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Dapagliflozin Induced Acute Tubulo-Interstitial Nephritis: A Case Report and Literature Review

Nida Saleem*, Saima Bashir, Syed Nayer Mahmud, Muhammad Haneef

Nephrology Department, Shifa International Hospital, Islamabad, 00000, Pakistan
*Corresponding author: nidasaa1968@gmail.com

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Abstract We report a case of an elderly male patient, who presented with acute kidney injury on background of diabetic nephropathy, secondary to dapagliflozin induced acute tubulo-interstitial nephritis requiring hemodialysis sessions. Histopathological findings are consistent with moderate tubulo-interstitial inflammation with mixed lymphocytic and eosinophilic inflammatory deposits. The patient responded well to cessation of causative medication and upon initiation of high dose steroids. The direct cause and effect relationship between dapagliflozin initiation and development of acute tubulo-interstitial nephritis is indicative of dapagliflozin being responsible for marked renal deterioration, as seen in this patient.

Keywords: *Acute interstitial nephritis (AIN), Diabetes, dapagliflozin, SGLT2 inhibitors, acute kidney injury (AKI)*

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1. Introduction

SGLT-2 inhibitors are the class of novel anti-diabetic agents known to correct hyperglycemia by inhibition of glucose reabsorption through sodium-glucose cotransporter protein leading to glycosuria and osmotic diuresis. These drugs are known for multiple potential benefits other than adequate glycemic control. These include osmotic diuresis induced blood pressure and weight reduction, correcting hyperuricemia, controlling proteinuria and most importantly, addressing cardiovascular disease risk factors and reducing hospitalization for heart failure [1]. However, several side effects of these drugs have been known, which consists of hypotension, hyperkalemia, fractures, malignancy, urinary and genital tract infections [2]. In June 2016, Food and Drug Administration (FDA) declared warning concerning possible risk of acute kidney injury with dapagliflozin and canagliflozin after diagnosis of 101 patients with AKI, from March 2013 to October 2015, following their administration [3]. Out of these 101 patients, 28 received dapagliflozin. 96 patients required hospitalization and 15 patients had undergone hemodialysis. However, after this declared warning, several studies and meta-analysis have been performed reporting overall reduction in the risk of AKI with SGLT2 inhibitors [4,5]. Recently, 2 cases have been reported regarding occurrence of osmotic nephrosis [6] and acute tubular necrosis [7] with canaglifozin and dapagliflozin respectively. Here, we report the first case of dapagliflozin induced acute tubulo-interstitial nephritis requiring hospital admission and subsequent hemodialysis.

2. Case

81 years old male, resident of Islamabad, is a known case of diabetes mellitus since 2006, hypertension since 2016, bilateral osteoarthritis of knee joint, benign prostatic hyperplasia since 2018, diabetic retinopathy and chronic kidney disease with a baseline creatinine of 1.5mg/dL since 2018. Also, he is a chronic smoker, around 1 pack per day for the last 30years. He has been on regular follow ups for the last 5 years. His routine home medications include carvedilol, glipizide, sitagliptin, tamsulosin/dutasteride and aspirin. On follow up visit, his HbA1C was found to be around 8%. In order to achieve adequate blood sugar control, tablet dapaglifozin was added at a dose of 10mg once daily. 1 month later, on follow up visit, he presented with complaints of bilateral lower extremity edema and slight reduction in urine output for the last 1 month. Besides this, there were no complaints of anorexia, nausea, vomiting, fever and lower urinary tract symptoms. He remained compliant with the advised treatment with no history of intake of over the counter medications or any NSAIDs. He was vitally stable with a BMI of 33.3kg/m^2. There was bilateral mild pitting lower limb edema as well. His systemic examination was unremarkable.

Incidentally, his serum creatinine came out to be markedly raised from baseline of 1.53 to 7.89mg/dl. His labs were repeated the next day, which showed serum creatinine of 9.73mg/dL. He was then admitted for further workup and for possible initiation of hemodialysis.

His intensive investigations were performed in order to determine the cause of his renal impairment. The table below shows his laboratory findings.

