CASE REPORT

Dapagliflozin as a cause of acute tubular necrosis with heavy consequences: a case report

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Abstract A 50-year-old man with type II diabetes, hypertension and dyslipidemia, presented with non-oliguric acute kidney injury (AKI) and anemia. Renal biopsy showed acute tubular necrosis (ATN) with extensive cytoplasmic vacuolization and areas of tubulitis. These findings were ultimately attributed to dapagliflozin, which he started 3 months earlier due to poor glycemic control. ATN with similar microscopic findings has been described with larger doses of dapagliflozin in non-clinical trials. Our patient was started on dialysis and remained dialysis-dependent for 4 weeks while his renal function improved gradually thereafter. Sixteen months after initial presentation he is being followed as an outpatient with chronic kidney disease (CKD) stage 3a. Dapagliflozin belongs to a novel class of antidiabetic drugs for which clinical trials show great beneficial effects on cardiovascular outcomes and glycemic control and as with many new drugs, their safety profile is being constantly revised. We report the first biopsy-proven ATN caused by dapagliflozin. Great caution together with continuous monitoring of renal function is advised when implementing SGLT-2 inhibitors in clinical practice.

Keywords Acute tubular necrosis (ATN) · Dapagliflozin · SGLT-2 inhibitors · Diabetes

Introduction

Sodium–glucose cotransporter type 2 (SGLT-2) is responsible for the reabsorption of approximately 90% of filtered glucose in the kidney. The glucuretic effect of SGLT-2 inhibitors leads to improved glycemic control, weight loss and blood pressure reduction through osmotic diuresis. While awaiting the results of important phase III studies [1–3] regarding the widespread use of SGLT-2 inhibitors in clinical practice, published data from the EMPA-REG study have already created great expectations over the utility of these new antidiabetic drugs. Their beneficial effects on cardiovascular mortality and morbidity could be a major breakthrough in comprehensive diabetes management [4]. On the other hand, caution is still advised regarding possible adverse events like bladder cancer, bone fractures and AKI [5]. These large randomized controlled trials are expected to report in the following 2 years, shedding light on such matters.

Herein we report the case of a man with kidney biopsy-confirmed severe ATN due to dapagliflozin use. This is probably the first report of such an association in clinical practice.

Case report

A 50-year-old man presented with fatigue, anorexia and nausea. He had a history of diabetes, hypertension and dyslipidemia. His medication consisted of vildagliptin, metformin, atorvastatin, carvedilol, candesartan and low-dose aspirin, all of which he was receiving for at least 3 years. Three months before admission dapagliflozin 10 mg/day (Forxiga) was added to his regimen due to poor glycemic control, which he stopped after approximately 11 weeks, when he

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started feeling unwell. The patient reported a gradual worsening of his symptoms over the next few weeks, without any sign suggestive of a major clinical event. Throughout this 3-month period he reported normal ambulatory blood pressure and urine output, which were confirmed during his hospitalization. Physical examination was unremarkable. Laboratory results revealed AKI with serum creatinine 22.4 mg/dl, urea 467 mg/dl, and anemia with hemoglobin 9.5 g/dl (Table 1). All the above parameters were within normal values 3 months before presentation. Urinalysis showed proteinuria, glucosuria, pyuria, hematuria and the presence of few granular (described as “muddy brown”) and waxy casts. Urine culture was sterile and renal ultrasound was normal. Dialysis was initiated through a right internal jugular central venous catheter.

A kidney biopsy was performed 2 days after admission. Serum protein electrophoresis, immunofixation, complement levels, antinuclear antibodies, ANCA, anti-GBM, ferritin, vitamin B12 and folate levels were normal. No evidence of hemolysis was seen on peripheral blood smear and direct Coombs was negative. Anemia’s diagnostic workup was completed with a bone marrow biopsy which revealed no abnormalities. Thus patient’s anemia was attributed to AKI. Kidney biopsy revealed diffuse ATN with cytoplasmic irregular vacuolization, denuding of tubular basement membranes and focal findings of tubulitis. Few eosinophils were noted among mononuclear cells in the interstitium. Immunohistochemical assessment of cell proliferation using ki-67 marker showed evidence of active regeneration (Fig. 1).

The presence of non-oliguric AKI, taken together with the absence of physical findings or significant clinical

events, pointed to the diagnosis of nephrotoxic ATN. Our team focused on medical history and the patient was interviewed thoroughly. Pre-renal AKI was ruled out based on his reporting of normal blood pressure at home, absence of oliguria and an unremarkable physical examination. It should be stressed out that our patient visited the emergency department being ambulant. Common nephrotoxins, namely NSAIDs, aminoglycosides, illicit drugs, mushrooms and herbs, including local aristolochia species, and heavy metal exposure were ruled out on multiple occasions. Dapagliflozin was considered the most probable cause by each of the authors, after obtaining the patient’s history. Four weeks after initial presentation our patient remained dialysis-dependent. We decided to initiate a short course of corticosteroids starting with 32 mg of methylprednisolone daily, rethinking the possibility of AIN and planning a follow-up biopsy to assess prognosis. Two days later his serum creatinine started to decline and the second biopsy was cancelled. We believe that this rapid improvement could not be attributed to corticosteroid therapy, since active regeneration was already visible in our patient’s biopsy specimen 4 weeks earlier. Nevertheless, we continued corticosteroids for up to 3 months with gradual tapering until discontinuation. The patient was discharged 5 weeks after presentation with a serum creatinine of 2.5 mg/dl. After 14 months of follow-up, his serum creatinine is 1.5 mg/dl accounting for an eGFR (CKD-EPI) of 53 ml/min/1.73 m².

