**Exceptional Case**

**Acute interstitial nephritis due to sodium-glucose co-transporter 2 inhibitor empagliflozin**

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**ABSTRACT**

Biopsy-proven acute interstitial nephritis (AIN) secondary to sodium-glucose co-transporter 2 (SGLT2) inhibitors has not been described previously. Here, we report on the management of a patient with severe acute kidney injury that developed 6 weeks after starting empagliflozin. The cause was confirmed as AIN on renal biopsy. Our patient recovered, without the need for dialysis, with discontinuation of empagliflozin and corticosteroid treatment. This novel clinical observation is likely to occur more frequently as these drugs are increasingly being prescribed, given that recent randomized controlled trials including EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) showed SGLT2 inhibitors can decrease cardiovascular mortality, among other benefits, in high-risk diabetic populations.

**Keywords:** acute interstitial nephritis, acute kidney injury, empagliflozin, SGLT2 inhibitor

**BACKGROUND**

Sodium-glucose co-transporter 2 (SGLT2) inhibitors will likely become more widely used following the results of recent large randomized controlled trials that demonstrated improved cardiovascular outcomes and slower progression of chronic kidney disease (CKD). There is an acknowledged initial drop in glomerular filtration rate (GFR) when starting SGLT2 inhibitor therapy, hypothesized to be due to reduced trans-glomerular pressure, which then should stabilize.

We report a patient who presented with acute kidney injury (AKI) due to biopsy-proven acute interstitial nephritis (AIN), with a convincing timeline to pinpoint empagliflozin as the causative agent. To the authors’ knowledge, this is the first published case of AIN due to an SGLT2 inhibitor.

**CASE REPORT**

A 63-year-old woman presented with a 5-week history of gradually increasing lethargy, malaise and poor appetite. She was found to have Stage 3 AKI by Acute Kidney Injury Network criteria, with a serum creatinine of 381 μmol/L (normal range 50–120 μmol/L), having been 60 μmol/L 3 months prior. She denied any other symptoms, including rash and fever, on systems enquiry. Her background included well-controlled hypertension and Type 2 non-insulin-dependent diabetes for 10 years.
Empagliflozin had been commenced 6 weeks before her presentation. Additional medications—atorvastatin, calcichew D3 forte, diltiazem, enalapril and metformin—were all long-standing (>2 years). She took no over-the-counter medications, supplements or illicit drugs.

On examination, the patient appeared euvolaemic. Blood pressure was 183/86 mmHg. Serum eosinophils, ANCA, anti-glomerular basement membrane, complement, anti-nuclear antibodies, anti-double stranded DNA, rheumatoid factor, anti-Ro, anti-La, immunoglobulins, electrophoresis, free light chains, hepatitis B, C and HIV testing were all either negative or normal. Urinalysis showed erythrocytes + and glucose ++++, in keeping with SGLT2 inhibitor use. Protein-to-creatinine ratio (taken while serum creatinine was stable) was 168 mg/mmol. Albumin creatinine ratio 3 months previously was 3.9 g/mol. Chest radiograph was normal. Ultrasound and computed tomography urogram revealed a normal left kidney and an enlarged right kidney at 157 mm, without calculi or hydronephrosis.

The patient was initially managed with intravenous fluid therapy and suspension of enalapril, empagliflozin and metformin. Despite supportive measures, her creatinine remained static. On Day 7, she underwent a renal biopsy, which confirmed the diagnosis of AIN (see Figure 1). While awaiting the results of the biopsy, her creatinine peaked on Day 10 at 466 μmol/L and she was started on intravenous methylprednisolone 500 mg daily for 3 days, followed by oral prednisolone 60 mg daily. Given the time course, a diagnosis of AKI due to empagliflozin-induced AIN was made, and the drug was permanently discontinued. Her renal function started to improve within 3 days of steroid therapy, but she developed significant glucocorticoid-associated hyperglycaemia that required insulin commencement. Prednisolone was decreased to 35 mg daily after 2 weeks, then gradually tapered down to zero over the next 6 weeks. After 8 weeks of treatment, her creatinine improved to 123 μmol/L.

**DISCUSSION**

SGLT2 inhibitors block proximal renal tubule transport proteins to cause glycosuria and natriuresis [1]. By reducing transglomerular pressure, they can cause an initial drop in GFR, which then should stabilize, similar to angiotensin-converting enzyme inhibitor initiation. The EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial [2] compared empagliflozin to placebo in 7020 patients with Type 2 diabetes at high risk of cardiovascular events. At 3.1-year follow-up, it found a 38% relative risk reduction in death from cardiovascular causes in the empagliflozin arm and slower progression of CKD. Weight loss, blood pressure lowering and a modest reduction of HbA1c are other hypothesized health benefits.

Any drug has the potential to cause drug-induced AIN (DI-AIN); therefore, it is vital to remain vigilant when initiating any medication. Our patient presented in an oligosymptomatic fashion without the classic findings of fever, rash or eosinophilia. This non-specific presentation is common in DI-AIN [3] but can make diagnosis challenging. Renal biopsy therefore remains the gold standard for diagnosis [4].

The strong temporal relationship in our case argues convincingly that empagliflozin was the causative agent of the biopsy-substantiated AIN, given that the patient’s symptoms began 1 week after drug commencement. We treated with 8 weeks of corticosteroids, in keeping with evidence that longer durations do not achieve greater renal recovery [3]. Our patient suffered the impact of hospital admission, the risks of renal biopsy and required insulin for glucocorticoid-induced hyperglycaemia.

The potential benefits of SGLT2 inhibitors greatly outweigh the risks of side effects; a small initial drop in GFR due to haemodynamic effects should be expected and tolerated if not progressive. However, this case should prompt clinicians to obtain baseline renal function when starting empagliflozin and contemplate the diagnosis of DI-AIN if new non-specific symptoms develop or a progressive AKI occurs after SGLT2 inhibitor initiation.

**PATIENT CONSENT**

We are grateful to the patient for the informed consent to publish this case report.

**AUTHORS’ CONTRIBUTIONS**

Each named author contributed to the design, drafting, revision and approval of the report.
CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part. The subject of the case report has given their informed consent for publication.

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