Table 1. Post-Admission Laboratory Workup

TLC (cells/cmm)	11980	Serum creatinine (mg/dL)	**9.73**
Hemoglobin (g/dL)	13.8	BUN (mg/dL)	**54**
Platelet count (cells/uL)	255000	Serum sodium (mEq/L)	140
HbA1C (%)	7.5	Serum potassium (mEq/L)	**5.5**
Urine R/E	Protein: +, glucose: +, RBCs: 3-5/HPF, blood:+	Serum bicarbonate (mEq/L)	**12**
ACR (mg/g)	29	Serum calcium (mg/dL)	**7.5**
ESR (mm/hr)	55	Serum phosphorous (mg/dL)	**8.2**
Serum glucose (mg/dL)	141	LDH (units/L)	394
Serum albumin (mg/dL)	3.9	c3	1.45 (normal)
HBsAg	negative	C4	0.29 (normal)
Hep C Ab	negative	ANCA	negative
INR	1.03	Anti-GBM	negative
Uric acid (mg/dL)	5.3		

Abbreviation: TLC: total leucocyte count, HbA1C: hemoglobin A1C, ACR: albumin to creatinine ratio, HBsAg: hepatitis B surface antigen, Hep C Ab: hepatitis C antibody, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, c4, c4: complement 3 and 4, ANCA: antinuclear cytoplasmic antibody, Anti-GBM: anti glomerular basement membrane antibody, INR: international normalized ratio.

The above table shows markedly deranged serum creatinine, blood urea nitrogen (BUN), serum potassium and bicarbonate levels. There is no evidence of significant proteinuria and all his serological workup came out to be negative. His abdominal ultrasound showed bilateral grade 1-2 echogenic and normal sized kidneys, and prostate was 32grams with post void volume of 19mL.

Post admission, he received tablet calcium acetate, sevelamer acetate, tamsulosin/dutasteride, glipizide, sodium bicarbonate and insulin as per sliding scale. In order to correct electrolyte and acid base abnormalities, hemodialysis was initiated after insertion of right femoral non-tunneled dialysis catheter.

After 3 session of hemodialysis, his renal biopsy was performed to identify the underlying cause of renal impairment. Renal biopsy showed evidence of diabetic glomerulopathy class 2a, moderate hypertensive vasculopathy and moderate acute tubulo-interstitial nephritis. 3 out of 10 glomeruli were globally and 1 out of 10 was segmentally sclerosed. There was moderate tubular damage along with tubular necrosis and reparative changes as well. Within the tubules, colloid, cellular and red cell casts were seen. Also, the tubular basement membrane was thickened and tortuous. Tubules were mildly atrophied. There was no evidence of tubular dilatation, vacuolization and crystals. There was moderate mixed inflammation comprising of lymphocytes, plasma cells, neutrophils and eosinophils. Mild interstitial fibrosis was also present. These features are described in the light microscopic figures below.

