, he was admitted to the emergency department with diarrhoea and vomiting, associated with decreased consciousness. The blood analysis showed

	Day 1	Day 2	Day 3
pH	7.12	7.35	7.4
Bicarbonate (mmol/l)	7.8	18.6	21.2
Lactate (mmol/l)	1.4	1.3	1
Base excess (mmol/l)	-19.9	-5	-2.3
Creatinine (mg/dl)	0.42	0.39	0.42
Sodium (mmol/l)	135	140	138
Potassium (mmol/l)	4.4	3.6	3.5
Chloride (mmol/l)	106	108	106
Anion gap	25.6	17	14.2

Table 1. Daily laboratory results of case 1, showing the resolution of euglycemic metabolic acidosis within a span of 48 hours.

	Day 1	Day 2	Day 5
pH	7.04	7.25	7.39
Bicarbonate (mmol/l)	10.3	16.7	24.8
Lactate (mmol/l)	1.7	1.4	1.9
Base excess (mmol/l)	-19.7	-9.9	-0.2
Creatinine (mg/dl)	4.11	2.33	1.56
Sodium (mmol/l)	133	138	134
Potassium (mmol/l)	6.5	4.7	4.3
Chloride (mmol/l)	106	113	102
Anion gap	23.2	13.3	14.2

Table 2. Laboratory results of case 2, showing the resolution of euglycemic metabolic acidosis within a span of 96 hours.

glucose 140 mg/dl, creatinine 4.11 mg/dl, sodium 133 mmol/l, potassium 6.5 mmol/l, lactate 1.7 mmol/l, pH 7.04, bicarbonate 10.3 mmol/l, chloride 106 mmol/l, anion gap 23.2 mEq/l *(Table 2)*.

The clinical diagnosis was acute prerenal kidney failure secondary to diarrhoea. He also presented euglycemic high anion gap metabolic acidosis (> 12 mEq/l), probably induced by SGLT2 inhibitors.

Treatment was initiated with furosemide, bicarbonate, exchange resins, and rehydration. Eplerone, sacubitril/valsartan, and dapagliflozin were suspended. After 48 hours, the patient regained normal consciousness and showed improvement in the blood analysis *(Table 2)*. After 5 days of hospitalization, he was discharged with good clinical and analytical evolution.

CASE REPORT 3

The patient was a 75-year-old woman with a medical history of atrial fibrillation (AF), HF, AHT, CKD and a herniated disc at L4-L5, with no toxic habits. She received regular medication that included apixaban, eplerenone, bisoprolol, dapagliflozin and oral iron supplements.

In July 2023, she was diagnosed with cecum adenocarcinoma (stage IV) with lung involvement and loss of expression of repair genes. She was received first-line treatment with pembrolizumab.

In October 2023, she was admitted to the emergency department with a temperature of 38.7 ºC, tachypnoea and decreased consciousness. Her arterial pressure was 73/42 mmHg. The blood analysis showed creatinine 1.51 mg/dl, NT-proBNP 24901 pg/ml, CRP 4.85 mg/dl, procalcitonin 0.2 ng/ml, leukocytes 6.54 x 10^3/µl. The urine test showed urine pH 5.5, glycosuria 500 mg/dl, positive nitrites and leukocyturia >1350 /µl. A urine culture was performed and revealed the presence of *Enterobacter cloacae* >100.000 CFU/ml susceptible to ciprofloxacin and trimethoprim/sulfamethoxazole. The patient was hospitalized with urosepsis associated with use of SGLT2 inhibitors, and antibiotic therapy was initiated with ciprofloxacin and IV rehydration. During her stay, she presented decompensated heart failure in the context of sepsis with oxygen desaturation (74%) which required high-flow oxygen therapy, methylprednisolone, morphine chloride and furosemide for clinical control. She was discharged after 9 days when the clinical and analytical symptoms resolved.

CASE REPORT 4

The patient was an 83-year-old man, with a medical history of AHT, dyslipidemia and ischemic cardiomyopathy, an ex-smoker of 20 cigarettes per day for 45 years. He received regular medication that included acetylsalicylic acid, amlodipine, bisoprolol, furosemide and dapagliflozin.

In May 2020, he was diagnosed with squamous cell carcinoma of the lung (stage IV) with contralateral involvement (PD-L1 10%). He received second-line treatment with nivolumab.

