Renal vein thrombosis complicating severe acute pyelonephritis with renal abscesses and associated bacteraemia caused by extended-spectrum beta-lactamase producing *Escherichia coli*

Stelios F. Assimakopoulos¹ · Pantelis Kraniotis² · Charalambos Gogos¹ · Markos Marangos¹

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Abstract

Acute pyelonephritis might be complicated by the formation of renal and perirenal abscesses and very rarely by renal vein thrombosis, which is a life-threatening condition. The main causative agents of acute pyelonephritis are enterobacteriaceae with the incidence of extended-spectrum beta-lactamase (ESBL)-producing strains increasing worldwide. We present the case of a 71-year-old Greek man with history of diabetes mellitus and recent hospitalization, who suffered from severe pyelonephritis with renal abscesses formation and associated bacteraemia caused by ESBL-producing *Escherichia coli*, complicated by extensive thrombosis of the ipsilateral renal vein and its branches, protruding also in the inferior vena cava. Our patient was effectively treated with anticoagulants and targeted antibiotic therapy, respectively, consisted of low molecular weight heparin transitioned to oral acenocoumarol for 3 months and 2-week course of intravenous meropenem followed by oral fosfomycin for additional 3 weeks as quidded by clinical and computed tomographic follow-up. In conclusion, in complicated urinary infections, caused by ESBL-producing enterobacteriaceae, oral fosfomycin might represent an effective option for step-down therapy of carbapenems, allowing the shortness of the duration of patient's hospitalization and carbapenem use.

Keywords Urinary tract infections · Renal abscess · Renal vein thrombosis · Extended-spectrum beta-lactamase · ESBL · Fosfomycin

Introduction

Renal vein thrombosis is a very rare and life-threatening complication of acute pyelonephritis [1]. To our knowledge, only seven cases of RVT complicating acute pyelonephritis have been described in the literature [1]. The main pathogen implicated as a causative agent in renal abscesses is by far *Escherichia coli* (*E. coli*), while there is a continuously increasing prevalence of community-acquired urinary infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae [2, 3]. We describe herein, a case of severe pyelonephritis with the formation of multiple

renal abscesses and bacteraemia, due to ESBL-producing *E. coli*, complicated by extensive thrombosis of the ipsilateral renal vein and its branches, protruding also in the inferior vena cava.

Case report

A 71-year-old man with a past medical history of diabetes mellitus type II and recent hospitalization (2 months ago), for surgical repair of right scrotal hernia, presented fever (39.5 °C) with rigors and dysuria 2 weeks before admission to our clinic. Urinalysis showed pyuria, bacteriuria and nitrites presence, and ciprofloxacin 500 mg bid was empirically administered by his urologist. Urine culture grew *E. coli* resistant to b-lactams including aztreonam, b-lactam/b-lactamase inhibitors (piperacillin–tazobactam MIC > 16/4 µg/ml), fluoroquinolones, trimethoprim/sulfamethoxazole and sensitive to aminoglycosides amikacin and netilmicin, carbapenems and colimycin. Ciprofloxacin was discontinued and amikacin was prescribed 1 g once a

✉ Stelios F. Assimakopoulos
sassim@upatras.gr

¹ Division of Infectious Diseases, Department of Internal Medicine, University General Hospital of Patras, 26504 Patras, Greece

² Department of Radiology, University General Hospital of Patras, 26504 Patras, Greece

day intramuscularly with gradual clinical improvement and resolution of fever the fourth day of treatment. However, due to increase in creatinine values from 1.0 mg/dL pre-treatment to 2.1 mg/dL the seventh day of treatment, amikacin was discontinued. 4 days later patient's symptoms relapsed with fever 39.5 °C with rigors, anorexia, nausea and flank pain and the next day he was referred to our hospital for further evaluation and treatment. Physical examination revealed a shivering man with 39.5 °C of temperature, blood pressure 130/70 mm Hg, pulse rate 110 beats per minute, respiratory rate 14 breaths per minute with an oxygen saturation of 98% on room air. He weighed 74 kg with a BMI of 25.6 kg/m² and a height of 170 cm. Right costovertebral angle tenderness (Giordano sign) was observed on palpation. The physical examination was otherwise unremarkable. Blood tests showed leucocytosis (19,300/mm³ with 87% polymorphonuclear predominance), normal hemoglobin levels 13.6 g/dL and platelets count of 337,000/μL. CRP levels were elevated at 28.5 IU/L (normal value <0.5 IU/L). Biochemical tests revealed hyperglycaemia of 380 mg/dL (without diabetic ketoacidosis), normal levels of aminotransferases, direct and indirect bilirubin and lactate dehydrogenase, while also renal function had returned to normal with creatinine levels of 1.1 mg/dL and urea 36 mg/dL. Prothrombin and partial thromboplastin times were normal, d-dimers were increased at 2.49 μg/ml and fibrinogen was also increased at 613 mg/dL. Urinalysis showed greater than 100 white blood cells and 100 bacteria per high-power field, microscopic haematuria with 30–40 red blood cells per high-power field and

