

# Complicated urinary tract infections associated with diabetes mellitus: Pathogenesis, diagnosis and management

Mouna Feki Mnif, Mahdi Kamoun, Faten Hadj Kacem, Zainab Bouaziz, Nadia Charfi, Fatma Mnif, Basma Ben Naceur, Nabila Rekik, Mohamed Abid

Department of Endocrinology, Hedi Chaker Hospital, 3029 Sfax, Tunisia

### ABSTRACT

Diabetes mellitus has a number of long-term effects on the genitourinary system. These effects predispose to bacterial urinary tract infections (UTIs) in the patient with diabetes mellitus. Complicated UTIs are also common and potentially life-threatening conditions. They include emphysematous pyelonephritis, emphysematous pyelitis/cystitis, xanthogranulomatous pyelonephritis, renal/perirenal abscess, and renal papillary necrosis. Improved outcomes of these entities may be achieved by early diagnosis, knowledge of common predisposing factors, appropriate clinical and radiological assessment, and prompt management. Herein we review complicated UTIs associated with diabetes mellitus in terms of pathogenesis, clinical manifestations, radiological features, and current management options.

**Key words:** Diabetes mellitus, emphysematous cystitis, emphysematous pyelitis, emphysematous pyelonephritis, renal abscess, renal papillary necrosis, xanthogranulomatous pyelonephritis

## INTRODUCTION

Diabetes mellitus is a major risk factor for urinary tract infections (UTIs) and is also associated with increased risk of certain complicated UTIs such as emphysematous pyelonephritis (EPN), emphysematous pyelitis (EP), emphysematous cystitis (EC), xanthogranulomatous pyelonephritis (XGP), renal/perirenal abscess, and renal papillary necrosis (RPN). Such conditions are potentially life-threatening and require prompt evaluation and management.<sup>[1]</sup>

Herein we review complicated UTIs associated with diabetes mellitus in terms of pathogenesis, clinical

manifestations, radiological features, and current management options.

## PATHOGENESIS

The increased frequency of UTIs in diabetic patients is likely due to several mechanisms including the presence of glycosuria, neutrophil dysfunction and increased adherence of the bacteria to uroepithelial cells. Factors that increase the risk of UTIs in diabetes include age, metabolic control, diabetic nephropathy, autonomic neuropathy and vascular complications.<sup>[1]</sup>

Emphysematous complications in the kidney or the bladder are likely to be due to the presence of organisms that rapidly ferment glucose and produce carbon dioxide. Impaired transport of metabolic end products due to impaired tissue perfusion in diabetes may also contribute.<sup>[2]</sup>

The pathogenesis of XGP is still obscure. In this condition, renal tissue is destroyed and replaced by hard, yellow

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**Corresponding Author:** Dr. Mahdi Kamoun, Department of Endocrinology, Hedi Chaker Hospital, Magida Boulila Avenue, 3029 Sfax, Tunisia.  
E-mail: mahdi\_kamoun@yahoo.fr

xanthogranulomatous material. Suggested etiologies of XGP include chronic renal obstruction and infection, alterations in lipid metabolism, lymphatic obstruction, and renal ischemia. Patients with XGP commonly have diabetes or immunodepression.<sup>[3,4]</sup>

Renal abscess is an uncommon infection of the urinary tract. It can develop by one of two general mechanisms: Hematogenous spread and ascending infection from the bladder.<sup>[5]</sup> Diabetes mellitus is a risk factor for the development of renal abscess in association with ascending infection. Anatomical abnormality in the urinary tract such as vesicoureteral reflux and renal stones is usually present. Perinephric abscess usually occurs because of disruption of a corticomedullary renal abscess or an obstructing renal pelvic stone.<sup>[5,6]</sup>

Pathogenesis of RPN is presumed to be due to a marginal change in vascular supply leading to infarction and sloughing of papillae.<sup>[7]</sup> Its etiology includes diabetes, analgesic abuse, sickle cell disease, pyelonephritis, renal vein thrombosis, tuberculosis, and obstructive uropathy. More than half the patients with RPN have two or more of these causative factors.<sup>[7]</sup>

