Emphysematous pyelonephritis and sepsis in a diabetic female patient caused by extended-spectrum beta-lactamase-producing Escherichia coli – case report

Abstract

Emphysematous pyelonephritis (EPN) is a rare, severe, spontaneous gas-forming infection of renal parenchyma and its surrounding areas. EPN was detected in diabetic patients. A 49-year-old female with type I diabetes mellitus presented with severe thrombocytopenia, acute kidney injury (AKI) and was in need of haemodialysis treatment. She had impaired liver function tests, with active urine sediment, indicating severe upper urinary tract infection with suspected sepsis. The contrast enhanced CT scan of the abdomen showed multiple areas of air density in renal parenchyma and perirenal regions, suggestive of left-side EPN. The blood and urine cultures reported growth of extended-spectrum beta-lactamase (ESBL) producing Escherichia coli. The final diagnosis of emphysematous pyelonephritis complicated with severe sepsis and AKI was established. The patient was managed conservatively with wide-spectrum antibiotics, fluid resuscitation, consistent blood sugar control, and haemodialysis treatment. Percutaneous drainage techniques (PCD) and nephrectomy were postponed because of the initial clinical response to the antibiotics treatment. However, the patient experienced sudden clinical deterioration and died only a few hours after the established diagnosis. An autopsy was not performed upon the patient’s family’s request. EPN should be highly suspected in poorly controlled diabetic patients with urinary tract infection and should be promptly recognized and aggressively treated. The patients with multiple risk factors had high mortality, even with timely diagnosis and combined (conservative and surgical) treatment.
1 Introduction

Emphysematous pyelonephritis (EPN) is a rare, life-threatening, acute necrotizing infection of the renal parenchyma and perirenal tissues caused by gas-forming uropathogens (1,2). Kelly H. and MacCallum reported the first case of EPN in 1898. Since then, all the following cases have been described mostly as single case reports, predominantly in female patients with poorly controlled diabetes mellitus or obstruction of the urinary tract (3). Escherichia coli and Klebsiella pneumonia were the most common causative pathogens isolated in up to 90% of the reported cases (4). EPN was mainly unilateral, with predominant left side involvement (60%) (1-4).

The symptoms of EPN were nonspecific, and more than 70% of cases presented with the classic triad of upper urinary tract infections (fever, flank pain, and pyuria) (1,2,4). In patients presenting with sepsis, septic shock, thrombocytopenia, altered consciousness, and acute kidney injury (AKI), EPN might have a fulminant course leading to death in 54.4% of the cases, despite the aggressive therapy (5,6).

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The management of patients with EPN consists of fluid resuscitation, antibiotics, consistent blood sugar control, surgical or percutaneous drainage (PCD), and/or nephrectomy (3-5). There is no well-defined algorithm for management and treatment (conservative vs. PCD vs. nephrectomy). The treatment is guided by individual experience, severity of clinical presentation, risk factors, and evolution of the clinical symptoms (4).

We report a case of left-side EPN in a diabetic female caused by ESBL-producing Escherichia coli, who presented with sepsis and AKI with a need for hemodialysis treatment.

2 Case presentation

A 49-year-old female was admitted to our hospital with high inflammatory parameters, suspected sepsis, severe thrombocytopenia, high fibrin degradation products, and acute kidney injury. The symptoms had started three days before admission, with high fever (up to 39°C), vomiting, diarrhoea, dysuria, and left flank pain. In the next few days, the clinical picture rapidly deteriorated with spontaneous bleeding from the mouth, dyspnoea, and oliguria. The patient had a medical history of poorly controlled type I diabetes mellitus, hypertension, coronary artery disease with PCI stenting (July 2022), surgically treated endometrial carcinoma (year 2005), and frequent cutaneous suppurative infections, treated with antibiotics. On physical examination, the patient was febrile (38°C), with heart rate of 105 beats per minute, blood pressure of 110/65 mmHg, normal oxygen saturation, with slight petechial bleeding on the lower extremities, and pain in the left flank region on percussion.