presence of nitrates. Urine and blood cultures grew *E. coli* with the same antibiogram as reported in the patient's pre-hospital evaluation. Initial imaging evaluation of the right kidney and ureter with ultrasonography did not show evidence of urinary flow obstruction but multiple hypoechoic cystic lesions with inner diaphragms were detected in the right renal parenchyma. Further imaging evaluation with abdominal computed tomography (CT scan) with intravenous iodine contrast medium showed extensive thrombosis of the right renal vein and its branches protruding to the inferior vena cava (Fig. 1a) and right kidney pyelonephritis with multiple renal abscesses the largest exhibiting a diameter of 2.1 cm (Fig. 1b). Thrombophilia screening including protein S, protein C, antithrombin deficiency, factor V Leiden, prothrombin 20210A and MTHFR (C677T) mutations, homocysteine plasma level, paroxysmal nocturnal hemoglobinuria flow cytometry flair, antiphospholipid antibodies, lupus anticoagulant, anti-cardiolipin and b2 glycoprotein-1 autoantibodies turned out negative.

The patient was treated with intravenous meropenem 2 g (in 3-h intravenous infusion) every 8 h and anticoagulation with low molecular weight heparin, which was transitioned to oral acenocoumarol. The patient became asymptomatic and afebrile the fourth day of his hospitalization with gradual reduction of inflammatory markers. A repeated CT imaging performed 10 days after the initial CT, showed reduction of renal abscesses dimensions, which were measured up to 1.5 cm in their maximum diameter as compared to 2.1 cm at the initial imaging. Intravenous

Fig. 1 **a, c, e** Volume-rendered coronal reformatted CT images. Renal parenchymal phase post IV contrast. Imaging at patient's initial presentation (**a**), at 5-week interval of antibiotic and anticoagulant treatment (**c**), and at 12-week interval of anticoagulant therapy (**e**). **b, d, f** Minimum intensity projection (MinIP) reformatted images. Renal parenchymal phase post IV contrast at presentation (**b**), at 5 weeks (**d**), and at 12 weeks (**f**). **a** There is thrombus within the right renal vein (arrow) and its branches (arrowhead). The thrombus is protruding in the inferior vena cava (asterisk). **b** Two of the largest abscesses

are depicted in the right kidney (arrows). **c** There is no thrombus in the right renal vein and its branches. However, a small residual component still exists in the inferior vena cava (asterisk). **d** There are only small residual changes (arrows), in the corresponding positions of the abscesses depicted in **b**, consistent with the formation of scar tissue, 5 weeks after treatment. There is no appreciable interval change in the lower pole renal cyst, on the right. **e** The residual inferior vena cava thrombus seen in previous image is now imperceptible (circle). **f** A typical scar is left in the renal parenchyma (arrow)

meropenem was administered for a total of 14 days. The patient was discharged on oral fosfomycin 3 g once daily for 3 days followed by every-other-day 3 g dosing and acenocoumarol with an INR target of 2.5 (2.0–3.0). On this treatment, the patient remained asymptomatic and afebrile and a repeated retroperitoneal CT performed 3 weeks after his hospital discharge demonstrated that the extensive right renal vein thrombosis had completely resolved and only a small residual thrombus had remained in the inferior vena cava (Fig. 1c). The renal abscesses had also resolved with only small residual changes, consistent with the formation of scar tissue (Fig. 1d). Oral fosfomycin was discontinued and acenocoumarol was administered for additional 7 weeks (total duration of anticoagulation 3 months as provoked deep venous thrombosis). A follow-up CT performed at 3 months after the initial CT imaging, showed that the residual inferior vena cava thrombus seen in the previous CT had been totally resolved (Fig. 1e), while a typical scar was left in the renal parenchyma (Fig. 1f). To date, 2 years later, no relapse of the patient's pyelonephritis/renal abscess and renal vein thrombosis has occurred.

