

Single Case

Emphysematous Pyelonephritis in a Patient on SGLT2 Inhibitor Therapy: A Rare Clinical Case Report

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Keywords

Emphysematous pyelonephritis · SGLT2 inhibitor · Dapagliflozin · Case report

Abstract

Introduction: Emphysematous pyelonephritis is a rare but potentially life-threatening urinary tract infection characterized by the formation of gas in the renal parenchyma, collecting system, and perinephric tissue. The condition typically develops in patients with specific predisposing factors such as diabetes mellitus, congenital or acquired obstructive uropathies, or individuals taking immunosuppressive agents. Rarely can the disease occur in patients with other predisposing factors, such as the use of SGLT2 inhibitors, but this is quite uncommon. The incidence of urinary tract infections associated with their use is still debatable, but cases of emphysematous pyelonephritis associated with SGLT2 inhibitors have been described in medical literature. **Case Presentation:** We present a rare case of a patient with emphysematous pyelonephritis without classical risk factors for the disease, who was taking an SGLT2 inhibitor. **Conclusion:** Although the frequency of urinary tract infections following the use of SGLT2 inhibitors is relatively low, their widespread application for treatment of numerous socially significant diseases underscores the necessity for specialists to be aware with all potential risks associated with their use, including the development of severe urinary tract infections.

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Introduction

Urinary tract infections are among the most commonly encountered infectious diseases in society. Emphysematous, also known as gas-producing infections, account for a small percentage of urinary tract infections but hold significant clinical importance due to their high

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mortality rate, reaching nearly 40% [1, 2]. The main risk factors for such infections include diabetes mellitus (>90% of cases), congenital or acquired obstructive uropathies, and the use of immunosuppressive medications [1, 3].

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) constitute a new class of medications for treatment of type 2 diabetes, heart failure, and chronic kidney disease. These molecules block the sodium-dependent glucose cotransporter in the proximal tubule, leading to increased glucose excretion in the urine [4]. The presence of glucosuria is a predisposing factor for urinary infections [5]. The frequency and risk of urinary tract infections in patients using sodium-glucose cotransporter-2 inhibitors are still under investigation. Typically, cases of mild urinary infections are reported, with severe bacterial urinary infections being much rarer [6]. Documented cases of emphysematous infections associated with the use of SGLT2 inhibitors are scarce. The CARE checklist has been completed by authors for this case report, attached as an online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000539390>).

Case Presentation

A 60-year-old male with coronary artery disease, NYHA class 3 heart failure, obesity, and chronic kidney disease G3a stage, had been on dapagliflozin (an SGLT2 inhibitor) 10 mg q.d., for approximately 1 year. His other medications included rosuvastatin/ezetimibe 20/10 mg q.d., clopidogrel 75 mg q.d., acetylsalicylic acid 100 mg q.d., torsemide 5 mg q.d., metoprolol 50 mg b.i.d. During this period, the patient experienced a urinary tract infection with a multidrug-resistant strain of *Escherichia coli*. The patient did not have a history of sexually transmitted infections. According to medical documentation available, his left ventricular ejection fraction was 30% with evidence of left atrial and left ventricular dilation. The patient presented to the emergency department (ED) with complaints of left lumbar pain radiating to the groin, fever up to 38°C, and vomiting. Laboratory results showed Hb 167 g/L, WBC 10.8 G/L, PLT 190 G/L, serum creatinine 160 µmol/L, CRP 42 mg/L, urine with abundant leukocytes, erythrocytes, bacteria, and glucosuria. The patient was examined by a urologist upon ultrasonography without absolute evidence of obstruction (Fig. 1), and antibiotic therapy with cefixime was started in the outpatient setting after the patient refused hospital admission.

Over the next 3 days, despite the treatment, the patient's condition worsened, with decreased urine output and qualitative changes in consciousness, necessitating admission to the ED. Upon physical examination, the patient's general condition was compromised: febrile 38.1°C, intoxicated, dehydrated, hypotensive, agitated, abdomen was tender on palpation, pain was noted in the left lumbar area as well. Laboratory tests revealed Hb 150 g/L, WBC 10.5 G/L, PLT 104 G/L, CRP 466 mg/L, procalcitonin 163 ng/mL, serum creatinine 661 µmol/L, urea 36.1 mmol/L, potassium 6.4 mmol/L, AST 287 U/L, albumin 31 g/L, sodium 139 mmol/L, blood sugar, and HbA1c within normal range, with no evidence of obstructed drainage (Fig. 2).

After being consulted with a surgeon, urologist, and nephrologist, the patient was referred to the nephrology clinic for conservative treatment of acute kidney injury. The following probable diagnoses were discussed: Acute Kidney Injury stage III according to KDIGO scale due to sepsis of unclear origin. Urine and blood cultures were obtained. Upon ultrasonography, the left kidney was enlarged. An increased anechoic area in the renal pelvis was observed (Fig. 3). A computer tomography (CT) scan of the abdomen and pelvis revealed left-sided pyelonephritis with air collections in the renal collecting system and moderately dilated renal pelvis, without evidence of obstruction, with inflammatory changes in the left perinephric fat tissue (Fig. 4).

