



COVID-19 and Emphysematous Pyelonephritis Caused by *Candida glabrata*: An Exceptional Entity

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Abstract

Introduction: Emphysematous Pyelonephritis (EPN) is a necrotizing gas producing infection of the renal parenchyma that commonly occurs in patients with diabetes. EPN requires early diagnosis and treatment due to the possible life-threatening septic complications.

Case Report: A 75-year-old female with Diabetes Mellitus (DM) was hospitalized for a 10-day history of fever, left flank pain and nausea. Physical examination of the patient showed fever and left flank tenderness. Laboratory investigations revealed elevated inflammatory markers and hyperglycemia. Computed Tomography (CT) of the abdomen showed a large, obstructing calculus in the lower-pole calyx of the left kidney, associated with gas in the left excretory cavities. The use of empiric antibiotics started with ceftriaxone and diabetes was controlled. Drainage was indicated using double-J ureteral catheter. Urine culture grew *Candida glabrata*. On day 7 of treatment with fluconazole, the patient presented thrombocytopenia, dyspnea and a reappearance of fever. It was thus replaced by Caspofungin. COVID-19 polymerase chain reaction test from a nasal swab was positive. Thoracic CT scan showed COVID-19 typical infiltrates with an estimated 10% involvement. The patient required oxygen and corticosteroid therapy. She also presented ionic disorders including hypokalemia and severe hyponatremia. The evolution was towards death.

Conclusion: EPN is a serious, systemic infection, with a high potential for complication and death. Fungal etiology should be ruled out for patients not responding to the initial antibiotics.

Keywords: Emphysematous pyelonephritis; Diabetes; *Candida glabrata*; COVID-19

Introduction

Emphysematous Pyelonephritis (EPN), a rare and serious necrotizing infection, is a potentially life-threatening disease. EPN is characterized by the presence of gas in the renal parenchyma, perinephric tissue, and/or the urinary tract. It has been closely associated with poorly controlled Diabetes Mellitus (DM) and urinary tract structural abnormalities and immunosuppression [1].

The most frequently reported causative pathogens are *Escherichia coli* and *Klebsiella pneumoniae*, with rare reports of other Gram negative and anaerobic organisms [2,3]. Fungal etiology has rarely been reported [4]. *Candida albicans* is the most frequent agent of Candiduria, since it is part of the oropharyngeal, gastrointestinal and genital tract microbiota [5]. Other species of *Candida* spp., such as *Candida glabrata*, are not frequent in immunocompetent individuals. However, they were reported among diabetic patients [5]. Here, we report a case of an uncontrolled diabetic female patient diagnosed with emphysematous pyelonephritis caused by *Candida glabrata* associated with COVID-19 infection.

Case Presentation

A 75-year-old diabetic female was admitted to the hospital due to high-grade fever, severe left flank pain and nausea started 10 days before admission. There was no other previous medical history. On admission, the patient had a fever of 39°C. Tenderness of the left flank was noted on examination. Laboratory investigations revealed leukocytosis of 11400/mm³ with 88% of neutrophils and hyperglycemia. Elevated C-Reactive Protein levels (CRP) at 132 mg/L were noted. Blood cultures and cytobacteriological examination of urine were collected on admission. Computed Tomography (CT) of the abdomen with the use of contrast material revealed a large, obstructing calculus in the lower-pole calyx of the left kidney, associated with gas in the left excretory cavities (Figure 1). Abdominal CT showed a perirenal fat infiltration and a moderate dilatation renal pelvic calyx system (Figure 2, 3). The contralateral kidney was normal. Based on CT scan results, the diagnosis

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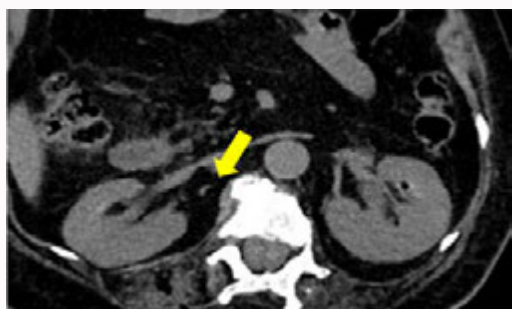


Figure 1: Axial section of abdominal computed tomography scan showing signs of gas collections in the renal calyx (arrow).