## CLINICAL PICTURE OF COMPLICATED URINARY TRACT INFECTIONS IN DIABETES

### Emphysematous pyelonephritis

EPN is a severe, necrotizing form of multifocal bacterial nephritis with gas formation within the renal parenchyma. More than 200 cases have been reported in literature so far.<sup>[8]</sup> Underlying poorly controlled diabetes mellitus is present in up to 90% of affected patients.<sup>[9]</sup>

The commonest offending organisms are *Escherichia coli* and *Klebsiella* followed by *Proteus*.<sup>[9]</sup> The diagnosis of EPN is often delayed because the clinical manifestations are nonspecific and not different from the classic triad of upper UTI (i.e., fever, flank pain and pyuria).<sup>[9]</sup> Acute respiratory distress syndrome, disseminated intravascular coagulopathy, acute renal failure, disturbance of consciousness, and shock can reveal some severe forms.<sup>[8,9]</sup> Diabetic ketoacidosis is a very uncommon presentation, and only few cases has been reported so far.<sup>[8,10,11]</sup>

EPN requires a radiological diagnosis. Conventional radiography may demonstrate gas bubbles overlying the renal fossa. Ultrasonography (US) characteristically shows an enlarged kidney containing high-amplitude echoes within the renal parenchyma.<sup>[12]</sup> Computed tomography (CT) is the imaging procedure of choice to confirm the presence and extent of parenchymal gas.<sup>[9]</sup> A radiological classification

has been proposed based on the location of the gas in the kidney as follows: Class 1: Gas confined to the collecting system, class 2: Gas confined to the renal parenchyma, class 3A: Perinephric extension of gas or abscess, class 3B: Extension of gas beyond the Gerota fascia and class 4: Bilateral or emphysematous pyelonephritis in a solitary kidney.<sup>[2]</sup>

### Emphysematous pyelitis

EP is defined as the presence of gas localized to the renal collecting system. In contrast to EPN, only 59% of subjects had diabetes presumably due to a higher proportion of patients with obstruction in this group.<sup>[13]</sup> *E. coli* is again the most common organism. Patients have similar clinical symptoms to patients with noncomplicated pyelonephritis: Fever, nausea, vomiting, and abdominal pain. Leukocytosis and pyuria are observed in most patients. At conventional radiography, gas is seen filling and outlining the ureters and pelvicaliceal system. US or intravenous urography (IVU) may demonstrate an obstruction.<sup>[14]</sup> CT best delineates gas within the collecting system and helps exclude complications, such as renal or perirenal fluid collections, frank abscesses, or EPN.<sup>[15]</sup>

### Emphysematous cystitis

EC is a rare entity characterized by pockets of gas in and around the bladder wall produced by bacterial or fungal fermentation. More than 50% of patients with EC have diabetes mellitus. *E. coli* is the most common infecting organism.<sup>[16]</sup>

The clinical presentation of EC is nonspecific and ranges from incidental diagnosis on abdominal imaging to severe sepsis. Patients may complain of irritative symptoms, abdominal discomfort or hematuria. The presence of pneumaturia is a rare, although more specific, clinical finding.<sup>[17,18]</sup>

The radiographic findings provided the first and the only diagnostic clue. Nevertheless, CT is considered to be the preferred method of diagnosis because of its high sensitivity and specificity in the detection of abnormal gas and its anatomical extension.<sup>[19]</sup>

## XANTHOGRANULOMATOUS PYELONEPHRITIS

XGP is a rare entity representing 1% of all renal infections.<sup>[3]</sup> It most often occurs in middle-aged women with a history of recurrent UTIs. Two forms of XGP, a diffuse form (85%) and a focal form (15%), are well known. The typical presenting symptoms include flank pain, fever, malaise, anorexia, and weight loss. A unilateral renal mass can usually be palpated.<sup>[3]</sup> Urine cultures

most often reveal *E. coli* and *Proteus mirabilis*. Classic urographic triad in diffuse XGP consists of unilaterally decreased or absent renal excretion, a staghorn calculus, and a poorly defined mass or diffuse renal enlargement. Sonography typically reveals echogenic calculi and multiple hypoechoic structures representing purulent loculations.<sup>[3,4]</sup> CT is the mainstay of diagnostic imaging for XGP and is helpful in demonstrating extension of the process into adjacent organs. The most frequent findings in the CT scan are calculi, hydronephrosis, kidney enlargement, expansion of the calices, renal pelvis contraction, and hypodense areas, with parenchyma destruction.<sup>[3,4]</sup> The final diagnosis of XGP is based on histology, usually after nephrectomy.<sup>[3]</sup>