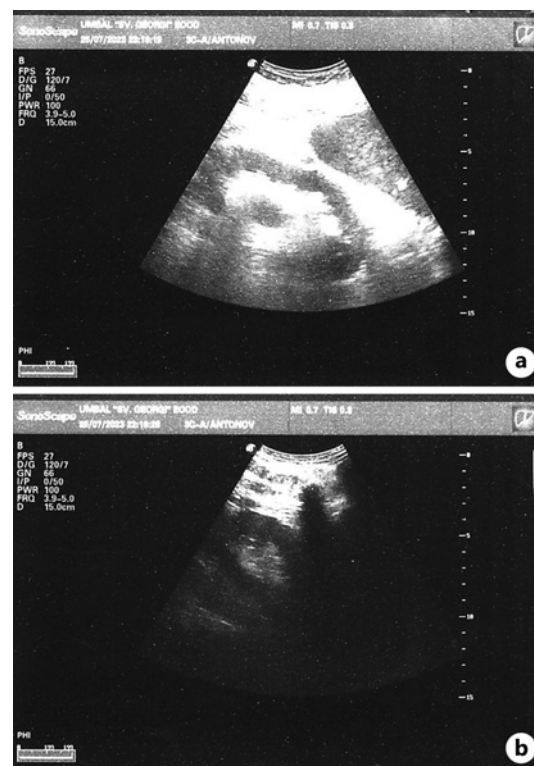


Fig. 1. Renal ultrasound at the first ED visit. **a** Left kidney – anechoic area in the renal pelvis. **b** Right kidney is unremarkable.

A diagnosis of emphysematous pyelonephritis was confirmed. The case was discussed with an urologist. A joint decision was made to continue with conservative therapy, including broad-spectrum antibiotic treatment (meropenem, levofloxacin, metronidazole), active fluid and electrolyte supplementation and symptomatic medications. Due to persistent elevation of blood urea nitrogen and creatinine levels, emergency hemodialysis was initiated. Despite the therapeutic measures taken, the patient remained anuric, febrile, with progressive thrombocytopenia. Microbiological investigations of urine and blood did not reveal evidence of microbial growth.

A decision was made to perform interventional treatment and a double-J stent was placed, resulting in the drainage of purulent urine. Over the following days, with continued antibiotic therapy and hemodialysis, the patient’s overall condition improved, diuresis was restored, but high blood urea nitrogen and creatinine levels persisted. As a result, the patient remained on dialysis treatment for the next 2 months. Subsequently, a gradual improvement in renal function was observed. The double-J stent was removed.

Three months after the onset of the disease, the patient presented for a follow-up visit. Laboratory test results came negative for urinary tract infection or inflammation, eGFR was back to baseline, and renal ultrasound was unremarkable for residual structural abnormalities. A follow-up CT scan was scheduled in accordance with current emphysematous pyelonephritis management algorithms. However, the patient did not consent to the examination and it was not performed.

Discussion

Emphysematous pyelonephritis is a rare, life-threatening necrotizing infection with gas formation in the renal parenchyma, the collecting system, and perinephric tissue. The condition is observed primarily in patients with certain predisposing factors, most commonly

Fig. 2. Renal ultrasound on the left kidney at the second ED visit. Kidney was enlarged but otherwise unremarkable.

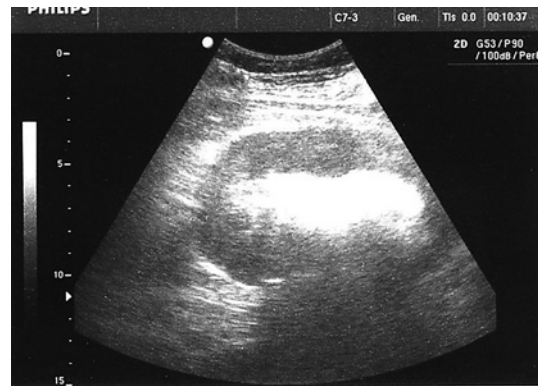
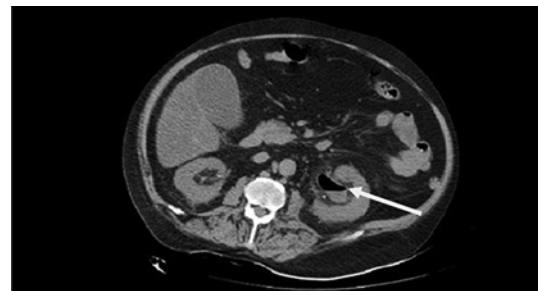


Fig. 3. Renal ultrasound on the left kidney at the time of the CT scan. Left kidney shows enlargement. Increased anechoic area in the renal pelvis.



Fig. 4. CT image of the patient. The asterisk marks gas collections in the left kidney.



diabetes mellitus, obstructed drainage (regardless of the cause), and immunosuppressive therapy [3, 7]. The disease is more common in women, likely due to their increased susceptibility to urinary tract infections. The left kidney is affected more often than the right [7]. In most cases, the typical microorganisms leading to urinary infections are isolated, including *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, but clinicians should also be vigilant for rarer opportunistic pathogens, including fungal infections, anaerobic microorganisms, etc. [3, 8–10].

