LETTER TO THE EDITOR

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Empagliflozin-induced severe osmotic nephrosis and acute renal injury in advanced chronic kidney disease

Dear Editor,

Diabetic kidney disease remains a significant disease burden globally and is associated with increased medical costs once chronic kidney disease (CKD) ensues.[1,2] Therefore, optimisation of CKD management through glycaemic control and albuminuria reduction are key strategies for retarding renal deterioration. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new class of antidiabetic medications that has garnered vast interest since increasing evidence has highlighted—apart from their glycaemic lowering properties—notable cardio- and reno-protective effects.[1,2] However, concerns of increased acute kidney injury (AKI) have been raised and a few studies reported tubular injury and osmotic nephrosis with SGLT-2 use.[3,4] We present a case of biopsy-proven osmotic nephrosis and severe acute renal injury following an inadvertent overdose of empagliflozin in a patient with advanced CKD (defined as ≤30mL/min/1.73m^2 body surface area).

Case study. A 65-year-old Malay woman with advanced diabetic kidney disease presented to the emergency department in June 2020 with a 5-day history of vomiting, diarrhoea and lethargy. She had a history of type 2 diabetes, hypertension, and locally advanced endometrial cancer in remission. Her medications consist of an empagliflozin and metformin combination tablet (Jardiance Duo®), linagliptin, glipizide, indapamide and iron polymaltose, all of which she had been receiving from her primary care physician for at least 2 years. Her baseline creatinine was 160–180µmol/L and estimated glomerular rate (eGFR) was 27–32mL/min/1.73m^2. Two weeks before her admission she unintentionally doubled her dose of Jardiance Duo® and thus, took a total of 50mg of empagliflozin and 2g of metformin in a day. On admission, she had oliguric acute kidney injury (kidney disease: improving global outcomes [KDIGO] stage 3) with decompensated high anion gap metabolic acidosis, hyperlactataemia, hypoglycaemia, anaemia and concomitant leukocytosis with neutrophilia. She remained haemodynamically stable, afebrile and clinically euvolemic. Her physical examination was unremarkable. Her laboratory values revealed a serum creatinine of 948µmol/L, urea 34.5mmol/L, potassium 4mmol/L, bicarbonate 8mmol/L, venous pH 7.1, lactate 5.2mmol/L, white cell count 19x10^9/L, haemoglobin 9.2g/dL, and platelets 317 x 10^9/L. Her urinalysis showed active sediments with pyuria (314 white cells/high power field [HPF]) and haematuria (11 red cells/HPF), her urine culture yielded *Escherichia coli* (>100,000 colony-forming unit/mL), and her urine protein: creatinine ratio was 189mg/mmol. Her renal ultrasound was unremarkable apart from changes consistent with CKD and bilateral simple cysts, and her chest X-ray was clear. Secondary workup including serum protein electrophoresis, immunofixation, complement levels, anti-double-stranded DNA, anti-nuclear antibodies, anti-neutrophilic cytoplasmic antibodies, anti-glomerular basement membrane antibodies, hepatitis B, hepatitis C, and human immunodeficiency virus was negative. There was no evidence of haemolysis. Haemodialysis was initiated on admission. Concomitantly, an adequate trial of intravenous volume expansion was administered but this did not lead to significant improvement in kidney function and the patient remained oliguric. A kidney biopsy was subsequently performed which revealed acute tubular necrosis and diffuse osmotic nephrosis on a background of diabetic glomerulosclerosis with 25% tubulointerstitial fibrosis (Fig. 1). Immunofluorescence was negative and there were no electron-dense deposits. The cause of the patient's severe renal injury was multifactorial, owing to the haemodynamic effects of empagliflozin, and contributed by pre-renal AKI secondary to infective gastroenteritis. In the absence of clinical symptoms, or radiological and histological evidence of a urinary tract infection, the bacteriuria was unlikely a major contributory factor of AKI. Treatment was supportive with cessation of empagliflozin. She required 1 session of intermittent dialysis and was weaned off dialysis following renal recovery. Her creatinine improved to a new baseline of 296µmol/L 2 weeks later.