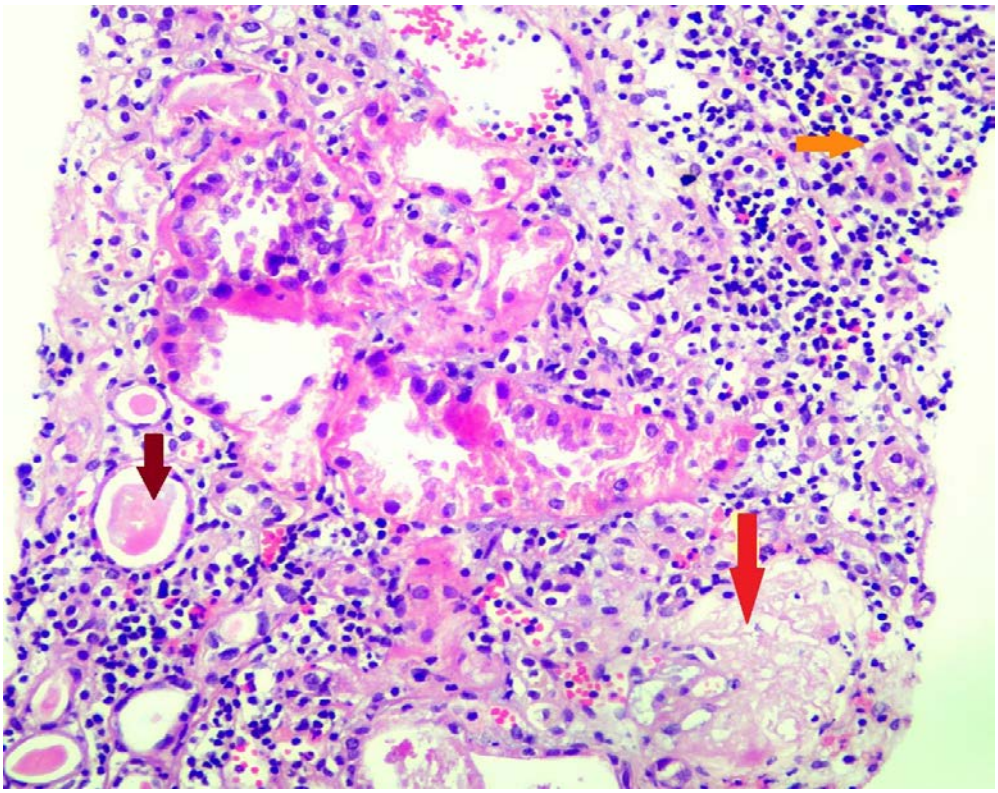

Figure 1. H and E staining (X20) Sclerosed glomeruli (red arrow); marked interstitial infiltrates (orange arrow); flattened tubular epithelium with colloid cast (maroon arrow)

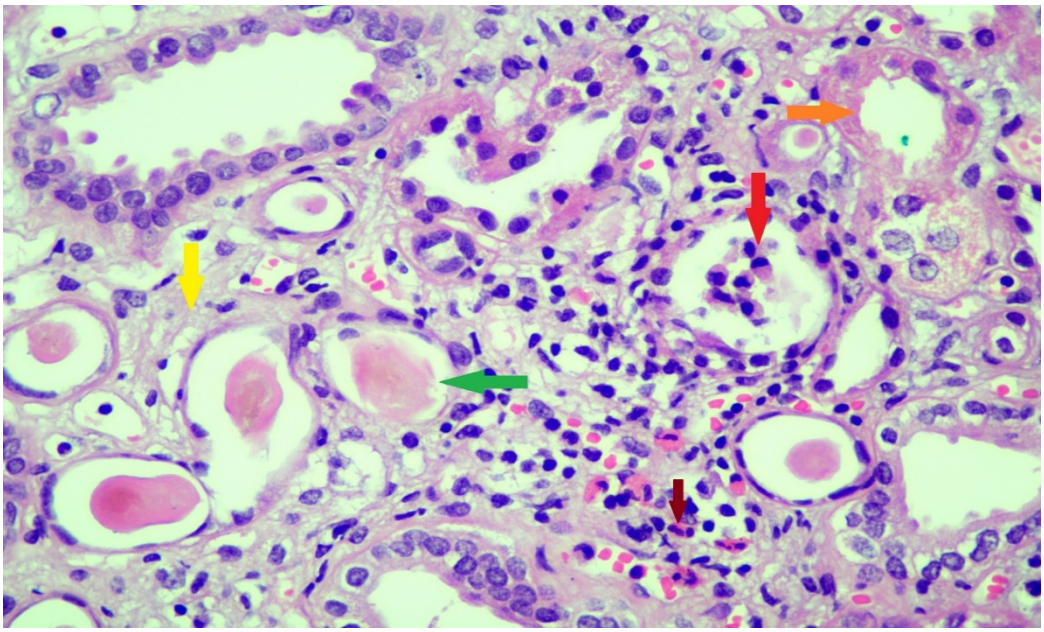

Figure 2. H and E staining (X40) Eosinophilic rich interstitial inflammation (maroon arrow); moderate tubular damage with loss of brush border and nuclear damage (orange arrow); white cell cast (red arrow); mild interstitial fibrosis (yellow arrow); tubular flattening with colloid cast (green arrow)

Immunofluorescence showed presence of linear IgG deposits along glomerular basement membrane and non-specific IgM deposits in the sclerosed glomeruli.

He was then started on injection methylprednisolone 40 mg twice daily. It was given for 3 days followed by conversion to oral prednisolone 6 tablets once daily. After starting steroids, his urine output improved to around 2500 ml per 24hours. After 3 sessions, his hemodialysis was withheld and non-tunneled dialysis catheter was removed. His serum creatinine started to decline as well, 3 days after steroids commencement. He was then discharged on tablet prednisolone, tamsulosin/dutasteride, glipizide, glargine, sitagliptin and omeprazole. His serum creatinine came down from 7.88 to 3.5 mg/dL and then to 2.6 mg/dL over a course of 15 days.

The table below summarize the laboratory findings of pre and post initiation of dapagliflozin and findings post cessation of dapagliflozin and initiation of steroids.