In April 2023, the patient was admitted to the emergency department with decreased consciousness and a temperature of 39.1 ºC. AT was 83/52 mmHg. An emergency blood analysis showed creatinine 1.5 mg/dl, CRP 14.09 mg/dl, procalcitonin 0.47 ng/ml, 25 x 10^3/µl leukocytes, 18.88 x 10^3/µl neutrophils. The urine analysis showed urine pH 7.5, glycosuria 300 mg/dl, negative nitrites, and leukocyturia > 150/µl. A urine culture was performed and revealed *Escherichia coli* >100.000 CFU/ml susceptible to gentamicin, cefixime and cefuroxime. The clinical diagnosis was urosepsis and the patient was admitted to the Department of Medical Oncology and treated with gentamicin. The symptoms resolved after 7 days of hospitalization and the patient was discharged.

CASE REPORT 5

The patient was a 74-year-old man with a medical history of AHT, DM and chronic HF, an ex-smoker of 40 cigarettes per day for 50 years and a non-drinker. He received regular medication with canagliflozin, metformin, semaglutide, acetylsalicylic acid and bisoprolol.

In June 2023, he was diagnosed with invasive urothelial carcinoma pT4 N1 and had undergone cystoprostatectomy and pelvic lymphadenectomy. In September 2023, he presented pulmonary and lymph node involvement and started chemotherapy with carboplatin and gemcitabine, which he still was receiving at the time of admission.

He was admitted to the Department of Medical Oncology with a temperature of 38 ºC and decreased consciousness. He presented severe hypotension (AP: 63/42 mmHg), elevated acute phase reactants (CRP: 22.13 mg/dl) and acute prerenal kidney failure (Cr: 2.89 mg/dl). Dopamine perfusion and abundant fluid replacement were administered. A urine culture was performed and revealed *Candida glabrata*. The diagnosis was a severe fungal urinary tract infection (UTI) associated with the use of SGLT2 inhibitors. The patient received treatment with anidulafungin for 14 days with good evolution in the clinical and analytic parameters, and he was discharged after suspending the SGLT2 inhibitors.

DISCUSSION

Despite the evidence of the efficacy of drugs belonging to the family of SGLT2 inhibitors in the treatment of common disorders associated with significant morbidity and mortality rates such as T2D, HF and CKD, we believe that it is necessary to acknowledge their potential secondary effects in certain categories of patients. These secondary effects include severe hypoglycemia, diabetic ketoacidosis, severe bacterial or fungal UTIs, necrotizing fasciitis of the perineum (Fournier's gangrene) and hypersensitivity reactions[3-5].

In 2015, the U.S. Food and Drug Administration (FDA) published a report that warned of an increased risk of metabolic acidosis with mild hyperglycemia in patients treated with SGLT2 inhibitors[6]. The exact cause behind this process is unknown, although two possible mechanisms that might be involved are the increased renal glucose loss that reduces its availability as an energy substrate, and the

	CASE REPORT 1	CASE REPORT 2	CASE REPORT 3	CASE REPORT 4	CASE REPORT 5
Sex	Woman	Man	Woman	Man	Man
Age range	50-60	60-70	70-80	80-85	70-80
Oncological diagnosis	Low grade neuroendocrine tumor pT2a N2	Clear cell renal cell carcinoma stage IV	Cecum adenocarcinoma stage IV	Squamous cell carcinoma of the lung stage IV	urothelial carcinoma stage IV
Year of diagnosis	2019	2021	2023	2020	2023
Progression, PFS	Yes, 34 months	No, 29 months	No, 3 months	Yes, 32 months	Yes, 3 months
Line of treatment	Second line	First line	First line	Second line	First line
Oncological treatment	Everolimus	Pembrolizumab-axitinib	Pembrolizumab	Nivolumab	Carboplatin-gemcitabine
Toxic habits	Tobacco	Tobacco, alcohol	No	Tobacco, alcohol	Tobacco
Comorbidities	AHT, hyperparathyroidism, DM	AHT, DM, dyslipidaemia, asthma, HF, hypothyroidism, L4-L5 spinal disc herniation	Atrial fibrillation, chronic HF, AHT, dyslipidaemia, repeated UTI, CKD and L4-L5 spinal disc herniation	AHT, dyslipidaemia and ischemic cardiomyopathy	AHT, DM and chronic HF
Treatments	Atorvastatin, candesartan, hydrochlorothiazide, dulaglutide, insulin glargine, empagliflozin	Ebastine, eplerenone, acetylsalicylic acid, pregabalin, bisoprolol, sacubitril-valsartan, omeprazole, salbutamol, fluticasone, febuxostat, levothyroxine, dapagliflozin and oxygen therapy	Apixaban, duloxetine, eplerenone, bisoprolol, omeprazole, dapagliflozin, mirtazapine, atorvastatin, megestrol and oral iron.	Acetylsalicylic acid, amlodipine, atorvastatin, bisoprolol, dutasteride/ tamsulosin, furosemide, dapagliflozin and omeprazole	Canagliflozin, metformin, semaglutide, acetylsalicylic acid, omeprazole and bisoprolol.
Reason for emergency admission	Abdominal pain, splenic infarct	Decreased consciousness, diarrhoea, vomiting, acute kidney failure	Decreased consciousness, hypotension, fever	Decreased consciousness, hypotension, fever	Decreased consciousness, hypotension, fever
Complications	Euglycemic metabolic acidosis, elevated anion gap	Euglycemic metabolic acidosis, elevated anion gap	Bacterial urosepsis	Bacterial urosepsis	Fungal urosepsis
Resolution	Yes	Yes	Yes	Yes	Yes