Discussion. Following current evidence-based medicine, the patient was started on empagliflozin for diabetic control, anti-proteinuric effects, and retardation of CKD progression. The proposed mechanism for reno-protection is centred around the reduction of intraglomerular pressure. SGLT-2 inhibitors induce glycosuria by inhibiting the reabsorption of glucose in the proximal tubule. This induces proximal tubule natriuresis that activates tubuloglomerular feedback, leading to afferent vasoconstriction.[5,6] This effect, together with increased tubular back pressure from increased fluid delivery to the distal tubule through osmotic effects

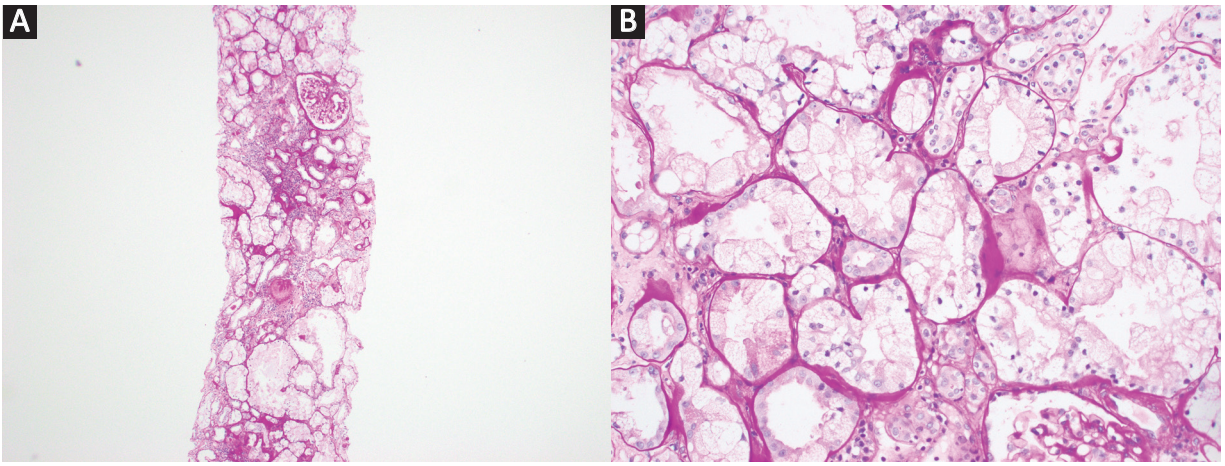

Fig. 1. Histological images, periodic acid-Schiff (PAS) stain. (A) Low power view, x2 magnification; renal cortical tissue with acute tubular injury featuring pale and swollen proximal tubules. (B) High power view, x20 magnification; proximal tubules with isometric fine vacuolisation of the cytoplasm (osmotic tubulopathy) and 25% tubulointerstitial fibrosis.

from non-reabsorbed glucose, consequently lowers intraglomerular pressure.[7] There is limited evidence on the renal sequelae following an overdose. Extrapolating from its vasoconstrictive effect on the afferent arteriole and its diuretic properties, it is not surprising that AKI ensues after an overdose. A case study reported AKI in a healthy patient following an overdose of ipragliflozin (1,500mg) and olmesartan (800mg), which resolved once blood ipraglifozin lowered to an acceptable level.[8] Osmotic nephrosis, the predominant lesion in our patient's histology report, was likely associated with empagliflozin use. This has also been reported with canagliflozin and dapagliflozin.[3] Osmotic nephrosis is associated with the use of hyperosmotic agents and can occur in severe hyperglycaemia, or in glycosuria induced by SGLT-2 inhibitors.[3] It occurs within a week of the inciting event and is acutely reversible on withdrawal of the causative agent. Correspondingly, our patient's kidney function recovered with cessation of SGLT-2 inhibitor use.

Presently, there is limited evidence on SGLT-2 use in patients with advanced CKD, with the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) study being the only published randomised controlled trial showing continued benefit in such patients.[9] Notably, earlier trials did not include patients with advanced CKD. SGLT-2 inhibitor use remains contraindicated at eGFR 30mL/min/1.73m^2 or less. The American Diabetes Association standard of care only endorses SGLT-2 inhibitor use for diabetic patients with eGFR ≥30mL/min/1.73m^2 and macroalbuminuria (>300 mg/g).[10] Further information regarding risk profiling is needed and may be revealed in the ongoing randomised controlled EMPA-KIDNEY trial, which will evaluate the renal and cardiovascular benefits of SGLT-2 in patients with eGFR as low as 20mL/min.

Our patient with advanced CKD developed severe acute renal injury following an overdose of empagliflozin. This is the first reported case of histologically proven osmotic nephrosis associated with empagliflozin. With current evidence showing overwhelming cardiovascular and renal benefits, notwithstanding glucose-lowering effects, SGLT-2 inhibitor use is progressively being incorporated into standard practice. Further studies are needed to delineate individual safety profiles, patient selection and optimal dosing recommendations for its continued use in advanced CKD patients.

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