The laboratory investigations on admission showed high procalcitonin and C-reactive protein (CRP) levels with anaemia, severe thrombocytopenia, and high fibrin degradation products but normal haemostatic parameters. Urine analysis showed excess white blood cells (WBC) with nitrites and bacteria. The test for SARS-CoV-2 infection was negative. The patient had slightly impaired liver function tests with mixed hyperbilirubinaemia and high lactate dehydrogenase (LDH) of 1022 U/L (normal <248 U/L) (Table 1). Urgent abdominal ultrasound reported a slightly enlarged left kidney with increased parenchymal echogenicity and two small calculi in the left kidney with no hydronephrosis. The patient was diagnosed with acute
pyelonephritis, sepsis, and/or suspected disseminated intravascular coagulation (DIC). The empirical double parenteral antibiotic treatment with ceftriaxone and ciprofloxacin was started immediately.

On hospital day 2, the patient was treated with urgent hemodialysis due to oliguria and continuous rise of serum creatinine levels, with temporary clinical improvement. The contrast-enhanced CT scan of the abdomen reported an enlarged left kidney with multiple areas of air density in renal parenchyma and perirenal regions, suggestive of left-sided emphysematous pyelonephritis (Figure 1). The right kidney had normal CT findings. The peripheral blood smear revealed predominant neutrophilia (86%) with toxic granulations and rarely fragmented erythrocytes. After 24 hours, blood and urine cultures reported growth of resistant Escherichia coli (ESBL positive). Coproculture for Shiga toxin-producing Escherichia coli was negative. Direct and indirect Coombs test and serological identification for atypical pulmonary pathogens (pneumoslide) were negative. The final diagnosis of emphysematous pyelonephritis complicated with severe sepsis and AKI was established. The empirical double parenteral antibiotic treatment was changed to the intravenous application of carbapenems (meropenem 500 mg IV q8hr). A multidisciplinary team consisting of a nephrologist, an infectologist, and a urologist decided on conservative patient management because of the initial good clinical response with decreased serum procalcitonin levels. However, the patient experienced sudden clinical deterioration with hypotension, bradycardia, respiratory insufficiency, and acute neurological suffering. The patient died only a few hours after the diagnosis was set. An autopsy was not performed upon the patient’s family’s request.

3 Discussion

Emphysematous pyelonephritis is characterized by spontaneous gas-forming infection of the renal parenchyma and the surrounding areas (1,2). The exact pathogenesis and mechanisms of gas production in EPN are still unknown. The majority of published cases emphasized the presence of high tissue glucose in patients with poorly controlled diabetes as an excellent microenvironment for severe infection and

Table 1: Laboratory analyses on admission and on the second day of the hospitalization of the patient.

<table>
<thead>
<tr>
<th>Classification</th>
<th>On admission</th>
<th>2nd day</th>
<th>Referent values</th>
<th>On admission</th>
<th>2nd day</th>
<th>Referent values</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (x10⁹/L)</td>
<td>5.4</td>
<td>11.1</td>
<td>4.0-9.0</td>
<td>50</td>
<td>67</td>
<td>10-34</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>10.9</td>
<td>10.5</td>
<td>15-50</td>
<td>81</td>
<td>101</td>
<td>36-126</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>85.6</td>
<td>85.6</td>
<td>35-80</td>
<td>18</td>
<td>23</td>
<td>10-45</td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td>50.21</td>
<td>27</td>
<td>&lt; 0.5</td>
<td>65</td>
<td>111</td>
<td>&lt; 20.6</td>
</tr>
<tr>
<td>C-reactive protein mg/L</td>
<td>358</td>
<td>411</td>
<td>&lt; 6</td>
<td>33.7</td>
<td>73.2</td>
<td>&lt; 6.6</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>91</td>
<td>88</td>
<td>120-180</td>
<td>14.58</td>
<td>10.38</td>
<td>3.5-6.1</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>25</td>
<td>37</td>
<td>150-450</td>
<td>326</td>
<td>45-109</td>
<td></td>
</tr>
<tr>
<td>Albumin g/L</td>
<td>33</td>
<td>34</td>
<td>35-50</td>
<td>8.2</td>
<td>2.0-4.0</td>
<td></td>
</tr>
<tr>
<td>Serum lactate dehydrogenase (U/L)</td>
<td>1022</td>
<td>1464</td>
<td>&lt; 248</td>
<td>6791</td>
<td>9273</td>
<td>0-500</td>
</tr>
<tr>
<td>Serum creatine kinase (U/L)</td>
<td>73</td>
<td>419</td>
<td>24-173</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The growth of enteric gram-negative bacteria (E. Coli, Proteus mirabilis, Klebsiella pneumoniae) and fungi (Candida albicans) (7). The mentioned microorganisms obtain energy through the fermentation of glucose via the glycolytic pathway. The overgrowth of microorganisms leads to glucose metabolizing with massive production and accumulation of carbon dioxide and hydrogen in tissues, with consecutive infarction and further renal parenchyma damage (5,7). The presence of diabetic microangiopathy also impairs the clearance of these metabolic waste products and promotes vascular thrombosis and tissue inflammation. In cases of urinary tract obstruction, compromised renal circulation due to an increased intrapelviccalyceal pressure leads to poor tissue perfusion that favours the growth of gas-producing bacteria and failure of the antibacterial therapy (7).