Discussion

Renal vein thrombosis occurs mainly due to systemic hypercoagulable states, the most common being nephrotic syndrome with urinary losses of anticoagulant proteins [4]. Other prothrombotic aetiologies of renal vein thrombosis include hyperhomocysteinemia, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, renal cell carcinoma or other active malignancy, renal transplantation, trauma, postpartum, oral contraceptive use and sepsis syndrome [5–10]. Only seven previous cases of RVT complicating acute pyelonephritis or renal and perirenal abscesses have been described [1].

The potential mechanism of renal vein thrombosis in the presented bacteremic patient might be an endotoxin-induced procoagulant state. Endotoxin, a lipopolysaccharide found in the cell wall of Gram-negative bacteria, might promote a prothrombotic state through changes in the endothelial surface, by increasing the expression of the gene encoding tissue factor (procoagulant molecule) and by rising endothelial cell production of the fibrinolytic inhibitor plasminogen activator inhibitor-1 [11]. A mechanism of disseminated intravascular coagulation in the context of our patient's serious infection is not supported by laboratory findings because there was no thrombocytopenia or increased markers of haemolysis (indirect bilirubin and lactate dehydrogenase), coagulation parameters were not prolonged and fibrinogen was not decreased.

The therapeutic approach to our patient was directed towards two parallel directions; anticoagulant treatment for

renal vein thrombosis and effective antimicrobial therapy of the ESBL-producing *E. coli*-induced renal infection and bacteraemia. Since no underlying thrombophilic condition was found, we considered that renal vein thrombosis was provoked in our patient by his serious acute pyelonephritis and renal abscesses. Low molecular weight heparin with subsequent oral anticoagulation for 3 months, as commonly used in other provoked thromboembolic states, proved to be an effective treatment, as also demonstrated in other reported similar cases of renal vein thrombosis complicating renal infection [1, 12].

The causative agent of our patient's renal infection and bacteraemia was demonstrated to be an ESBL-producing *E. coli* strain. ESBL are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins and the monobactam aztreonam, while emergence of plasmid-mediated quinolone resistance in ESBL-producing isolates has become a global problem for treating these infections [2]. Despite sensitivity of our patient's pathogen to aminoglycosides, induction of renal toxicity excluded this therapeutic option. In this context, carbapenem use was reasonable and almost inevitable. Alternative to carbapenems options include the beta-lactam/beta-lactamase inhibitor combinations of piperacillin–tazobactam, ceftolozane–tazobactam and ceftazidime–avibactam [13]. The last two options were not available in Greece when this case occurred, while piperacillin–tazobactam was not used owing to increased MIC ($> 16/4 \mu\text{g/mL}$) [13, 14].

Renal abscesses < 5 cm in diameter, are initially treated with antimicrobial therapy alone (without drainage) [15]. In case of clinical response, the intravenous antimicrobial treatment is instituted for 2 weeks followed by oral step-down therapy, which is extended for at least two additional weeks, depending on the results of radiographic follow-up [16]. However, in the case of ESBL-associated upper urinary tract infections, the selection of oral step-down therapies is problematic, because these pathogens are commonly resistant to available oral options such as amoxycillin/clavulanate, oral cephalosporins, trimethoprim–sulfamethoxazole and fluoroquinolones.

Fosfomycin is an old agent that remains active against ESBL-producing *E. coli* strains, but it is currently only approved for a 3 g single-dose treatment of uncomplicated lower urinary tract infections. Two sequential studies, the PROOF and FOCUS, are being implemented and planned, respectively, to test the optimal dosing and the efficacy of fosfomycin over levofloxacin as oral step-down therapy in complicated urinary tract infections including pyelonephritis [3]. Pending these results, in our patient, we selected to give three consecutive daily oral doses of 3 g fosfomycin as a loading scheme, followed by every-other-day 3 g dosing for additional 3 weeks. This treatment schedule was proven an effective carbapenem step-down oral therapy,

as demonstrated by the complete resolution of clinical and radiological signs of renal infection and by the absence of relapse during follow-up.

In conclusion, we presented a rare case of extensive renal vein thrombosis complicating severe pyelonephritis with multiple abscesses formation and associated bacteraemia, caused by an ESBL-producing strain of *E. coli*. Our patient was effectively treated with anticoagulants, low molecular heparin transitioned to acenocoumarol, for 3 months and targeted antibiotic therapy consisted of 2-week course of intravenous meropenem followed by oral fosfomycin for additional 3 weeks as quidded by clinical and computed tomographic follow-up. In complicated urinary infections, caused by ESBL-producing enterobacteriaceae, oral fosfomycin might represent an effective option for oral step-down therapy of carbapenems, but results from randomized clinical studies are needed.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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