Figure 2: Coronal section of abdominal computed tomography scan showing perirenal blurring.

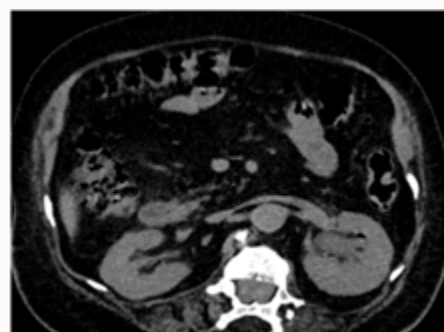


Figure 3: Axial section of abdominal computed tomography scan showing moderate dilatation of renal pelvic calyx system.

Table 1: Classification of emphysematous pyelonephritis in native kidneys [2].

Class 1	Gas in the collecting system
Class 2	Gas in the renal parenchyma with no extension beyond the organ
Class 3A	Gas and/or abscess in the perirenal space
Class 3B	Gas and/or abscess in the pararenal space
Class 4	Bilateral emphysematous pyelonephritis or affecting single solitary kidney

Discussion

EPN, a severe necrotizing kidney infection [6], occurs mostly in patients with DM and in females. Factors related to its pathogenesis included participation of gas-forming pathogens, tissues with a high concentration of glucose, impaired tissue perfusion and compromised immune system [2,6]. While DM is the most common predisposing factor for EPN, it has not been associated with increased mortality [7]. Other common risk factors for developing EPN include urinary tract obstruction, immunosuppression and end stage renal disease. A patient with a urinary tract obstruction has a 25% to 40% chance of developing secondary EPN [1,7].

Our patient was at an increased risk for developing EPN as her DM was not controlled and imaging showed kidney stones and urinary tract obstruction. Previous studies indicate that *Candida albicans* is the most frequently isolated species. However, an increase in the occurrence of non-albicans species of *Candida* has been reported, mainly due to the common use of fluconazole [8].

We report herein the sixth case of EPN caused by *Candida glabrata*, and we review all reported cases by searching PubMed publications till September 2023 [4,9-12] (Table 2). This review revealed that the majority of patients with EPN were females (5/6). The comorbidities associated with the development of EPN were diabetes among all cases and induced immunosuppression in a kidney transplant patient.

EPN can initially present with nonspecific symptoms, including fever, dysuria, hematuria, and abdominal pain. However, a sudden clinical deterioration might occur leading to septic shock [13]. Abdominal pain was present among all patients. In our case and the other reported cases, *Candida glabrata* was isolated in the urine culture. Except the case reported by C. Cases- Corona et al. [12], blood cultures were negative.

Management of EPN is based on radiological findings. The first and most widely used classification is that proposed by Huang et al. [2] (Table 1). However, no classification has been validated for EPN

of EPN Class 1 was confirmed in front of the presence of gas in the collecting system (Table 1).

The patient received empiric antibiotics based on ceftriaxone. Her diabetes was controlled with insulin therapy. Drainage was indicated using double-J ureteral catheter. The evolution was marked by the persistence of fever. Urine culture grew *Candida glabrata* which was sensitive to fluconazole (Minimum Inhibitory Concentration [MIC]: 2), echinocandins (MICs: caspofungin 0.03) and amphotericin B (MIC: 0.5). Fluconazole at a dose of 800 mg on day 1, followed by 400 mg per day was added to ceftriaxone. The disease evolution was initially favorable with a resolution of fever and abdominal pain. The patient's general condition improved.

On day 7 of treatment with fluconazole, we noted the reappearance of fever associated with dyspnea. Her oxygen saturation was 88% in room air and her respiratory rate of 22 breaths/min. Laboratory investigations revealed an elevated CRP at 224 mg/L and thrombocytopenia reaching 74000/mm³. Fluconazole was the most implicated in this thrombocytopenia. It was thus replaced by Caspofungin at a dose of 70 mg on day 1, then 50 mg per day. COVID-19 polymerase chain reaction test from a nasal swab was positive. Thoracic CT scan showed COVID-19 typical infiltrates with an estimated 10% involvement. The patient required oxygen and corticosteroid therapy. She had also presented ionic disorders including hypokalemia and severe hypernatremia. The evolution of the disease was towards death.

Table 2: Summary of all reported patients with *Candida glabrata* emphysematous pyelonephritis in the literature.