The clinical manifestation of EPN tends to be non-specific and similar to the clinical presentations of classic upper urinary tract infections (uncomplicated acute pyelonephritis). Thrombocytopenia, AKI, altered consciousness, sepsis, and septic shock with high mortality were present in cases caused by multidrug-resistant bacteria (e.g., extended-spectrum beta-lactamase-producing bacteria) and/or patients with multiple risk factors (1-7). Diabetes, female gender, obstructive uropathy, and hypertension are well-known predisposing risk factors for the development of EPN and were found in more than 96% of all diagnosed cases. Immunocompromising diseases, such as tuberculosis, alcohol and drug abuse, neurogenic bladder, and acquired immunodeficiency syndrome, were often present among non-diabetic EPN patients (2). Rarely, EPN might also be seen in patients with

Figure 1: The contrast enhanced CT scan of the abdomen. Image is showing enlarged left kidney with multiple areas of air density in renal parenchyma, and perirenal regions, suggestive for left-sided emphysematous pyelonephritis: red arrow on image A and B – axial view and image C and D – coronal view. Image is from authors’ own archive.
autoimmune liver cirrhosis, hepatitis B infection, and hepatocellular carcinoma (8).

Our patient presented with severe thrombocytopenia, spontaneous mouth bleeding, anaemia, acute kidney injury, impaired liver function tests with mixed hyperbilirubinaemia, high LDH, and CRP levels, and active urine sediment, which indicated a severe upper urinary tract infection with sepsis. The absence of fragmented erythrocytes in peripheral blood smear and normal haemostatic parameters excluded the disseminated intravascular coagulation (DIC) diagnosis. A fulminant course of the upper urinary tract infection in a high-risk diabetic female accompanied with no response to dual empirical antibiotic treatment raised the suspicion of sepsis with ESBL-producing Escherichia coli. The patient’s initial antibiotic therapy was changed to an intravenous application of carbapenems. ESBL-producing bacteria were responsible for 6.3% to 37.8% of cases with acute pyelonephritis (APN) (9). Park et al. identified acute pyelonephritis with ESBL-producing bacteria as an independent prognostic factor for sepsis, septic shock, and poor treatment outcome (9). Almost one-third (31.7%) of EPN cases were caused by ESBL-producing bacteria (10). The ESBL-positive E. coli and ESBL-positive Klebsiella spp. were the most frequently isolated strains (22.2% and 9.5%, respectively) (9). Highly virulent strains of ESBL-positive E. coli, such as a special CTX-M-15-positive ST131 clonal group, have very high antibiotic resistance and were associated with emphysematous pyelonephritis with a fulminant course (10). Countertuitively, no significant association of ESBL infection was found with the patient’s admission to the intensive care unit or with increased mortality (11).

Prompt radiological diagnosis is vital for patients with EPN as early recognition could expedite the medical treatment, potentially avoiding more invasive interventions, including nephrectomy. The abdominal ultrasound in EPN typically shows echogenic foci in the kidney with posterior “dirty shadowing” caused by a reverberation artifact from the air. However, in severe cases, as in our patient, the significant amount of air might completely obscure the kidney and make ultrasound differentiation from surrounding bowel gas even impossible (12). Hence, CT is often necessary to make an accurate diagnosis of EPN. To avoid delay in diagnosis, Kone et al. proposed that a CT scan should be performed in all diabetic patients who have unexplained fever and systemic symptoms (13). CT provided better visualization and precise assessment of the amount of gas, the degree of renal parenchymal destruction, the presence of fluid collections, focal necrosis, and abscess (14). According to CT scan findings, Huang and Tseng et al. classified patients with EPN into the following classes: Class 1: gas in the collecting system only; Class 2: gas in the renal parenchyma without extension to the extrarenal space; Class 3A: extension of gas or abscess to the perinephric space; Class 3B: extension of gas or abscess to the pararenal space; and Class 4: bilateral EPN or solitary kidney with EPN (14). The severity of the process increases with each class, with Class 4 representing the worst form of EPN. This classification has an important predictive value for patients’ outcome and is part of all prognostic scoring systems.

