Tubulointerstitial Nephritis after Using a Sodium-glucose Cotransporter 2 Inhibitor

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Abstract:
We herein report a case of acute kidney injury (AKI) due to tubulointerstitial nephritis (TIN) after starting empagliflozin in a diabetic patient. The patient developed stage 1 AKI with proteinuria and elevated tubulointerstitial markers. A renal biopsy showed acute TIN with lymphocytic infiltration into the interstitium. The patient’s renal function improved after discontinuation of empagliflozin and steroid administration. Sodium-glucose cotransporter 2 (SGLT2) inhibitor-induced AKI has been reported, but the underlying mechanism remains unclear, potentially because few patients with SGLT2-inhibitor-induced AKI have undergone a renal biopsy. We report the present case in the hope that it will help clarify the mechanism.

Key words: acute kidney injury, diabetes mellitus, empagliflozin, sodium-glucose cotransporter 2 inhibitors, tubulointerstitial nephritis

Introduction

Recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been used for the treatment of early type 2 diabetes mellitus (T2DM). SGLT2 inhibitors are widely known as drugs that directly work on the kidney to regulate blood glucose, which is different from the action of conventional drugs for diabetes that promote insulin secretion (1). Recent clinical studies have confirmed that SGLT2 inhibitors, such as canagliflozin, dapagliflozin, and empagliflozin, promote cardiovascular safety by significantly reducing cardiovascular events (2-4). SGLT2 inhibitors are also expected to exert nephroprotective effects in early chronic kidney disease (CKD) and moderately advanced CKD (3, 4). A four-year longitudinal study demonstrated a long-term nephroprotective effect in patients treated with empagliflozin (5). In addition, the CANVAS and CRESCENDO trials demonstrated nephroprotective effects in patients treated with canagliflozin (3, 6).

However, several reports have described the occurrence of acute kidney injury (AKI) after starting SGLT2 inhibitors (7). In June 2016, the U.S. Food and Drug Administration (FDA) warned of an association between two SGLT2 inhibitors (canagliflozin and dapagliflozin) and AKI (8, 9). The mechanism underlying AKI is thought to be caused by an initial drop in the glomerular filtration rate (GFR) due to reduced trans-glomerular pressure or kidney medullary hypoxia (10, 11), but the clear mechanisms have not yet been elucidated. This uncertainty may exist because few patients undergo a kidney biopsy, which is the only way to histologically differentiate tubulointerstitial nephritis (TIN) from osmotic nephropathy or diabetic nephropathy. The mechanism by which SGLT2 inhibitors induce AKI is generally considered to be osmotic diuresis, which has been supported by case reports and biopsy-performed cases (11-13). Another possible mechanism of AKI is TIN, but to our knowledge, there have only been two reported cases of TIN caused by SGLT2 inhibitors. One was in a dog treated with high-dose empagliflozin (14), and the second was a patient with a 10-year history of treatment for T2DM (15).

We herein report another case of biopsy-proven acute tu-
bulointerstitial nephritis (ATIN) caused by an SGLT2 inhibitor in a patient with a short history of diabetes.

**Case Report**

A 78-year-old woman presented to our hospital with acute kidney disease in the winter of 2019. Approximately one month earlier, she had been diagnosed with T2DM, and empagliflozin (10 mg orally) had been prescribed. She had a history of hypertension and dyslipidemia without any problems and was being treated with long-standing medications of amlodipine, telmisartan, and pravastatin. There was no family history of diabetes or kidney disease. Her serum creatinine level was 0.89 mg/dL, without proteinuria at baseline. Although her blood pressure and blood glucose levels were within the normal range, she was positive for urine protein excretion and had experienced a decline in her renal function since one month after the initiation of empagliflozin. Therefore, she was referred to our hospital.

On a physical examination, her blood pressure and pulse were 119/76 mmHg and 107 beats/min, respectively (Table). She had no other symptoms, such as a fever or rash. She also did not have any symptoms associated with autoimmune diseases or vasculitis, such as joint pains, Raynaud’s phenomenon, numbness or dry eyes etc. The examination revealed renal dysfunction with a serum creatinine level of 1.38 mg/dL, an estimated GFR (eGFR) of 28.9 mL/min/1.73 m², and a urine protein to creatinine ratio of 0.74 g/gCr. There was also an abnormal increase in the tubule-interstitial markers urinary N-acetyl-β-D-glucosaminidase (NAG) 24.1 μg/min, γ-glutamyltranspeptidase 3240 μU/g creatinine, and β2-microglobulin 58,988 μg/g creatinine. Ultrasonographic imaging revealed no signs of hydronephrosis, and both kidneys were of normal size. Drug-induced nephropathy was suspected, and she was started on a dipeptidyl peptidase-4 (DPP-4) inhibitor instead of the SGLT2 inhibitor.