Table 2. Effects of Dapaglifozin on Laboratory Parameters

Lab Investigations	Pre Dapa Initiation	Post Dapa Initiation	Post Dapa Cessation and Steroids Initiation
Serum creatinine (mg/dL)	1.53	**9.73**	1.52
BUN (mg/dL)	18	**54**	18
Serum potassium (mEq/L)	4.7	**5.5**	3.9
Serum bicarbonate (mEq/L)	19	**12**	24
Serum phosphorous (mg/dL)	3.4	**8.2**	2.9
Serum calcium (mg/dL)	9.7	**7.5**	8.5

Abbreviation: Dapa: dapagliflozin, BUN: blood urea nitrogen

As shown by the table, there is clear association of dapagliflozin with acute interstitial nephritis leading to renal function derangement.

Twenty days later, his serum creatinine came down to 1.52 mg/dL and his steroids were gradually tapered off. In addition to this, he was counselled regarding avoidance of dapagliflozin in future.

3. Discussion

In summary, we reported a case of dapagliflozin induced tubulo-interstitial nephritis on background of diabetic glomerulopathy, who responded well to the drug discontinuation and steroids commencement.

On review of literature, several mechanisms have been described regarding reno-protective effects of SGLT2 inhibitors. These consist of reduction in glomerular hypertension and hyper-filtration by promoting afferent arteriolar vasoconstriction. Also, it has been suggested SGLT2 inhibitors play a role in reduction of oxidative stress and interstitial fibrosis [2]. In contrast to this, several possible mechanisms of SGLT2 inhibitor induced AKI has been mentioned. Firstly, these drugs have propensity to cause osmotic diuresis, ultimately leading to hypotension and pre-renal AKI. Secondly, hyperuricosuria induced AKI by crystal and non-crystal mechanisms. Thirdly, glycosuria induced increased fructose generation leading to oxidative stress and inflammation [8]. Furthermore, osmotic nephrosis and acute tubular necrosis has also been reported as an inciting factor for AKI. Our patient has moderate tubulo-interstitial nephritis, which has developed rapidly and needed hemodialysis after initiation of dapagliflozin. The definitive drug and disease association and drastic response to steroids in our patient signifies the likely diagnosis.

The possible mechanism of tubular damage might be secondary to reduced post glomerular tubular perfusion leading to hypoxic tubular injury. The propensity of hypoxic medullary injury is further aggravated by co-exiting diabetes, associated with microvascular damage.

Besides this, due to natriuresis and glycosuria, these tubules are exposed to more osmolar load leading to marked tubular damage. This hypothesis [9] can be applied in our patient as well.

In one Canadian study, it was concluded that dapagliflozin reduces AKI incidence even in elderly population (median age 70years) [10]. This is in contrast

to our patient, who developed AIN at an old age. The possible reasons for AIN in this patient are preexisting long standing complicated diabetes, chronic kidney disease with baseline eGFR of around 40mL/min/1.73m^2, chronic smoking and morbid obesity. However, in contrast to risk factors mentioned in previous studies, which include history of intake of drugs like NSAIDs, ACEi/ARBs, diuretics [2,9] and preexisting cardiovascular disease; none has been present in our patient.

As effectiveness of dapagliflozin at a GFR below 60mL/min is reduced [2], therefore, it can be concluded that before initiating SGLT2 inhibitors, risk to benefit ratio must be taken into account. Besides this, it is imperative to monitor renal functions post-initiation of SGLT2 inhibitors especially when considering their use in high risk population. Additionally, the role of periodic monitoring of urinary biomarkers of tubular injury like KIM-1, NGAL may need consideration. Most importantly, special attention must be given to modify the grade of eGFR at which SGLT2 inhibitors are contraindicated.

4. Conclusion

We reported the first case of dapagliflozin induced acute tubulo-interstitial nephritis leading to hemodialysis dependent AKI. This case has pointed out certain salient points, which include importance of considering dapagliflozin as a culprit medication in a patient with acute renal impairment. Secondly, on initiation of dapagliflozin, frequent renal function monitoring may be considered early on. Thirdly, it is imperative to avoid dapagliflozin in a high risk patient or patient with pre-existing renal impairment, especially with eGFR less than 45mL/min. Lastly, even in a patient with ongoing CKD, diagnostic confirmation of deranged renal function with renal biopsy is of utmost importance.

Abbreviation

eGFR: Estimated glomerular filtration rate
CKD: Chronic kidney disease
AKI: Acute kidney injury
AIN: Acute interstitial nephritis
SGLT2: Sodium glucose co-transporters
NSAIDs: Non-steroidal anti-inflammatory drugs
ACEi: Angiotensin converting enzyme inhibitors
ARBs: Aldosterone receptor blockers
NGAL: Neutrophil gelatinase associated-lipocalcin
KIM-1: Kidney injury molecule-1

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