The pathogenesis of emphysematous pyelonephritis is not fully understood, but the leading predisposing factors are believed to include the presence of gas-forming bacteria, high glucose levels in tissues (leading to rapid bacterial growth), impaired tissue perfusion, abscess formation, and compromised immune response due to impaired blood supply [7].

SGLT2 inhibitors are a relatively new class of drugs with multiple pleiotropic effects. We still have conflicting data from various analyses and studies regarding whether the use of SGLT2 inhibitors increases the incidence of urinary tract infections in patients. It should be noted that due to the mild course of urinary tract infections, many patients are not admitted to hospital, and receive outpatient treatment, resulting in a decrease in the number of reported cases.

In a study involving 853 patients with type 2 diabetes on oral medication, the overall incidence of urinary tract infections in the SGLT2 inhibitor group was 33.49%, while their incidence in the group without SGLT2 inhibitors was 11.72%. All types of urinary infections were included in this study, whether documented in a healthcare facility or not. The authors report a threefold higher risk of developing urinary tract infections associated with the use of SGLT2 inhibitors [11]. In a 2015 report, the US Food and Drug Administration identified 19 cases of urosepsis in patients treated with SGLT2 inhibitors [12]. However, in large meta-analyses and population studies, SGLT2 inhibitors are generally not associated with an increased risk of urinary tract infections [13]. Only the VERTIS CV study demonstrated a significant increase in the risk of urinary tract infections associated with SGLT2 inhibitor therapy. Approximately 12% versus 10% of participants randomized to ertugliflozin and placebo, respectively, had urinary tract infections [14].

A systematic review of 86 randomized clinical trials involving over 50,000 patients shows that SGLT2 inhibitors are associated with an increased risk of genital infections, but these medications are not associated with a higher risk of developing urinary tract infections. The report indicates that high doses of dapagliflozin may be associated with a higher risk of urinary tract infections [15].

To date, only a few case reports describing patients on SGLT2 inhibitor therapy who develop emphysematous pyelonephritis have been published. In all reported cases, patients had comorbidities such as diabetes mellitus, congenital or acquired obstructive uropathies, or underwent immunosuppressive treatment [16–20].

In the present case report, the patient is a man without diabetes mellitus, immunosuppression, or obstructed drainage, as typically seen in cases of emphysematous pyelonephritis. The only possible predisposing factor is the use of an SGLT2 inhibitor. Microbiological studies did not isolate a causative agent, likely due to the initiation of antibiotic treatment in outpatient conditions.

As of now, there is no established protocol regarding the optimal diagnostic approach to emphysematous pyelonephritis. Imaging studies are of vital importance, and although ultrasonography is a valid option, urologic computed tomography (CT) is the modality of choice when it comes to EPN [1]. According to some researchers, conservative treatment comprising active fluid-electrolyte supplementation, monitoring of blood glucose levels, and active antibiotic treatment should be followed by immediate nephrectomy [7]. The development of minimally invasive surgery, such as the placement of double-J stents, percutaneous drainage, and percutaneous nephrostomy, has led to a significant reduction in mortality rates compared to conventional therapy and nephrectomy [3]. The classification proposed in 2000 by Huang and Tseng is a fundamental method for determining the disease class and serves as a starting point for its treatment [8]. In the initial report by Huang and Tseng, all patients with class 1 and 2 EPN required percutaneous nephrostomy tube or ureteral stents. However, current evidence suggests that patients with less severe symptoms (such as class 1 and 2 EPN) and no urinary obstruction could have excellent outcomes with noninvasive treatment only. In patients with poor EPN control (especially class 3 and 4 patients) who do not respond to initial conservative management and percutaneous drainage, a subsequent nephrectomy remains necessary [1]. Despite the patient having CT evidence of emphysematous pyelonephritis class 1, where conservative

treatment is typically performed, in the reported case interventional treatment was necessary due to the lack of improvement, worsening of the thrombocytopenia, the tendency toward hypotension, and the initiation of urgent hemodialysis. Thrombocytopenia, septic shock, and the need for hemodialysis are specifically mentioned as negative predictive factors in patients on conservative treatment [21].

Conclusion

Emphysematous pyelonephritis represents a rare but potentially life-threatening infection with a high mortality rate, necessitating prompt diagnosis and treatment. Therefore, specialists need to be aware of the key predisposing factors, leading to its development. They should also consider other albeit rarer predisposing conditions, including the use of SGLT2 inhibitors. Although the frequency of urinary tract infections following the use of SGLT2 inhibitors is relatively low, their widespread application for treatment of numerous socially significant diseases underscores the need to be familiar with all potential risks associated with their use, including the development of severe urinary tract infections such as emphysematous pyelonephritis.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.A. collected clinical information, drafted the manuscript, and was responsible for the critical revision of the manuscript for important intellectual content. N.D. and M.V. supported the data collection and helped draft the manuscript. All authors participated in revising the draft manuscript and approving the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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