Two weeks later, her renal function had slightly improved with a serum creatinine level of 1.20 mg/dL, and a renal biopsy was performed. A histological examination revealed that approximately 70% of the area consisted of tubular atrophy and interstitial fibrosis with an infiltration of cells. TIN was noted diffusely, and cell infiltration was more predominant around the tubule than around the glomerulus. The glomerulus showed slight changes without mesangial cell proliferation, and the arteries showed moderate arteriosclerosis, while arteriolar hyalinosis was not observed in the arterioles. Although interstitial eosinophilic infiltration was not increased, immunostaining showed that the infiltrating cells were lymphocytes (CD45) and monocytes (CD68), and T cells (CD3) were more strongly stained than B cells (CD22) (Figure). Based on the pathological findings, since the acute phase for TIN is accompanied by infiltration of immune cells and poor findings for diabetic changes, we diagnosed the patient with empagliflozin-induced TIN.

Six weeks after the SGLT2 inhibitor was discontinued, the patient’s serum creatinine level was 1.18 mg/dL, and her renal function had not improved; therefore, 20 mg of prednisolone once daily was started. Her renal function gradually improved with steroid use, and the amount of steroid was reduced by 5 mg each month to a dosage of 5 mg. Three months after the start of steroid administration, her serum creatinine level improved to 0.95 mg/dL with no detectable proteinuria. A DLST performed after steroid administration was negative for SGLT2 inhibitors.

Written informed consent was obtained from the patient, along with permission to publish the details and tissue images per hospital guidelines. As all reported investigations were clinically indicated, this report does not require approval of the Hospital Ethical Committee, in accordance with the government’s Ethical Guidelines for Medical and Health Research Involving Human Subjects.

**Discussion**

We encountered a case of ATIN caused by an SGLT2 inhibitor. The patient developed AKI one month after taking empagliflozin as the initial treatment for diabetes. Although she was under treatment for hypertension and dyslipidemia, no additional or changed medications, other than SGLT2 inhibitors, were given before the onset of renal dysfunction. A renal biopsy revealed ATIN with lymphocyte and monocyte infiltration, while the finding of diabetic nephropathy was poor. Based on these findings, we diagnosed the patient with TIN due to empagliflozin. This diagnosis was also supported by the clinical course wherein the renal function improved after the discontinuation of empagliflozin and steroid administration.

To our knowledge, this case is the second report of biopsy-proven TIN caused by an SGLT2 inhibitor. The first case, reported by Ryan et al. (15), showed histological findings of ATIN with lymphocytic infiltration in the interstitium under the background change of diabetic nephropathy. These findings were from a renal biopsy performed after 6 weeks of empagliflozin use in a patient who had had T2DM for 10 years (15). In our study, the findings of diabetic nephropathy were poor, and we also performed immunostaining for cell surface antigens and revealed that the infiltrated cells were positive for CD3 (expressed on T cells), CD45 (T cells), and CD68 (macrophages) and negative for CD22 (B cells). Since the infiltrated cells were predominately T cells and macrophages, a mechanism involving cell-mediated immunity was suspected in our case. Typical allergic reactions, such as interstitial eosinophilic infiltration, septic abscess urine, and eosinophilia, were not observed. Whether or not empagliflozin induces cell-mediated immunity caused by renal damage is unclear at present. However, it is interesting that the renal impairment onset occurred more than four weeks after treatment initiation, which is rather slow among adverse drug reactions (16).

Urinary tract infections, hypoglycemia, and dehydration due to osmotic diuresis are widely recognized side effects of SGLT2 inhibitors. Between January 2013 and September
Table. The Patient’s Data at the First Visit.

| Physical characteristics |  |
|--------------------------|--|
| Age                      | 74 years old |
| Body mass index          | 30.4 kg/m²   |
| Systolic blood pressure  | 119 mmHg     |
| Diastolic blood pressure | 76 mmHg      |
| Heart rate               | 107 /min     |

| Blood examinations        |  |
|---------------------------|--|
| White blood cell          | 10,200 /µL |
| Eosinophils               | 0.6 %      |
| Hemoglobin                | 11.8 g/dL  |
| Platelets                 | 354,000 /µL|
| Albumin                   | 4.1 g/dL   |
| Uric acid                 | 2.5 mg/dL  |
| Urea nitrogen             | 17 mg/dL   |
| Creatinine                | 1.38 mg/dL |
| Estimated glomerular filtration rate | 28.9 mL/min/1.73m² |
| Sodium                    | 140 mEq/L  |
| Potassium                 | 4.3 mEq/L  |
| Chloride                  | 109 mEq/L  |
| C-reactive protein        | 0.38 mg/dL |
| Triglyceride              | 143 mg/dL  |
| High density lipoprotein-cholesterol | 60 mg/dL |
| Low density lipoprotein-cholesterol | 77 mg/dL |
| Hemoglobin A1c            | 6.5 %      |
| Immunoglobulin G          | 1,596 mg/dL|
| Immunoglobulin A          | 515 mg/dL  |
| Immunoglobulin M          | 67 mg/dL   |
| Complement 3              | 150.2 mg/dL|
| Complement 4              | 42.4 mg/dL |
| 50% hemolytic complement activity | >60 U/mL |
| Antinuclear antibody      | <40 times  |
| Anti-Ro/SSA antibodies    | -          |
| Perinuclear-antineutrophil cytoplasmic antibody | <1.0 U/mL |
| Cytoplasmic-antineutrophil cytoplasmic antibody | <1.0 U/mL |
| Immunoelectrophoresis     | No findings|

| Urine examinations        |  |
|---------------------------|--|
| Protein/creatinine        | 0.74 g/gCr  |
| Protein                   | -           |
| Red blood cells           | <1 /HPF    |
| White blood cells         | <4 /HPF    |
| Flat epithelial cells     | 1-4 /HPF   |
| Tubular epithelial cells  | 1-4 /HPF   |
| Hyaline casts             | 1-9 /WF    |
| Epithelial casts          | 1-9 /WF    |
| Granular casts            | 1-9 /WF    |
| N-acetyl-β-D-glucosaminidase | 24.1 U/g creatinine |
| β2 microglobulin          | 58,988 µg/g creatinine |

HPF: high power field, WF: whole field

2016, 18,915 reports of adverse events caused by SGLT2 inhibitors were submitted to the FDA Adverse Event Reporting System (FAERS). Of these, 1,224 were acute renal failure after the start of oral administration of this drug (8), suggesting that SGLT2 inhibitor use can be associated with an increased risk of AKI. However, very few patients with SGLT2 inhibitor-induced AKI underwent a renal biopsy, and histological findings are needed to investigate the underlying mechanisms. There have been a few reports of biopsy-proven AKI caused by SGLT2 inhibitors (dapagliflozin and canagliflozin), and most showed histological findings of osmotic nephropathy (12, 13, 17). Hahn et al. reported the potential mechanisms of renal injury caused by SGLT2 inhibitors, including osmotic diuresis, uremia, and tubular oxida-
Figure. Tubulointerstitial nephritis in the patient after empagliflozin use. Low- (A: ×40, D: ×100) and high- (B, C, E-I: ×400) power views of renal interstitium stained with Hematoxylin and Eosin staining (A, B), periodic acid-Schiff stain (C), and Elastica Masson stain (D-F). (A, B, D) Tubular atrophy and interstitial fibrosis were observed diffusely in approximately 70% of the area. (A, B) Tubular interstitium showed infiltration mainly composed of lymphocytes and monocytes. (C) The glomerulus had slight mesangial matrix expansion without mesangial cell proliferation. (E) The small and medium-sized arteries showed moderate arteriosclerosis with fibroelastosis, (F) while arteriolar hyalinosis was not observed in the arterioles. (G: CD3, H: CD22, I: CD68) Immunostaining showed cells expressing CD3 (T cells) and CD68 (macrophages) but did not show cells expressing CD22 (B cells). Cells expressing CD3 and CD68 infiltrated more strongly around the tubular region than around the glomerulus.

tive stress (10). It has also been suggested that concomitant use of SGLT2 inhibitors with diuretics, ACE inhibitors, and angiotensin receptor blockers increases the risk of developing osmotic nephropathy, based on their pharmacological actions (8). Interestingly, both the patient in our case and in Ryan et al. used drugs that carry a risk of causing osmotic nephropathy (ACE inhibitors and angiotensin receptor blockers) in addition to SGLT2 inhibitors. The histological findings confirmed ATIN, and osmotic nephropathy, such as tubular epithelial cell vacuolation or detachment, was not observed. This suggests that AKI due to TIN and renal damage after the administration of SGLT2 inhibitors must be included in FDA reports. Thus, the cause of AKI induced by SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) is not clearly understood. In particular, few cases of biopsy-proven osmotic nephropathy have been reported in empagliflozin-induced AKI. Despite the potential risk, a meta-analysis revealed that SGLT2 inhibitors have a more positive effect on CKD progression than their risk of causing renal damage (7), and empagliflozin seems to confer a lower renal risk (18).

In summary, TIN should be considered in patients with renal injury after SGLT2 inhibitor therapy. We recommend a renal biopsy be performed in patients who develop AKI after the use of SGLT2 inhibitors, especially in the early phase of diabetes.

The authors state that they have no Conflict of Interest (COI).

Acknowledgements
We thank the patient described for allowing us to share her details. We also thank Mrs. Kiyomi Kisu and Colleagues, Division of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Graduate School of Medicine, for conducting the immunological staining and providing support.
Yusuke Konta and Eiichiro Saito contributed equally to this work.

References

1. Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. Lancet Diabetes Endocrinol 1: 140-151, 2013.
2. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373: 2117-2128, 2015.
3. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377: 644-657, 2017.
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 380: 347-357, 2019.
5. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375: 323-334, 2016.
6. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380: 2295-2306, 2019.
7. Menne J, Dumann E, Haller H, Schmidt BMW. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: a systematic review and meta-analysis. PLoS Med 16: e1002983, 2019.
8. Perlman A, Heyman SN, Matok I, Stokar J, Muszkat M, Szalat A. Acute renal failure with sodium-glucose cotransporter-2 inhibitors: analysis of the FDA adverse event report system database. Nutr Metab Cardiovasc Dis 27: 1108-1113, 2017.
9. FDA Drug Safety Communication. FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR) [Internet]. 2016. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-kidney-warnings-diabetes-medicines-canagliflozin
10. Hahn K, Eijaz AA, Kanbay M, Lanaspa MA, Johnson RJ. Acute kidney injury from SGLT2 inhibitors: potential mechanisms. Nat Rev Nephrol 12: 711-712, 2016.
11. Perlman A, Heyman SN, Stokar J, Darmon D, Muszkat M, Szalat A. Clinical spectrum and mechanism of acute kidney injury in patients with diabetes mellitus on SGLT-2 inhibitors. Isr Med Assoc J 20: 513-516, 2018.
12. Phadke G, Kaushal A, Tolan DR, et al. Osmotic nephrosis and acute kidney injury associated with SGLT2 inhibitor use: a case report. Am J Kidney Dis 76: 144-147, 2020.
13. Pleros C, Stamataki E, Papadaki A, et al. Dapagliflozin as a cause of acute tubular necrosis with heavy consequences: a case report. CEN Case Rep 7: 17-20, 2018.
14. Bogdanffy MS, Stachlewitz RV, van Tongeren S, et al. Nonclinical safety of the sodium-glucose cotransporter 2 inhibitor empagliflozin. Int J Toxicol 33: 436-449, 2014.
15. Ryan R, Choo S, Willows J, Walker J, Prasad K, Tez D. Acute interstitial nephritis due to sodium-glucose co-transporter 2 inhibitor empagliflozin. Clin Kidney J 14: 1020-1022, 2021.
16. Kaku K, Chin R, Naito Y, et al. Safety and effectiveness of empagliflozin in Japanese patients with type 2 diabetes: interim analysis from a post-marketing surveillance study. Expert Opin Drug Saf 19: 211-221, 2020.
17. Watanabe S, Sawa N, Mizuno H, et al. Development of osmotic vacuolization of proximal tubular epithelial cells following treatment with sodium-glucose transport protein 2 inhibitors in type II diabetes mellitus patients3 case reports. CEN Case Rep 10: 563-569, 2021.
18. Tang H, Li D, Zhang J, et al. Sodium-glucose cotransporter 2 inhibitors and risk of adverse renal outcomes among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. Diabetes Obes Metab 19: 1106-1115, 2017.

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