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Recurrent Urinary Tract Infection In A Diabetes Mellitus Patient On Dapagliflozin: A Case Report

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I. Case Presentation

A 48-year-old female with a history of diabetes mellitus for more than five years, controlled with metformin 500mg 12 hourly, sitagliptin 50mg 12 hourly, and dapagliflozin 10mg once daily. One month after the introduction of dapagliflozin, she presented to the outpatient department with lower back pain and fever. Clinical examination revealed a temperature of 38°C and suprapubic tenderness. Initial investigations are depicted in table 1.

Table 1: Laboratory investigations

Investigation	Result	Reference range
Urinalysis	Color: Yellow Appearance: turbid pH: 5.5 Specific gravity: 1.025 Protein: negative Ketones negative Urobilinogen negative Nitrite negative Blood +1 Glucose +2 Bilirubin negative Leucocytes +3 RBC 10RBC/hPF Pus cells >1000 WBC Epithelial cells +1 Cast negative Crystal Negative Ova No ova seen	
CRP	9.8mg/L	0-5mg/L
CBC	WBC 7.8 x 10^3/uL Absolute granulocyte 4.71 x 10^3/uL	4.00 -10.00 X 10^3/Ul 2.00 – 7.00 X 10^3/uL
RBG	4.4mmol/L	4.0-8.0mmol/L

CRP c-reactive protein, CBC complete blood count, RBG random blood glucose

The patient was diagnosed with a UTI and treated with oral Amoxicillin-Clavulanate (625 mg 12 hourly) for five days. Two weeks later, after the completion of her initial antibiotics, the patient returned with complaints of lower abdominal pain for three days, a burning sensation during urination for one day, and low grade fever. A urine sample was collected and blood was drawn for investigations depicted in table 2.

Table 2: Laboratory investigations

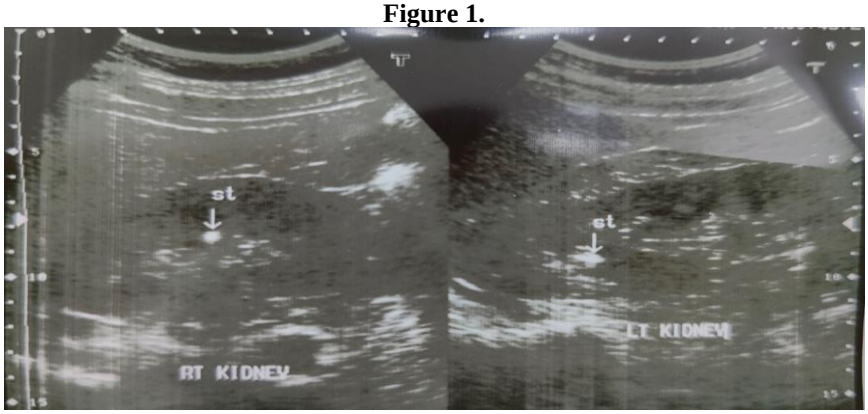
Investigation	Result	Reference range
Urinalysis	Color: Pale yellow Appearance: turbid pH: 7.5 Specific gravity: 1.020 Protein: negative Ketones negative Urobilinogen negative Nitrite negative Blood +1 Glucose +2	

	Bilirubin negative Leucocytes +3 RBC 10RBC/hPF Pus cells 66 WBC/hPF Epithelial cells +2 Cast negative Crystal Negative Ova No ova seen	
Blood culture	No growth seen	
Urine culture	Gram stain: Gram +ve yeast cell Organism isolated: *Candida albicans* Colony count > 10^5	
CRP	23.43mg/L	0-5mg/L
CBC	WBC12.6x10^3/uL, Absolute Granulocyte 8.5 x10^3/uL	4.00 -10.00 X 10^3/Ul 2.00 – 7.00 X 10^3/uL
RBG	9.0mmol/L	4.0-8.0mmol/L

CRP c-reactive protein, CBC complete blood count, RBG random blood glucose

The patient was treated with IV fluconazole; 800 mg loading dose, followed by 400 mg once daily for two weeks. Upon follow-up, urine culture was repeated and revealed *E. coli* (10^5 CFU), sensitive to amikacin, amoxicillin clavulanic acid, ampicillin, cefepime, cefotaxime, gentamicin, imipenem, meropenem, nitrofurantoin and piperacillin/tazobactam and resistant to TMP/SMX and ciprofloxacin. The patient was started on nitrofurantoin (100 mg 12 hourly for 7 days). However, she returned within four days with persistent lower urinary tract symptoms and fever. A KUB ultrasound in Figure 1 demonstrated bilateral micro nephrolithiasis (right 0.34 cm, left 0.24 cm). At this point, dapagliflozin was discontinued, and amoxyclav 625mg 12 hourly was given for 7 days. A follow-up appointment 10 days later revealed normal urinalysis.

Figure 1.



St, stone.