Discussion

SGLT-2 inhibitors emerged as a novel class of antidiabetic drugs in 2009 when dapagliflozin was first introduced in human trials. FDA approval of dapagliflozin was delayed until 2014 due to safety concerns, regarding possible linkage to bladder and breast cancer. Since then, numerous studies have revealed beneficial effects of this class of antidiabetics on cardiovascular outcomes, blood pressure, weight loss and glycemic control [6, 7]. Data analysis of the EMPA-REG study also showed that empagliflozin retards the progression of CKD in patients with type 2 diabetes at high cardiovascular risk [8], possibly by reduction of intraglomerular pressure and amelioration of diabetic hyperfiltration [9].

Regulatory reports raised concerns about safety issues regarding genital infections, bone fractures, cancers, volume depletion, acidosis and kidney disease, although scientific data did not confirm statistical significance of such associations, apart from an increased incidence of mycotic genital infections with the use of SGLT-2 inhibitors compared to placebo [6]. In June 2016, after 101 regulatory reports during a 31-month period, the FDA issued a strengthened warning about the risk of AKI with the use of canagliflozin or dapagliflozin. In approximately half of the cases,

Table 1 Patient’s laboratory results upon admission

WBC	12,600/ μ L	Urea	467 mg/dl
NEUT%	76.9	Glu	107 mg/dl
LYMPH%	10.5	Creatinine	22.4 mg/dl
MONO%	11.3	Uric acid	6.0 mg/dl
EOS%	0.8	ALP	87 U/L
BASO%	0.5	AST	9 U/L
HGB	9.5 g/dl	ALT	22 U/L
HCT	26.8%	γ -GT	23 U/L
MCV	72.7 fl	CPK	74 U/L
PLT	363,000/ μ L	LDH	371 U/L
Urine dipstick		Potassium	5.4 mmol/L
SG	1.015	Sodium	132 mmol/L
pH	5	Bil-T	0.6 mg/dl
Blood	+	Bil-D	0.2 mg/dl
Pro	++	CRP	3.5 mg/dl
Glu	+	Amylase	149 U/L
Ket	Trace		
Nit	–	24-h urine protein	0.72 g

Fig. 1 **a** Acute tubular injury with epithelial cell coarse vacuolization or flattened epithelium with detached cells leaving areas of tubular basement membrane covered by a thin layer of cytoplasm from adjacent cells (arrowhead). Necrotic luminal debris (transparent arrow). Regeneration with mitosis (black arrow). Interstitial mononuclear infiltration is also observed (HE $\times$ 200). **b** Flattened tubular epithelium with diminishing or loss of brush borders and cytoplasmic vacuolization (HE $\times$ 200). **c** Cytoplasmic vacuolization in higher magnification (HE $\times$ 400). **d** Among the interstitial inflammatory cells, some eosinophils are discerned (white arrows) (HE $\times$ 200). **e** Tubulitis in a non-atrophic tubule (black arrows) (PAS $\times$ 200). **f** Immunostain for the proliferation marker Ki-67. Note positive nuclear staining in several tubular cells (Ki-67 $\times$ 200)

AKI occurred within 1 month of drug initiation while most patients improved after drug discontinuation. Some patients had evidence of volume depletion or were taking potential nephrotoxic agents [10]. A recent article by Hahn et al. highlights possible pathophysiologic mechanisms of AKI caused by SGLT-2 inhibitors. Osmotic diuresis can lead to volume depletion, while uricosuria as a consequence of increased glucose–uric acid exchange in the proximal tubule, has the potential of direct tubular damage through crystal formation. High glucose concentrations in renal tubules may lead to altered fructose metabolism in S3 proximal tubular cells and eventually to local tubular injury from increased oxidative stress, uric acid generation and release of inflammatory chemokines [11]. Non-clinical studies of SGLT-2 inhibitors have shown various nephrotoxic properties involving the renal tubules, such as tubular karyomegaly, cell necrosis and interstitial nephritis–tubulitis, presenting in a dose-dependent manner.

Based on our research of the existing literature, this is the first biopsy-proven case of ATN caused by an SGLT-2 inhibitor. We acknowledge the limitation of not being able to provide a definitive link between the drug and the medical condition we encountered. Repetitive medical history obtained by each of the authors during hospitalization of the patient led us to this probable diagnosis of exclusion. Our patient did not show any signs of volume depletion at presentation, nor did he report taking any other drugs or herbs. According to our patient's history and physical findings, a slowly evolving nephrotoxic ATN appeared to us more probable than a drug-induced AIN, in which case signs of hypersensitivity (fever, rash, eosinophilia, etc.) could have existed, and major diffuse interstitial inflammation should have predominated among biopsy findings. Nevertheless, we have to admit that dapagliflozin-induced AIN cannot be ruled out with certainty, since long-standing AIN can be hard to differentiate from ATN even for the most

experienced pathologist [12]. Our patient's biopsy findings fit the description of renal toxicity caused by larger doses of SGLT-2 inhibitors than those used in clinical practice so far, according to data from non-human studies [5].

Our case emphasizes the need for close monitoring of renal function after prescribing SGLT-2 inhibitors. It raises questions about individual renal safety thresholds regarding optimum dosage and patient selection for this class of drugs, and stresses the importance of future research to explore the role of SGLT-2 inhibitors in current clinical practice.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Research involving human participants and/or animals This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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