Table 3. Clinical characteristics of the cases reported in our series. The table includes information on pre-existing comorbidities and current medication. In case 1, the administered SGLT2 inhibitor was empagliflozin, while in cases 2-4 was dapagliflozin, and in case 5 canagliflozin.

decrease in renal clearance of ketone bodies due to the stimulation of tubular reabsorption. To minimize the risk of these complications, the suspension of the use of SGLT2 inhibitors is indicated at least 24 hours prior to elective surgery, prior to intense physical activities and invasive procedures, or in situations that may involve prolonged fasting, as in case 1 of our series. In the described cases 1 and 2, the dissociation between glycemia and glycosuria, the low or absent ketonuria, and the lack of elevation in serum lactate led to suspicion regarding the involvement of SGLT2 inhibitors as an underlying mechanism of acidosis.

With regards to the urinary tract, one of the most common adverse reactions associated with the use of SGLT2 inhibitors are UTIs of fungal or bacterial origin (cases 3, 4 and 5). UTIs appear in between 2.3% and 15.6% of all patients treated with these drugs. Therefore, SGLT2 should not be used in patients with an history of repeated or recent UTIs. The patient in case 3 had a history of repeated UTIs (more than 5 episodes over the last 24 months), and in case 4 there was a history of two mild UTIs over the past year. The patient in case number 5 had a bacterial UTI the previous month. Even though, therapy with SGLT2 inhibitors was decided to be started or maintained for all patients.

If, during treatment with SGLT2 inhibitors, an isolated episode of UTI occurs in an otherwise healthy patient, it is possible to continue treatment with this type of antidiabetic drugs after their recovery. On the other hand, when these drugs trigger a severe infection, as in the three cases of urosepsis described in our series, it is necessary to suspend their use[5].

The mechanism through which these drugs lead to the development of urinary infections is still not well-known. One hypothesis is that glycosuria promotes the presence of fungi and bacteria in the urinary tract, although an increased frequency of UTIs has not been described in patients with familial glycosuria. This condition is caused by a mutation in the *SLC5A2* gene that encodes the SGLT2 channel. On the other hand, the hyperglycemia of patients with diabetes mellitus is associated with a weakening a weakened immune system, promoting the adherence of yeasts and other pathogens to the endothelium, and decreasesing the bactericidal activity of polymorphonucleated cells, among other effects[5,6]. Therefore, the immunosuppressant effect of chronic hyperglycemia in a compromised immune system combined with glycosuria, could trigger the development of urinary infections.

In spite of the widespread acceptance and implementation of these drugs in daily clinical practice, along with the clinical benefits demonstrated in different studies, we believe that it is necessary to adequately select patients who will receive treatment with SGLT2 inhibitors whenever there is a possibility of severe secondary complications, as those described in our case series. For patients with active cancer and a weakened immune system, it is essential to conduct a thorough analysis of the risk-reward ratio for each new drug introduced.

Further studies are necessary to determine the association between pre-existing comorbidities and the risk of developing severe complications secondary to the use of SGLT2 inhibitors.

REFERENCES

1. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 2020;**17**:761-772.
2. Dubrofsky L, Srivastava A, Cherney DZ. Sodium-Glucose Cotransporter-2 Inhibitors in Nephrology Practice: A Narrative Review. *Can J Kidney Health Dis* 2020;**7**:2054358120935701.
3. Tsai WC, Hsu SP, Chiu YL, Yang JY, Pai MF, Ko MJ, et al. Cardiovascular and renal efficacy and safety of sodium-glucose cotransporter-2 inhibitors in patients without diabetes: a systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open* 2022;**12**:e060655.
4. Zhang L, Tamilia M. Euglycemic diabetic ketoacidosis associated with the use of a sodium-glucose cotransporter-2 inhibitor. *CMAJ* 2018;**190**:E766-E768.
5. Esteban-Jiménez O, Navarro-Pemán C, Urieta-González L. Seguridad de los iSGLT-2. Revisión de las reacciones adversas notificadas a nivel nacional. *Semergen* 2018;**44**:23–29.
6. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections [Internet]. U.S. Food and Drug Administration. FDA; 2023 [last accessed: November 6, 2023]. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious