Chapter 31
Beyond Transplantation: Urinary Infectious Complications and Malignancy Risk in Autosomal Dominant Polycystic Kidney Disease

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Introduction

Polycystic kidney disease is the most common genetic kidney disorder; the autosomal dominant form accounts for 10% of cases of end-stage kidney disease (ESKD). The disease, which is attributed to mutations in PKD1 and PKD2 genes, is not only limited to the kidney but involves the formation of cysts in the liver, pancreas and seminal vesicles, vascular malformations in the brain and cardiovascular system and increased incidence of diverticulitis [1]. Kidney manifestations of the disease include rupture of cysts, presenting as hematuria or flank pain, nephrolithiasis, recurrent urinary tract infection, and chronic kidney disease with progression to ESKD. Kidney transplantation offers patients with ESKD the ability to recover their kidney function and alleviate symptoms associated with advanced kidney disease. However, the structural abnormalities associated with multi-organ cystic formations and vascular malformations are complications that persist post-transplant and must be periodically monitored. In this book chapter, we present a case highlighting the morbidity associated with recurrent urinary tract infections in autosomal dominant polycystic kidney disease (ADPCKD) patients post-transplantation and discuss the need for close monitoring of cystic malformations in the native kidneys given the increased risk for renal cell carcinoma (RCC) in this patient population.

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Patient History

A 57-year-old female with chronic kidney disease stage 5 secondary to ADPCKD, hypertension, rheumatoid arthritis, obesity status-post Roux-en-Y, and hypothyroidism underwent a preemptive living unrelated kidney transplant. At the time of transplant, her panel reactive antibody was 0%, and she had no preformed donor-specific antibodies. Her CMV serology was donor negative and recipient positive, and her EBV serology was donor and recipient positive. She received induction with anti-thymocyte globulin and steroids. Her maintenance immunosuppression included tacrolimus (target trough 8–10 ng/mL), prednisone 5 mg, and mycophenolate mofetil 1000 mg BID. She received prophylaxis with valganciclovir for 3 months and trimethoprim/sulfamethoxazole 400 mg/80 mg daily for 1 year. Her serum creatinine 4 weeks post-transplant was 0.9 mg/dL.

Before transplant, she had a history of several kidney cyst ruptures associated with back, pelvic and flank pain, hematuria, and nausea. She also had a long history of recurrent urinary tract infections (UTI), averaging two infections per year. Eight months before the transplant, she developed resistant extended-spectrum beta-lactamase (ESBL) *E. coli* urinary tract infections and had two infections within 2 months. After treatment, she was started on weekly fosfomycin for prophylaxis before transplant. At the time of transplant, she received intravenous ertapenem peri-operatively (7 days before surgery and continued for 4 days after) given screening urine culture was positive for multi-drug resistant (MDR) *E. coli,* and her double J stent was removed at 2 weeks rather than 4 weeks post-operatively.

Simultaneous bilateral native nephrectomy at the time of transplant was considered. However, this was ultimately not undertaken given concern for hemodynamic instability intra-operatively and to minimize the risk of surgical complications at the time of organ transplantation.

Question 1
What is the most common microorganism causing urinary tract infections post-kidney transplant?

A. E. coli.
B. Pseudomonas.
C. Staph aureus.
D. Klebsiella.
E. Enterococcus.

The correct answer is A.

Similar to non-immunocompromised patients, *E. coli* remains the most frequently isolated microorganism found on urine cultures accounting for more than 80% of UTIs. This is likely secondary to virulence adhesion structures intrinsic to the bacteria.

Clinical Course

She presented to the emergency department at 5 weeks post-transplant with fever, chills, malaise, nausea, and vomiting. Her labs on presentation revealed an acute kidney injury with a serum creatinine of 1.19 mg/dL, urinalysis was indicative of a urinary tract infection, and a urine culture subsequently demonstrated >100,000 MDR *E. coli*. She completed a 10-day course of IV ertapenem and was placed on nitrofurantoin for suppression. Two months later, she had an episode of cyst rupture associated with hematuria, back pain, nausea, and vomiting, which resolved with no associated febrile illness. The decision was made to undergo elective bilateral native nephrectomies given recurrent urinary tract infections despite suppressive therapy, as well as ongoing cyst rupture.

She ultimately underwent bilateral nephrectomy 4 months post-transplant, with no post-surgical complications. Pathology showed bilaterally enlarged kidneys with multiple large cysts consistent with ADPKD. The left kidney demonstrated focal microabscess with calcification and urate crystals. There were incidentally noted tubulopapillary adenomas in both kidneys (2 mm on the right and 2.5 mm on the left) (Fig. 31.1).

She was maintained on suppressive antibiotic therapy with nitrofurantoin for additional 3 months after bilateral nephrectomy. She has had no documented urinary tract infections since.

Question 2
Which diagnostic modality is recommended to screen for renal cell cancer in the native kidneys post-kidney transplantation?

