Two cases of fungal cyst infection in ADPKD: is this really a rare complication?

Laura Onuchic, Victor Augusto Hamamoto Sato, Precil Diego Miranda de Menezes Neves, Bruno Eduardo Pedroso Balbo, Antônio Abel Portela-Neto, Fernanda Trani Ferreira, Elieser Hitoshi Watanabe, Andreia Watanabe, Maria Cláudia Stockler de Almeida, Leonardo de Abreu Testagrossa, Pedro Renato Chocair and Luiz Fernando Onuchic

Abstract

Background: Cyst infection is a prevalent complication in autosomal dominant polycystic kidney disease (ADPKD) patients, however therapeutic and diagnostic approaches towards this condition remain unclear. The confirmation of a likely episode of cyst infection by isolating the pathogenic microorganism in a clinical scenario is possible only in the minority of cases. The available antimicrobial treatment guidelines, therefore, might not be appropriate to some patients.

Case presentation: We describe two unique cases of kidney cyst infection by Candida albicans, a condition that has not been previously described in literature. Both cases presented clear risk factors for Candida spp. infection. However, since there was no initial indication of cyst aspiration and culture, antifungal therapy was not immediately started and empirical treatment was initiated as recommended by the current guidelines. Antifungal treatment was instituted in both cases along the clinical course, according to their specificities.

Conclusion: Our report highlights the possibility of Candida spp. cyst infection. Failure of clinical improvement with antibiotics should raise the suspicion of a fungal infection. Identification of infected cysts should be pursued in such cases, particularly with PET-CT, and when technically possible followed by cyst aspiration and culture to guide treatment. Risk factors for this condition, such as Candida spp. colonization, previous antimicrobial therapy, hemodialysis, necrotizing pancreatitis, gastrointestinal/hepatobiliary surgical procedure, central venous catheter, total parenteral nutrition, diabetes mellitus and immunodeficiency (neutropenia < 500 neutrophils/mL, hematologic malignancy, chemotherapy, immunosuppressant drugs), should be also considered accepted criteria for empirical antifungal therapy.

Keywords: Autosomal dominant polycystic kidney disease, Cyst infection, Fungal infection, Candida albicans, Antifungal treatment

Background

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disorder, affecting approximately 1 in 1000 individuals [1–3]. Urinary tract infections (UTI) are among the most prevalent complications in this disease, occurring in 30–50% of the patients throughout their lifetime [4, 5]. Renal cyst infection (CI) is of particular interest in this scenario, since it is associated with significant morbidity and mortality [6, 7]. Gram-negative bacteria are the typical causing agents in these episodes, most often related to the ascending urinary tract route [8, 9]. Interestingly, the urine sediment may be bland and urine culture negative in CI, because some cysts are not contiguous to the collecting system [1, 10]. While the diagnosis of this condition may be difficult, in recent years positron emission tomography/computed tomography (PET-CT) has become the most sensitive imaging technique to establish it [1, 3, 8, 11].

Although less usually, alternative etiologic agents and infectious routes have been also associated with renal CI
in several reports [10, 12]. Fungal CI, however, is recognized as a rare event in ADPKD, with very limited prior description [13, 14]. Notably, in this report we present two cases of fungal CI with distinct outcomes, bringing attention to *Candida albicans* as a potential causative agent in CI and to the possibility that this complication be more common than currently assumed.

**Case presentation**

**Case 1**

A 34-year-old female with ADPKD was referred for persistent fever and malaise for the past 33 days. She reported symptoms and signs consistent with vaginal candidiasis 2 months prior to admission followed by right kidney obstruction secondary to ureteral calculus, which led to double-J stent placement. Two days after the procedure she developed fever of 101 °F and diffuse right abdominal pain, still sustained at admission. No urinary or gastrointestinal symptoms were reported. Urine and blood cultures were negative; white blood cell count and C-reactive protein (CRP), however, were elevated (14,650/mm³ and 389 mg/L, respectively). Initial computed tomography (CT) was inconclusive for CI. The patient was placed on broad-spectrum antibiotic regimens for the following 2 months, including intravenous (IV) ciprofloxacin 500 mg bid for 5 days, IV cephepime 1 g bid for 6 days, IV imipenem 500 mg bid plus metronidazole 500 mg tid for 20 days, and IV meropenem 1 g tid plus vancomycin 1 g bid plus fluconazole 200 mg sid for 4 days. Despite this treatment, she displayed no clinical improvement and developed acute kidney injury likely secondary to unresolved infection and potentially to vancomycin nephrotoxicity, with a rise in serum creatinine from 0.38 to 2.3 mg/dL. The laboratory tests are summarized in Table 1.

Once transferred to our center, the patient was submitted to a positron emission tomography-computed tomography (PET-CT) scan (Fig. 1a) which revealed high F-18 Fluor-deoxi-glucose (FDG) uptake in multiple right kidney cysts (Fig. 1b). Ultrasound-guided percutaneous drainage of the dominant suspected cyst followed by direct Grocott’s methenamine silver staining of the cyst content led to the diagnosis of fungal elements consistent with *Candida* spp., followed by isolation of *Candida albicans* from culture of the collected material. She was then immediately restarted on IV fluconazole 200 mg sid. During a 10-day period of this therapy, however, the patient maintained fever and malaise, associated with weight loss, progressive decline in renal function and very high levels of serum C-reactive protein (153–310 mg/L, for a normal reference range below 5 mg/L), with no tendency towards improvement. Given the refractoriness to this treatment, she was submitted to right nephrectomy (Fig. 1c, an estimated 1380-mL kidney), which led to renal failure and initiation of hemodialysis. Histopathology analysis confirmed this finding, showing cystic and pericys-tic hypha and pseudohypha invasion (Fig. 1d-f). At that moment she presented an unexpected tonic-clonic seizure not related to a significant electrolytic or hemodynamic disbalance but instead to a non-aneurysmatic subarachnoid hemorrhage documented by CT, which prompted her transfer to the intensive care unit.

Prolonged hospitalization led to urinary infection by carbapenemase-resistant *Klebsiella pneumoniae* followed by septic shock. An over two-week therapy with broad-spectrum antibiotics (IV tigecycline 50 mg bid plus ertapenem 1 g sid plus meropenem 1 g bid plus PO phosphomycin 3 g sid each 3 days) led to no clinical improvement and a new CT revealed multiple left kidney cysts with enhanced wall thickening. The patient eventually required high doses of vaspressors. In this context, left nephrectomy was performed (1093-mL kidney), resulting in clinical improvement. When recovering from surgery, however, she presented left-lower-limb deep venous thrombosis, requiring systemic anticoagulation. Critical falls in hemoglobin levels during several attempts of this intervention, in turn, made necessary the placement of a cava vein filter. After a debilitating eight-month period, she was discharged to her local medical facility for chronic hemodialysis still presenting significant frailty. Two months later, however, she died following a diagnosis of acute pancreatitis.

**Table 1** Summary of the main patients’ laboratory tests

| Laboratory Tests                        | Case 1       | Case 2       |
|----------------------------------------|--------------|--------------|
| Serum Creatinine at admission          | 2.3 mg/dL    | 2.3 mg/dL    |
| White Blood Cell Count at admission    | 14,650/mm³   | 9040/mm³     |
| Reactive C-Protein at admission        | 389 mg/L     | 102.9 mg/L   |
| Urine Leucocytes at admission          | > 100/field  | 49,000/mL    |
| Urine Red Blood Cells at admission     | > 100/field  | 5000/mL      |
| Blood Culture                          | Negative     | Negative     |
| Urine Culture                          | *Candida albicans* | Negative     |
| Cyst Aspiration Culture                | *Candida albicans* | *Candida albicans* |
Case 2
A 34-year-old male with ADPKD was admitted due to abdominal pain for the past 2 days, predominantly in the right flank and associated with temperature reaching up to 99.6 °F. His medical history included the diagnosis of arterial hypertension and chronic kidney disease stage IIIB (CKD-EPI of 37 mL/min/1.73m²) as well as an episode of intestinal perforation followed by enterectomy in 2013. The patient had been hospitalized twice during the previous 2 months due to UTIs associated with CI and renal function decline. He clinically improved in both occasions following treatment with IV linezolid 600 mg bid plus meropenem 1 g tid for 6 weeks, being discharged to complete antibiotic treatment on a home-care basis.

His serum creatinine was 2.3 mg/dL on admission, white blood cell count was 9040/mm³ and CRP 102.9 mg/L, while urinalysis showed 49,000 leucocytes/mL and 5000 erythrocytes/mL (Table 1). CT scan revealed obstructive acute abdomen secondary to bridles, pneumoperitoneum and gas bubbles in fat tissue adjacent to the transverse colon and hepatic angle. He was therefore submitted to laparotomy, bridle lysis and cavity washing. The surgical intervention was successful however CRP levels remained high, supporting the performance of PET-CT. Enlarged kidneys with multiple cysts containing homogeneous liquid or heterogeneous dense hyperproteic material were detected (Fig. 1g). This imaging assessment also revealed perirenal fascia thickening and high FDG uptake in an exophytic cyst (blue arrow), yielding the diagnosis of renal cyst infection.

Discussion and conclusion
Renal and/or hepatic CI is a common complication in ADPKD, with an incidence of approximately 0.01 episode/patient/year [11, 15]. Several of its aspects, however, remain not well defined, including diagnostic criteria and methods as well as treatment options and...
regimens [6, 9, 12]. Previous studies propose that a definite diagnosis of CI should be based on cyst aspirate showing neutrophil debris and/or a pathogenic microorganism [6, 16]. With minor variations, a common algorithm defines as likely CI the presence of fever (temperature > 38.5 °C for > 3 days); abdominal pain (particularly a palpable area of renal or liver tenderness); CRP > 50 mg/L, and absence of recent, significant intra-cystic bleeding or other causes of fever [1, 3, 11, 16, 17].

Since positive cyst cultures are usually not available, likely CI is far more prevalent than definite CI in the clinical scenario. Some reports detected a high prevalence of cyst infection among patients with advanced stages of chronic kidney disease. Indeed, the first case series using PET-CT to investigate cyst infection in ADPKD reported that 12 out 36 (33.3%) patients were on dialysis support [11], a finding in accordance with our previous report that identified 6 out 24 patients in this condition [10]. Of note, neither of the two currently reported cases developed such a complication while on dialysis.

Antibiotic treatment algorithms targeting CI are not robustly defined, since the infectious agent is isolated in a minority of cases. Jouret et al. [8] confirmed the pathogenic bacteria with cyst fluid cultures in only 3 of the 27 analyzed likely CI episodes while Sallee et al. [11] reported five positive cyst cultures among 41 evaluated CI events. In this scenario, different antibiotic approaches have been proposed and used, however none of them includes antifungal drugs as part of initial and second-line regimens. Based on their appropriate concentration within the cyst and antibiotic spectrum against gram-negative bacteria, currently proposed schemes classically include fluoroquinolones, particularly ciprofloxacin or levofloxacin [1, 3, 6, 7, 9]. Failure to improve with antibiotics, however, should raise the suspicion of a fungal infection. There is no consensus, nevertheless, whether routine empirical antifungal therapy should be administered in non-neutropenic patients, even if they are critically ill, since most studies in this specific group have not shown a survival benefit [18]. In our cases, however, both patients had risk factors accepted as criteria for empirical antifungal therapy. Invasive candidiasis is a critical condition associated with mortality in the same level as septic shock (40–60% mortality rate). In this context, the presence of well-defined risk factors for this condition should always be evaluated by the designated clinician, especially in an inpatient setting. Identifying risk factors may lead to a quick and accurate diagnosis in clinical scenarios where invasive fungemia is unexpected or isn’t contemplated in initial guidelines, such as in the described cases. Upon admission, patient 1 presented important risk factors such as Candida colonization, exposure to antibiotics and use of a double-J catheter. Patient 2, in turn, presented long hospital stay, previous antimicrobial therapy and an emergency gastrointestinal surgical procedure. Other potential risk factors include hemodialysis, necrotizing pancreatitis, central venous catheter, total parenteral nutrition, diabetes mellitus and immunodeficiency (neutropenia < 500 neutrophils/mL, hematologic malignancy, chemotherapy, immunosuppressant drugs) [19, 20]. A fundamental point, moreover, is not to underestimate the diagnostic value of cyst puncture/culture in difficult cases. In intra-abdominal candidiasis, only 4–20% of cases will be candidaemic [21]. To optimize blood culture sensitivity, 40–60 mL blood collection is recommended in adults.

Candida spp. grow very well in standard blood culture broths [22]. The detection of fungal antigen has been a useful approach to the presumptive diagnosis of invasive fungal infection in populations other than ADPKD. In patients with blood-culture-negative invasive candidiasis, mainly with intra-abdominal infection, the 1,3-β-D-glucan assay presented a sensitivity of 88% [23]. Some false-positive results, however, have been reported due to cross-reactions with certain hemodialysis filters, a caveat that could limit its application in patients undergoing hemodialysis support [24, 25].

Only less than 5% of Candida albicans isolates are resistant to azole [26]. This finding was corroborated by a retrospective study that analyzed the susceptibility of 153 Candida albicans isolates to three different antifungal drugs [27]. Only 1% of these isolates were resistant to fluconazole and 3% presented dose-dependent susceptibility; 96% of them, therefore, were susceptible to fluconazole. This same study showed that all isolates were susceptible to anidulafungin and only one of the 153 was resistant to amphotericin B. We chose, however, not to attempt these therapies in our first case due to the following reasons: 1) In a previously reported C. kruzei kidney cyst infection, none of the six analyzed cysts presented amphotericin B levels that reached the MIC level for the C. kruzei recovered isolate [13]. The patient from this case report was, in fact, eventually submitted to bilateral nephrectomy; and 2) It is important to point out that none of the echinocandins are excreted in the urine as an active drug, therefore these drugs are not contemplated in Candida urinary tract infection treatment algorithms [28].

Notably, we now report two cases of fungal CI, a very unusual form of this complication. To our knowledge, these are the first two documented cases of Candida albicans renal CI; one with successful response to antifungal therapy and another with no improvement following this therapeutic approach, requiring nephrectomy to be resolved. Our report highlights fungi as potential etiologic agents for CI in ADPKD and the importance of including this possibility within the differential diagnosis.
in specific circumstances and clinical courses. Immuno-
deficient patients, previous prolonged antibiotic use and 
*Candida* colonization should call attention to this poten-
tial diagnosis. In addition, the identification of two cases 
of *Candida albicans* renal CI by our group raises the 
possibility that fungal CI may not be as rare as currently 
assumed. The relevance of such considerations is par-
ticularly high given that first and second-line antibiotic 
regimens currently applied to CI in ADPKD do not 
include antifungal agents. The efficacy of antifungal 
therapeutic strategies according to the identified speci-
mens and its susceptibility and, most importantly, their 
corresponding intracystic antifungal levels, however, re-
main to be established.

**Abbreviations**

ADPKD: Autosomal Dominant Polycystic Kidney Disease; AmB: Amphotericin 
B; CI: Cyst Infection; CRP: C-reactive protein; CT: Computed Tomography; 
FDG: F-18 (18F) Fluoro-deoxy-glucose; MRI: Magnetic Resonance Imaging; PET-
CT: Positron Emission Tomography/Computed Tomography; UTI: Urinary Tract Infection

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**Authors’ contributions**

LD provided clinical care for the patient, performed literature searches, 
drafted and revised the article; VAYHs provided clinical care for the patient 
and revised the article; PDI provided clinical care for the patient, performed 
literature searches, drafted and revised the article; EBE provided clinical care 
for the patient, performed literature searches, drafted and revised the article; 
APN provided clinical care for the patient and revised the article; FTF 
provided clinical care for the patient and revisied the article; EHW provided 
clinical care for the patient and revised the article; AW provided clinical care 
for the patient and revised the article; MCSA provided clinical care for the 
patient, performed literature searches, drafted and revised the article; LAT 
provided histologic diagnosis for the patient and revised the article; PRC 
provided clinical care for the patient, performed literature searches and 
revised the article; LFO provided clinical care for the patient, performed 
literature searches, drafted and revised the article. All authors have read 
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Not applicable.

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Written consent to publish this information was obtained from study 
participants or their relatives.

**Competing interests**

The authors declare that they have no competing interests.

**Author details**

1. Department of Medicine, Division of Nephrology, University of São Paulo 
School of Medicine, Avenida Doutor Arnaldo, 455 – Sala 4304, São Paulo, SP 
01246-903, Brazil. 2. Nephrology and Internal Medicine Service, Oswaldo Cruz 
German Hospital, São Paulo, Brazil. 3. Division of Infectious Diseases, University 
of São Paulo School of Medicine, São Paulo, Brazil. 4. Division of Pathology, 
University of São Paulo School of Medicine, São Paulo, Brazil.

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