Recently, Jain et al. proposed a prognostic scoring based on several adverse factors: age (>50 years), number of comorbidities (>2), leukocytosis, body mass index - BMI (> 30 kg/m2 or < 18 kg/m2), thrombocytopenia, serum creatinine levels (> 265 µmol/l), hypoalbuminaemia, Huang class II or III, hyponatraemia, and multidrug resistance (4). The patients are further classified into three groups: good-risk group (0-4 adverse factors), intermediate-risk group (5-7 adverse factors), and poor-risk group (8-10 adverse factors) (4). Based on the mentioned prognostic scoring model for risk stratification of these patients, the same authors developed an algorithm for managing patients with EPN. Prompt fluid resuscitation, wide-spectrum antibiotics, and consistent blood sugar control are cornerstones for effective treatment. Percutaneous drainage (PCD) and/or early or late nephrectomy is reserved for selected cases with initial conservative treatment failure (1,2,4,15). In the mentioned study, patients in the good-risk group were managed with antibiotics, followed by double J (DJ) stenting in case of a documented obstruction or percutaneous nephrostomy (PCN) if needed after stabilization. Percutaneous drainage was required in intermediate and poor-risk groups of patients with at least > 3 cm renal parenchymal collection (4). Early nephrectomy (EN) was reserved only for non-responders to other treatments. Treated with this algorithm for EPN management, patients in the good-risk group showed no mortality, and only one patient needed surgical treatment. From the intermediate-risk group, 14 patients (66.6%) were salvaged with PCD, and 3 (14.2%) survived after EN, with an overall mortality rate of 19%. All three patients (100%) from the poor-risk group have died (4).

Despite the morbidity and mortality of EPN, there are still conflicting reports regarding the most appropriate management. Over the years, the treatment of
EPN has evolved from early nephrectomy as a mandatory approach to less invasive kidney-sparing procedures (PCD). A recent systematic review of 210 patients with EPN demonstrated that the mortality from medical management alone was 50%, medical management combined with emergency nephrectomy was 25%, and medical management combined with percutaneous drainage was 13.5%. The mortality was significantly lower in patients undergoing PCD compared to other treatments (Pearson chi-square p <0.001), and only a small number of patients treated by this approach underwent delayed elective nephrectomy (16). Similar results were also obtained by other authors (17,18).

However, some studies, usually with a small number of patients, still recommended aggressive therapy due to the potentially life-threatening nature of the disease, favouring early nephrectomy (19).

According to the mentioned prognostic system, our patient was in the high-intermediate-risk group (7 adverse risk factors) with a 3A class on Huang and Tseng radiological scale. A multidisciplinary team selected conservative medical therapy as an initial treatment of choice for our patient because of the good clinical response to the applied wide-spectrum antibiotics. Emergency nephrectomy might be a reasonable option in our case since there were no drainable collections on the initial radiological imaging suitable for PCD. However, due to the growing number of studies favouring PCD as a golden standard for EPN management and the high risk of “on table dead”, our team suggested a control CT scan and a new assessment of renal collections for PCD. The patient died suddenly, only a few hours after obtaining the diagnosis.

4 Conclusion

Emphysematosus pyelonephritis should be highly suspected in poorly controlled diabetic patients with an upper urinary tract infection and should be promptly recognized and aggressively treated. ESBL-producing bacteria, especially Escherichia coli, might be the causative pathogen in a significant number of these patients. The patients should be promptly evaluated by CT scan and stratified according to their risk factors, which is a useful guideline for further management of these patients. Patients with multiple adverse risk factors were associated with high mortality, despite the timely diagnosis and combined (conservative and surgical) treatment.

Conflict of interest
None declared.

Inform consent of the relative of the patient
The close relative of the patient gave informed consent for the publication of her case.

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References
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