A. CT scan of the abdomen and pelvis.
B. MRI of the abdomen and pelvis.
C. Urine cytology.

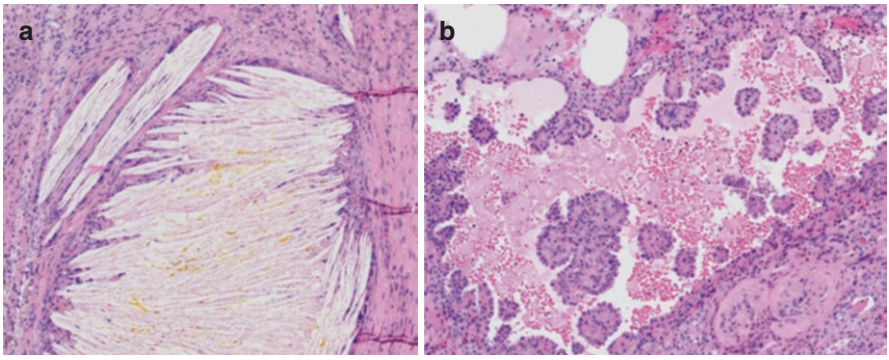

Fig. 31.1 Pathology of native kidneys post native nephrectomy (**a**) Aggregates of interstitial needle-shaped crystals with surrounding granulomatous reaction in areas of prior hemorrhage and tissue injury (**b**) Small papillary adenoma composed of fibrovascular cores lined by neoplastic epithelial cells

D. Ultrasonography.
E. None of the above.

The correct answer is E.

The incidence of renal cell carcinoma is increased in patients post-kidney transplantation, particularly those who have been on dialysis for longer periods prior to transplantation and have acquired cystic disease in their native kidneys. However, there is currently no evidence for the efficacy of a particular screening modality, nor there is a consensus on the frequency of screening that is indicated.

Discussion

UTIs are the most commonly occurring infection in kidney transplant (KT) recipients, with a wide range of prevalence between 20 and 80%. This variable reported incidence is in part due to the lack of uniform diagnostic criteria and the use of prophylactic antibiotics post-transplantation [2]. Notably, the peak incidence appears to be in the first 6 months post-transplant [3], which could be attributed to the use of induction immunosuppression and peri-operative instrumentation. The leading risk factors for UTI in KT recipients include advanced age, female gender, structural or anatomical abnormalities in the urinary tract system, diabetes mellitus, prior history of UTI, instrumentation, and intensity of immunosuppression [4]. Like non-transplanted patients, most UTIs are due to Gram-negative bacteria, with *E. coli* being the most frequently isolated microorganism on urine cultures.

Furthermore, the rate of occurrence of multi-drug resistant organisms (MDRO) has increased in recent years, with a study by Velioglu et al. reporting a rate of around 68% [5]. Interestingly, up to 85% of these isolates were resistant to sulfamethoxazole/trimethoprim (TMP-SMX), the most common antibiotic used for prophylaxis against Pneumocystis jirovecii post-transplantation. This is particularly concerning as UTIs due to MDROs have a threefold increased risk of recurrence in KT patients [6].

ADPKD patients have an increased risk of UTIs inherent to the anatomic abnormalities associated with enlarged cysts. A study comparing ADPCKD patients to non-diabetic patients found that the former had a significantly higher rate of post-transplant UTI (42.5% compared to the control group at 26%), and they were more likely to experience lethal infections [7]. On the other hand, a longitudinal study looking at 15-year outcomes of 534 ADPCKD patients compared to 4779 non-ADPCKD patients found that despite the increased prevalence of urinary tract infections in the ADPCKD arm, this was not statistically significant [8]. Rozanski et al. found similar patient and graft outcomes post-transplant in ADPCKD patients with pretransplant unilateral nephrectomies compared to those transplanted with intact native kidneys [9]. These results suggest that routine pretransplant nephrectomy in ADPCKD is not indicated, but an individualized approach must be considered for each patient based on their symptoms and inherent risk factors for UTIs.

In a single-center study of patients with ADPCKD who underwent native nephrectomy, UTI was the most common indication for native nephrectomy (45%), with most nephrectomies being performed post-transplant (71%) although the number of patients in this study was small [10]. Overall, nephrectomy for recurrent UTI in these patients was quite successful; of the 14 patients who underwent nephrectomy for UTI, 11 had resolution of their recurrent UTIs [10].

Patients with ADPCKD have been shown to have an increased risk of renal cell cancer that is independent of kidney function, as shown in a cohort study performed by Yu et al. of PCKD patients without CKD [11]. Aside from recurrent infections, native nephrectomy in patients with ADPCKD is indicated in cases with a concern for malignancy. A recent meta-analysis reported an incidence of 0.7% of de novo RCC in the native kidney and 0.2% in the transplanted kidney in kidney transplant recipients in general compared to an incidence of 0.005% in the general population [12]. Another study by Hajj et al. found that the prevalence of renal cell carcinoma in ADPCKD patients with chronic kidney failure was as high as 8.3%, and this increased to 12% when the authors accounted for patients who had been on dialysis for more than 1 year or had received kidney transplantation [13]. The latter, however, may be related to the development of acquired cystic disease rather than a direct association with the original underlying disease. Of note, the authors diagnosed RCC based on pathologic examination of kidneys following native nephrectomies for non-cancer-related indications.

Interestingly, the authors found that 36% of kidneys with RCC were also associated with papillary adenomas, which was present in our patient. Therefore, a high degree of suspicion should be kept for the development of RCC post-kidney transplantation, particularly in patients with ADPCKD as an underlying etiology of their kidney failure. However, there is no consensus on the optimal screening frequency and modality. This is left up to provider discretion.

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