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Case Report

A case of bilateral emphysematous pyelonephritis caused by *Candida albicans*

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ABSTRACT

Emphysematous pyelonephritis (EPN) is a life-threatening renal infection characterized by the formation of gas within the renal parenchyma and collecting duct system, as well as perinephric tissues. We herein report a case of bilateral EPN accompanied by the urinary tract infection caused by spherical growth of *Candida albicans* in a patient with underlying diabetes mellitus and prostate cancer. The diagnosis was assisted by computed tomography, urography, and gram staining. Despite immediate percutaneous catheter drainage and a 4-week course of antifungal treatment, the *C. albicans* infection was refractory, as indicated by continuous isolation from the urine, and the patient eventually died. A local autopsy of urinary organs revealed *C. albicans* in the renal tissue. EPN caused by *Candida* species frequently occurs in men, and almost all cases have underlying poorly controlled diabetes. This condition is subject to delayed diagnosis, which may lead to extended disease and high mortality. *Candida* species should be considered as causative microorganism for refractory EPN in patients with poorly controlled diabetes who are receiving antibiotic treatment. Gram staining may contribute to an early diagnosis of EPN caused by *Candida* species, which may require long-term antifungal therapy.

1. Introduction

Emphysematous pyelonephritis (EPN) is an acute life-threatening infection characterized by the production of gas in renal tissues. This infection is usually caused by enteric gram-negative bacilli, most frequently *Escherichia coli*, and is commonly associated with uncontrolled diabetes mellitus and obstructive uropathy [1,2]. Gas is produced either by proliferating gas-forming microorganisms or by renal hypoperfusion, which reduces gas elimination and increases the glucose concentration [3,4]. Bacterial EPN is associated with a rapid progression of gas formation and an overall mortality rate as high as 10–25% [5,6].

Fungal EPN is rare and not well described. However, *Candida* species, especially *Candida albicans*, are the most frequently isolated fungal species from urine [7]. This condition, called candiduria, is associated with risk factors such as an indwelling urethral catheter, surgical procedure, antibiotics usage, female sex, older age, diabetes mellitus, urinary tract disease, and immunosuppressive agents [8,9]. Treatment is not generally recommended for asymptomatic candiduria, except in cases involving patients in high-risk groups such as newborns, patients with neutropenia, and those undergoing urological intervention. By contrast, fluconazole is recommended for the treatment of symptomatic candiduria [10]. Here, we report an autopsy case of EPN caused by *C. albicans* in a patient with poorly controlled diabetes.

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Table 1
Laboratory findings on admission.

Blood cell count	
WBC	16,300/μl
neutrophils	68.7%
lymphocytes	28.6%
Hb	8.6 g/dl
Plt	51.2 × 10^4/μl
Serology	
CRP	18.3 mg/dl
Biochemistry	
TP	6.4 g/dl
Alb	1.5 g/dl
BUN	43 mg/dl
Cre	1.17 mg/dl
T-Bil	0.2 mg/dl
AST	11 IU/l
ALT	12 IU/l
ALP	260 IU/l
CK	13 IU/l
LDH	153 IU/l
Na	136 mEq/l
K	4.4 mEq/l
Cl	101 mEq/l
BS	557 mg/dl
HbA1c	9.9%
β-D glucan	130 pg/ml
Urine	
pH	5.5
Occult blood	3+
Protein	2+
Sugar	(−)
Sediment	
RBC	10–20/HPF
WBC	>100/HPF

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Plt, platelet; CRP, C-reactive protein; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; T-bil, total bilirubin; AST, aspartate aminotransferase; alanine aminotransferase; ALP, alkaline phosphatase; CL, creatine kinase; LDH, lactate dehydrogenase; BS, blood sugar; HbA1c, glycated hemoglobin.

2. Case report

A 91-year-old man was admitted to the hospital with a 10-day history of persistent fever, malaise, and anorexia. He had been administered chlormadinone acetate and dexamethasone (1 mg/day) for 13 years for the treatment of prostate cancer and a dipeptidyl peptidase-4 inhibitor and thiazolidine derivatives for 16 years for the treatment of diabetes mellitus. He had been bedridden for six months before admission, and had no history of urethral catheter insertion or urinary retention.

Upon admission, the patient's height and weight were 167 cm and 54.0 kg, respectively, and his body mass index (BMI) was 19.4 kg/m^2. His consciousness was alert, and his blood pressure, heart rate, respiratory rate, and body temperature were 128/66 mmHg, 108 beats/min (regular), 24 breaths/min, and 36.8 °C, respectively. A physical examination revealed dry mouth, decreased bilateral respiratory sounds, and tenderness in the left costovertebral angle. No other abnormal findings were observed during the physical examination, except symmetric muscle atrophy in the bilateral legs. Laboratory blood testing revealed a strong inflammatory response [white blood cell count (WBC), 16,300/μl and C-reactive protein (CRP), 18.3 mg/dl], renal dysfunction, hyperglycemia, and poorly controlled diabetes [glycated hemoglobin (HbA1c), 9.9%] (Table 1). Urinalysis revealed hematuria, proteinuria, and pyuria (Table 1). Plain abdominal computed tomography (CT) revealed bilateral renal cysts, left hydronephrosis, and air bubbles in the left kidney and left urinary tract (Fig. 1A and B). These findings of necrotizing renal parenchyma with intraparenchymal gas led to the diagnosis of EPN.

Subsequently, 8.3-Fr catheters were placed in the left renal cyst and left renal pelvis for percutaneous catheter drainage (PCD). Empirical antibiotic therapy with meropenem (1 g thrice daily) was initiated for the treatment of EPN, while insulin therapy was

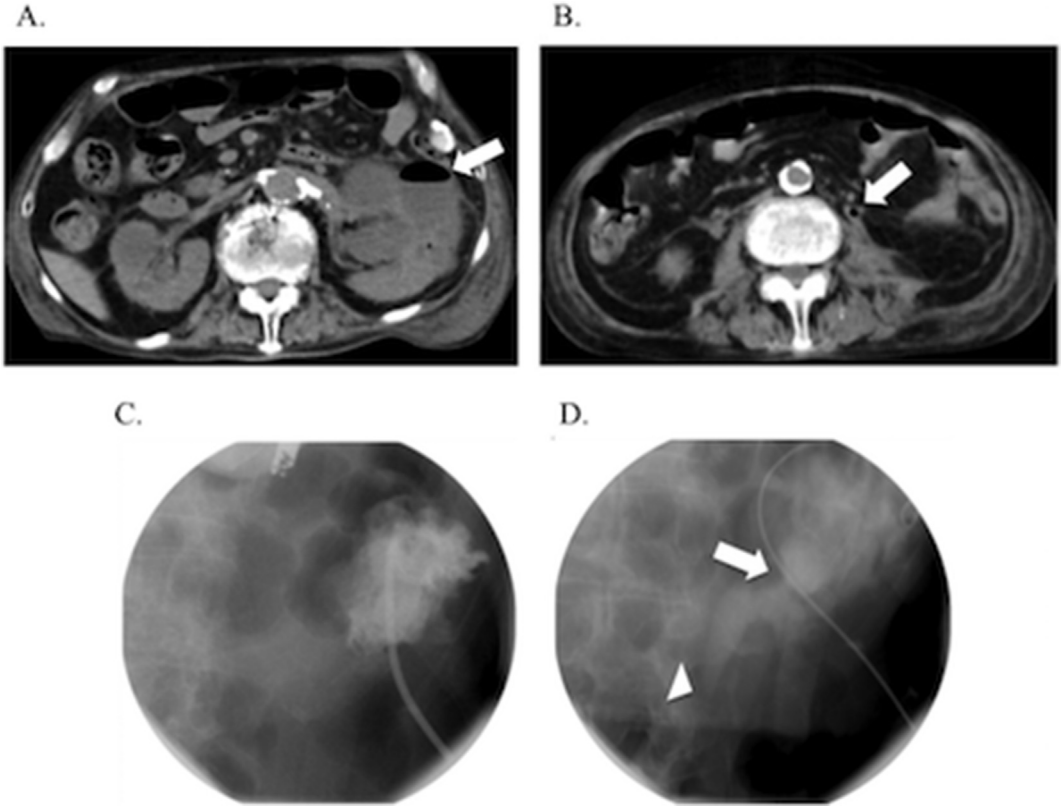

Fig. 1. Computed tomography images of left-sided hydronephrosis and gas formation in the left kidney cysts (A) and ureter (B). Urography of the left renal cyst (C). Connection between the cyst and left renal pelvis (arrow) and obstruction of the left urinary tract (arrowhead) (D).

initiated for diabetes control. The drainage tube from the left renal cyst yielded pus, and urography revealed obstruction of the left urinary tract (Fig. 1C) and of the connection between the renal cysts and renal pelvis (Fig. 1D). Subsequent catheter manipulation released the left urinary retention, causing a large amount of white, clumping pus in urine to flow into the bladder (Fig. 2A). Gram staining of the pus in urine revealed numerous neutrophils and yeasts with pseudohyphae (Fig. 2B). However, no microorganisms were isolated from a blood culture. *Candida*-related EPN was suspected, and intravenous fluconazole (400 mg once daily) was initiated. The left renal pelvis, cyst, and bladder were washed with saline every day. Two-day cultures of the specimen of pus with urine detected 10^5 colony-forming units (CFU)/ml of *C. albicans*, which was highly susceptible to antifungal agents (Table 2), and no other bacteria was grown. Finally, a diagnosis of EPN caused by *C. albicans* was made.

Subsequently, two sets of blood cultures were negative, and an ocular examination by an ophthalmologist revealed no complications of endophthalmitis. However, right hydronephrosis occurred 3 days after the diagnosis of left renal EPN (Fig. 2C). The patient was treated with additional PCD. Urography revealed that the right urinary tract was obstructed at the bladder transition (Fig. 2D), and the culture of a drainage catheter specimen detected *C. albicans* with an antifungal susceptibility identical to that obtained from the left EPN. After 3 weeks of antifungal therapy and continuous drainage, the patient's anorexia and costovertebral angle knocking pain improved, and the blood levels of inflammatory markers decreased (WBC, 5800/μl and CRP, 2.3 mg/dl). Although the amount of *C. albicans* isolated from drainage catheter decreased, the urine remained culture-positive. The patient died 30 days after admission due to aspiration pneumonia.

Table 2
Susceptibility of isolated *Candida albicans* to tested antifungal agents.

	MIC (μg/l)
Amphotericin B	0.5
Flucytosine	0.125
Fluconazole	0.25
Miconazole	0.25
Micafungin	0.06
Itraconazole	0.125
Voriconazole	0.015

A local autopsy of the urinary organs revealed that bilateral enlargement of the kidneys with cysts, medullary inflammation, and ureteral expansion (Fig. 3A). Only *C. albicans*, but not other microorganisms was grown by the culture of pus from the left renal pelvis, and not from the right kidney. A microscopic evaluation revealed numerous neutrophilic infiltrations in the bilateral renal medullae (Fig. 3B); however, yeast cells were observed only in the left kidney (Fig. 3C). A further pathological examination identified inflammatory cell infiltration in the bladder submucosa and localized adenocarcinoma (<2 mm) in the right prostate.

3. Discussion

Details of previously reported EPN cases caused by *Candida sp.* and our case are shown in Table 3 [11–21]. As noted, the present patient was elderly and had poorly controlled diabetes, both of which are risk factors for EPN and candiduria [2,8]. Notably, all reported cases were associated with uncontrolled diabetes mellitus, suggesting that this may be the most important risk factor for

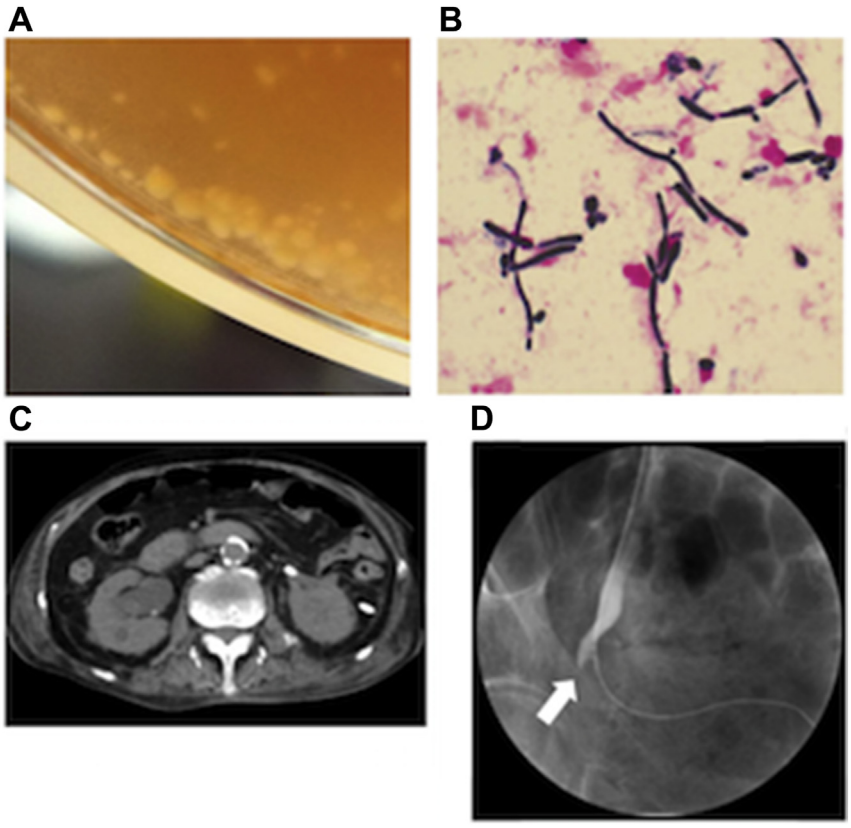

Fig. 2. Fungal balls from drainage (A). Gram stain of crushed fungal balls revealed neutrophils and yeast cells with pseudohyphae (magnification: × 1000) (B). Computed tomography image of the right-sided hydronephrosis (C). Urography of the right-sided urinary tract obstruction (D).

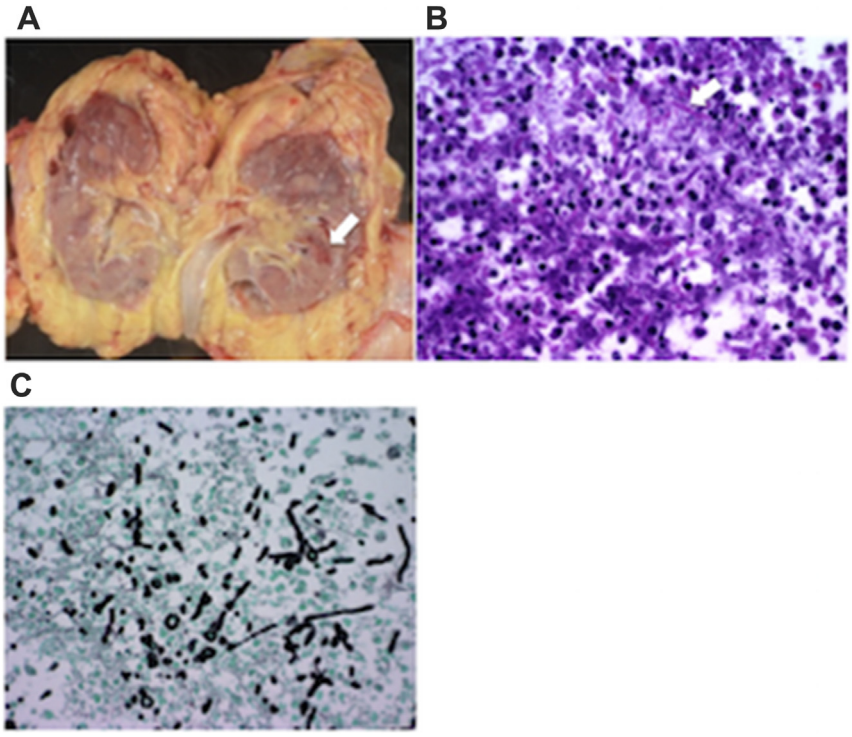

Fig. 3. Multiple cysts, ureter dilatation, and renal medullary inflammation (arrow) in the left kidney (A). Left-sided medullary inflammation with neutrophilic and mycelial infiltration (arrow) (hematoxylin and eosin; magnification: × 400) (B) and yeast cells with pseudohyphae (Grocott stain; magnification × 400) (C).

Table 3
Twelve cases of emphysematous pyelonephritis caused by *Candida* species.

Author Year	Age/Sex	Risk factors for urinary candidiasis [8,9]	*C.* species	Huang class	Treatment	Outcome
Seidenfeld SM. 1982 [11]	41/M	DM	*C. tropicalis*	N.D	Nephrectomy	Survived
Johnson JR. 1986 [12]	51/M	DM Horseshoe kidney Penile prosthesis implant	*C. albicans*	2	Nephrectomy	Survived
Jemal S. 1994 [13]	27/M	DM	*C.albicans*	3	Nephrectomy	Dead
Hildebrand TS. 1999 [14]	74/M	DM Prostate hypertrophy Urinary catheter	*C. tropicalis* *C. glabrata*	4	Amphotericin B	Survived
Wu VC. 2004 [15]	38/M	DM	*C. tropicalis*	4	PCD Fluconazole	Survived
Kamaliah MD. 2005 [16]	43/F	DM Female	*C. albicans*	3	Nephrectomy Fluconazole	Survived
Krishnasamy PV. 2010 [17]	51/M	DM	*C. tropicalis*	1	PCD Amphotericin B	Survived
Harrabi H. 2010 [18]	64/F	DM Female	*C. glabrata*	4	Amphotericin B	Dead
Ajili F. 2011 [19]	18/M	DM Megaurether	*C. albicans*	2	Nephrectomy Fluconazole	Survived
Bayrak O. 2012 [20]	46/F	DM Female	Unknown	3	Nephrectomy AFT	Dead
Bhat RA. 2012 [21]	60/F	DM Female	*C. parapsilosis*	3	Amphotericin B	Dead
Our case	91/M	DM Age Dexamethasone	*C. albicans*	4	PCD Fluconazole	Dead

Abbreviations: DM, diabetes mellitus; LC, liver cirrhosis; AFT, antifungal therapy; PCD, percutaneous catheter drainage; N.D, no data.

EPN caused by *Candida sp*. Furthermore, these cases were predominantly male (67%) and might be related to underlying urological diseases present in half of all male patients. However, the prostate adenocarcinoma in the present case was not sufficiently large to cause urethral constriction.

Huang et al. classified EPN into four categories according to the spread of gas on CT scans and proposed treatment strategies based on four risk factors, including thrombocytopenia, acute renal function impairment, disturbance of consciousness, and shock [22]. Classes 1, 2, 3, and 4 are respectively characterized by the spread of

gas limited to the collecting system, within the renal parenchyma without extension to the perinephric space, with extension to the perinephric space or pararenal space, and bilaterally. Approximately half of all bacterial EPN cases involve extended disease (Class 3 or 4), which is associated with higher mortality when compared with limited (Class 1 or 2) disease (29.5% vs. 5.0%) [1], and 10% were bilateral [1]. In contrast, 73% of cases of EPN caused by *Candida sp.* involved extended disease, and 36% were bilateral (Table 3).

Regarding treatment, PCD combined with antibiotic therapy is recommended for limited EPN or Class 3 EPN in low-risks, whereas nephrectomy is recommended for Class 3 EPN in high-risks. Bilateral PCD is recommended for Class 4 EPN because of the high risk leads to emergency nephrectomy. Our case was initially classified as Class 2 (only left kidney), but later progressed to Class 4 (bilateral kidneys) and was therefore treated with a combination of bilateral PCD and an antifungal agent. Nephrectomy was avoided because of the poorly controlled diabetes.

The tendency toward diagnostic delay and the rapid disease progression lead to the high mortality rate associated with *Candida sp.*-caused EPNs. The risk factors for EPN-associated mortality included thrombocytopenia, shock, altered sensorium, hemodialysis, extended EPN, and emergency nephrectomy [1,2]. In our case, extended EPN was the only applicable risk factor. In most cases of EPN, antibacterial but not antifungal agents are initiated empirically. However, gram staining of the urine contributed to early diagnosis and antifungal treatment initiation in our case.

The Infectious Diseases Society of America recommends fluconazole or amphotericin B as an antifungal agent in cases of pyelonephritis caused by *Candida* species [10]. In previously reported cases, *C. albicans* was the most frequent causative microorganism in cases of EPN caused by *Candida sp.*, followed by *C. tropicalis* and *C. glabrata*. We selected fluconazole in the present case because the patient's condition was not severe and a Gram stain of the pus revealed yeast with pseudohyphae, which is usually not a feature of *C. glabrata* [23,24]. Except for our case, all patients who received fluconazole therapy survived. Although no guidelines recommends a duration of antifungal treatment for this disease, previous reports describe 3–6 weeks of antifungal treatment [13–15,18]. In our case, *C. albicans* persisted in the left kidney after 4 weeks of antifungal treatment. The multiple cysts in the left kidney suggested potentially incomplete drainage, which may suggest that antifungal treatment should be continued until the culture becomes negative.

In conclusion, we report an autopsy case of bilateral EPN caused by *C. albicans*. Our findings suggest that *Candida* species should be considered as a causative microorganism of EPN in patients with diabetes and that Gram staining of specimens from infected foci may facilitate early diagnosis and treatment. Given its refractory nature, extended EPN due to *Candida* species may require a longer course of antifungal treatment with drainage.

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Conflicts of interest

None.

Authorship statement

All authors meet the ICMJE authorship criteria.

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