### Renal/perirenal abscess

A perinephric abscess is a collection of purulent material around the kidneys, with a presentation that is insidious. Diabetes is present in 30-40% of cases.<sup>[20]</sup> Presenting symptoms are often nonspecific. Only occasionally, a patient presents with a syndrome suggestive of acute pyelonephritis. The most common symptoms include fever, flank or abdominal pain, chills, dysuria, weight loss, lethargy, and gastrointestinal symptoms. A flank mass is palpable if the abscess is large or located in the inferior pole of the kidney space. The usual organisms include *E. coli*, *Klebsiella*, and *Proteus* species. IVU is often abnormal, but US or CT scan are the best means to establish the diagnosis of renal abscess. US or CT scan-guided aspiration of the abscess may then follow.<sup>[20]</sup>

### Renal papillary necrosis

RPN has a variable clinical course that ranges from a chronic, protracted, and relapsing form to an acute, rapidly progressive form. The acute progressive form is particularly rare, but the effects result in death from septicemia and renal failure. Patients with the more common chronic form may remain asymptomatic or symptomatic. The most common presenting symptoms in symptomatic patients include fever and chills, flank and/or abdominal pain, and hematuria. This condition should be suspected in diabetic subjects who develop recurrent episodes of UTI, renal colic, hematuria, obstructive uropathy, or unexplained renal failure.<sup>[21,22]</sup> IVU is the most sensitive investigation for RPN, but it is rarely used today because of the adverse effect of contrast media on renal function in diabetic patients. In patients with poor renal function, CT may demonstrate necrotic papillae allowing the diagnosis of RPN to be made.<sup>[21,22]</sup>

### Management of complicated UTIs in diabetes

The initial management of a patient with EPN is resuscitation; a three-pronged approach should be put

into place to address fluid/hemodynamic status, diabetic control and an antibiotic regimen. A decision must then be made as to whether medical therapy alone, percutaneous drainage or nephrectomy is required.<sup>[9]</sup>

Earlier series have stressed the need for urgent nephrectomy. With the advent of CT scanning, more powerful antibiotics, and better access to life support, an alternative conservative approach has emerged, based on appropriate antibiotics and percutaneous drainage.<sup>[9,23]</sup>

Nephrectomy is now limited to a select group of patients with EPN who are fit for surgery, and fulfill one or more of the following criteria: Possession of a nonfunctioning kidney; presentation of gross renal parenchymal destruction; existence of two or more risk factors (altered consciousness, thrombocytopenia, shock, and acute renal failure). Trials have been made with parental antibiotics and percutaneous drainage in classes 3A, 3B, and 4 in the absence of risk factors.<sup>[2,9]</sup>

Treatment of EP and EC involves broad-spectrum antimicrobial therapy, hyperglycemic control, and adequate urinary drainage with correction of any outlet obstruction. Patients with necrotizing infections will require more aggressive treatment that includes surgery.<sup>[18]</sup>

The gold-standard therapy for XGP is nephrectomy, which is total in the majority of cases. Nephrostomy before nephrectomy can be considered a method that facilitates surgery, because it allows a reduction in renal mass. Preoperative and postoperative broad-spectrum antibiotics and symptomatic management are also key factors for successful management of this condition.<sup>[3]</sup>

The development of antibiotics, advances in diagnostic modalities, and the introduction of nonsurgical intervention methods such as percutaneous drainage and aspiration have all contributed to the improved outcome of renal and perirenal abscesses. With these changes, the rate of complete recovery from renal and perirenal abscesses without surgery has increased, and reduced mortality has been documented in several studies.<sup>[20]</sup>

Treatment of RPN includes aggressive antibiotic therapy when infection is demonstrated. Relief of obstruction may also be required. The prognosis for this condition is not well defined.<sup>[21,22]</sup>

## CONCLUSIONS

Complicated UTIs are common and potentially life-threatening conditions in diabetic patients. These

entities include emphysematous conditions as well as renal/perirenal abscedation and RPN. Early diagnosis, knowledge of common predisposing factors, appropriate clinical and radiological assessment, and prolonged course of appropriate antibiotherapy are mandatory to improve prognosis.

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