Year Reference	Age	Sex	Country	Predisposing conditions	Complains	CT constatations	Antifungal treatment	Surgical procedures	Duration treatment	Disease evolution
1988 [11]	61	F	Toyonaka	Diabetes	Fever Abdominal pain	-	Miconazole	No	2 weeks	Healed
1999 [4]	74	M	Germany	Diabetes	Fever Flank pain stuporous mental condition	Gas in the upper pole of both kidney	Intravenous Amphotericin B Bladder instillation of Amphotericin B	No	6 weeks	Healed
2010 [10]	64	F	Tunisia	Diabetes	Fever Abdominal pain	-	Fluconazole	No	-	Death (Septic shock)
2020 [9]	43	F	Brazil	Diabetes Hypertension	Fever Abdominal pain	Enlargement of the left kidney Gas collection perirenal blurring	Fluconazole	Urinary tract drainage Double J catheter implantation Left total nephrectomy	4 weeks	Healed
2020 [12]	53	F	Spain	Diabetes Kidney transplant Induction IS	Abdominal pain Dysuria malaise	Perinephretic abscess+ multiple intraparenchymatous collections	Caspofungin Amphotericin B	Percutaneous drainage abscess Transplant kidney nephrectomy	3 weeks	Healed
2023 Our case	74	F	Tunisia	Diabetes	Fever Flank pain	Gas collection and obstructing calculus in left renal calyx + perirenal blurring	Fluconazole Caspofungin	Double J catheter implantation	-	Death

CT: Computed Tomography; F: Female; M: Male; IS: Immunosuppression

of fungal etiology, that's why, so we cannot assure their benefit to aid in the management of these cases [12].

The initial regimens included fluconazole (3/6), amphotericin B associated with bladder instillation (1/6) or associated with Caspofungin (1/6). The average treatment duration was 4 weeks (range 2 to 6 weeks). In addition, three patients underwent surgical procedures.

The management of EPN consists of both surgical and medical treatment. Traditionally, early nephrectomy has been considered as the treatment of choice in EPN. It should be considered in front of a poor prognosis or the absence of improvement on conservative treatment [13].

The therapeutic choice depends on the condition patient and radiological classification. Huang et al. had defined in his series 4 classes according to radiological findings, which were adopted by the majority of authors in recent publications [2]. For localized PNE, such as our case, percutaneous drainage and/or removal of an obstruction combined with medical treatment should give good results. However, Huang et al. [2], reported that the success rate of those who had nephrectomy was 90% (9 of the 10 patients). For patients treated medically, estimates of mortality were higher than for those required surgical treatment, 70% vs. 30%, respectively [14].

The antifungal of choice for urinary tract infection secondary to *Candida* spp. is fluconazole [4,8,15]. Antifungal resistance is a current concern, particularly in strains of *Candida glabrata*. This pathogen has a wide variability in susceptibility to fluconazole, with a high rate of resistance [8,16]. For urinary tract infections caused by fluconazole resistant *Candida glabrata*, the drug of choice is Amphotericin B [17]. Echinocandins may be an alternative with minimal adverse events [17]. These antifungal agents interfere with fungal cell wall synthesis and are considered effective against *Candida glabrata* [18].

In the case presented, fluconazole was used initially, and in an

empirical way (considering *Candida albicans* to be more frequent). When analyzing the culture with *Candida glabrata* later in the outpatient clinic, there was a report of sensitivity to fluconazole, considering that the treatment was correct. However, in front of the reappearance of fever, thrombocytopenia linked to fluconazole and the unavailability of amphotericin B, the patient was treated with Caspofungin.

Referring to Table 2, although the number of case reports is too small to draw definite conclusions, it appears that the evolution in patients treated conservatively is favorable. The evolution for our patient was initially favorable. However, the added immunosuppression secondary to COVID-19 infection worsened the prognosis.

Conclusion

EPN is a serious systemic infection with a high potential for complication and death. The poor management of DM and urinary tract obstruction are the major risk factors. It is crucial to identify the disease as soon as possible, in order to avoid the need for invasive treatments. Abdominal CT scan is the most effective tool for an early diagnosis. Fungal origin should be suspected in patients who didn't respond to the initial antibiotics. The joint work of a multidisciplinary team including nephrology, infectious diseases, endocrinology, radiology and urology is essential for the therapeutic success and the total recovery of the patient.

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