II. Discussion

Urinary tract infections are inflammation involving the bladder, ureters, kidney, and urethra and this infection can affect either one or more parts of the urinary tract[1]. Urinary tract infections can range from simple uncomplicated cystitis to urosepsis and eventually life-threatening septic shock[1]. Urinary tract infections are the leading cause of antibiotic use[1]. Approximately 12% of males and 40% of females will suffer one UTI in their lifetime[1]. Females are at a higher risk of UTI due to their anatomy – a short distance of approximately 4cm from the urethral opening to the bladder and a close distance between the urethra, vagina and anus[2]. Another contributing risk factor is a decreased level of estrogen in postmenopausal women[2]. Diabetes mellitus doubles the occurrence of UTI[2]. The prevalence of urinary tract infections (UTIs) in patients with type 2 diabetes mellitus (T2DM) is approximately 11.5%[3]. Individuals with diabetes mellitus are particularly vulnerable to UTIs due to immune system dysfunction and an increased tendency for bacteria to adhere to the urothelial lining[4]. Common organisms for uncomplicated UTI; *Staphylococcus saphrophiticus* (5-15%), *Klebsiella pneumonia*, *Enterococcus fecalis*, and *proteus spp*. Complicated UTI is associated with increased morbidity and mortality and common organisms are *Pseudomonas aeruginosa* and *Candida*[1,2]. The major risk factor for *Candida* is diabetes mellitus, prolonged antibiotic use and immunosuppression[1,2]. Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, is a newer class of antihyperglycemic agents used to manage type 2 diabetes mellitus[3]. SGLT2 inhibitors have a unique mechanism of action to lower the glucose levels in diabetes mellitus patients without relying on insulin[4,5]. These agents lower glucose levels by inhibiting the high-capacity glucose transporter SGLT2 in the proximal convoluted tubule of the nephron, reducing glucose reabsorption in the kidneys and promoting its excretion in the urine (glucosuria), without depending on insulin action[6]. Dapagliflozin has common side effects

such as; nasopharyngitis, diarrhea, headache, upper respiratory tract infections, hypoglycemia, DKA and an increase in parathyroid hormone[7]. While effective in glycemic control, SGLT2 inhibitors have been associated with an increased risk of urinary tract infections due to the mechanism of action that promotes glucosuria[7]. Additionally, they are linked to an increased risk of uncomplicated urinary tract infections (UTIs), as well as urosepsis or pyelonephritis[1,2].

In this patient, the initial presentation of lower back pain, fever, and suprapubic tenderness suggested a UTI, which was treated with a standard course of Amoxicillin-Clavulanate. Despite initial symptom relief, the patient's recurrent symptoms, and an elevated CRP and leucocytes in urinalysis, indicated persistent or unresolved infection. A urine culture confirmed *Candida albicans*, a rare but recognized pathogen in diabetic patients, possibly promoted by the dapagliflozin-induced glucosuria. Candida infections in the urinary tract are more common in diabetes mellitus patients due to impaired immune defenses, which are further challenged by a glucose-rich urinary environment that fosters fungal growth[8].

After initial treatment with IV fluconazole, a subsequent culture showed infection with *E. coli*, suggesting a possible shift in pathogens or a superimposed bacterial infection. However, despite appropriate antibiotic therapy, the patient's symptoms persisted, prompting a further investigation that revealed bilateral micro nephrolithiasis on ultrasound. Micro nephrolithiasis, though relatively small, could act as a nidus for recurrent infection and complicate the treatment of UTIs[9] in this patient.

The decision to discontinue dapagliflozin was appropriate in this context, as ongoing glucosuria may have continued to exacerbate the patient's risk of recurrent UTIs, especially in the presence of micronephrolithiasis[7,9]. Several studies support that SGLT2 inhibitors are associated with an increased risk of both simple and complicated UTIs, and these risks can be exacerbated by factors such as urinary stasis, renal calculi, and hyperglycemia, which were all relevant in this case[1,7,9]. The continuation of dapagliflozin may have caused Fournier gangrene which is potentially life-threatening[7].

This case also underscores the importance of follow-up and re-evaluation in diabetes mellitus patients with recurrent UTIs. The presence of micro nephrolithiasis and persistent symptoms despite appropriate therapy highlighted the need to consider alternative or additional causes for recurrent infections. Managing UTIs in diabetes mellitus patients with nephrolithiasis may require a multidisciplinary approach, involving not only endocrinology for glucose management but also nephrology or urology for addressing underlying urinary tract abnormalities.

In conclusion, this case highlights the complex interplay between diabetes mellitus, the use of SGLT2 inhibitors, and recurrent UTIs. The findings suggest a cautious approach in using SGLT2 inhibitors in patients with a history of recurrent UTIs or other risk factors for urinary tract complications, as discontinuation of dapagliflozin and treatment targeting the identified pathogens and urinary tract pathology ultimately led to symptom resolution.

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