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Renal cell carcinoma in a cat with polycystic kidney disease undergoing renal transplantation

Daniel J Adams[1], Jolie A Demchur[2] and Lillian R Aronson[3]

Abstract

Case summary A 10-year-old spayed female American Shorthair cat underwent renal transplantation due to worsening chronic kidney disease secondary to polycystic kidney disease. During transplantation, the right kidney grossly appeared to be more diseased than the left and was firmly adhered to the surrounding tissues. An intraoperative fine-needle aspirate of the right native kidney revealed inflammatory cells but no evidence of neoplasia. To create space for the allograft, a right nephrectomy was performed. Following nephrectomy, the right native kidney was submitted for biopsy. Biopsy results revealed a renal cell carcinoma. Although the cat initially recovered well from surgery, delayed graft function was a concern in the early postoperative period. Significant azotemia persisted and the cat began to have diarrhea. Erythematous skin lesions developed in the perineal and inguinal regions, which were suspected to be secondary to thromboembolic disease based on histopathology. The cat's clinical status continued to decline with development of signs of sepsis, followed by marked obtundation with uncontrollable seizures. Given the postoperative diagnosis of renal cell carcinoma and the cat's progressively declining clinical status, humane euthanasia was elected.

Relevance and novel information This case is the first to document renal cell carcinoma in a cat with polycystic kidney disease. An association of the two diseases has been reported in the human literature, but such a link has yet to be described in veterinary medicine. Given the association reported in the human literature, a plausible relationship between polycystic kidney disease and renal cell carcinoma in cats merits further investigation.

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Case description

A 10-year-old spayed female American Shorthair cat was referred to the Matthew J Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) for renal transplantation. The cat had a 1 year history of polyuria and polydipsia, and was diagnosed with polycystic kidney disease (PKD) by the referring veterinarian. During physical examination, both kidneys were markedly enlarged based on palpation. No other masses or organomegaly were appreciated, and peripheral lymph nodes were palpably within normal limits.

Initial hematologic analysis revealed a normocytic, normochromic, non-regenerative anemia (hematocrit 17.5%; reference interval [RI] 31.70–48.00%) and a lymphopenia (lymphocytes 0.414 $\times 10^3/\mu l$; RI 0.800–6.100 $\times 10^3/\mu l$). Serum biochemical analysis revealed moderate azotemia (blood urea nitrogen [BUN] 68 mg/dl [RI 15–32 mg/dl]; creatinine 2.7 mg/dl [RI 1.0–2.0 mg/dl]), hyperphosphatemia (phosphorus 6.8 mg/dl; RI 3.0–6.6 mg/dl) and mild hypomagnesemia (magnesium 1.8 mg/dl; RI 1.9–2.6 mg/dl). Urinalysis revealed borderline hyposthenuria

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(urine specific gravity 1.008), mild glucosuria (1+) and mild proteinuria (trace). No abnormalities were found when examining the urine sediment. A urine protein to creatinine ratio (1.32; RI 0–0.5) confirmed proteinuria. A concurrent urine culture was negative for any pathogens. Serum total thyroxine (1.49 µg/dl; RI 1.00–4.00 µg/dl) was within normal limits.

Thoracic radiographs were obtained to screen for concurrent disease and revealed no abnormalities. On abdominal ultrasound, multiple variably sized bilateral renal cysts and hepatic cysts were noted, consistent with PKD. Pyelectasia was observed, likely secondary to renal insufficiency. Cysts were as large as 19.2 mm in diameter in the left kidney and 23.5 mm in the right kidney.

The cat was systemically healthy aside from IRIS stage 3 chronic kidney disease (CKD) secondary to PKD and was considered an appropriate candidate for renal transplantation. The cat was administered darbepoetin (1 µg/kg SC) 8 days prior to surgery, blood typed and crossmatched to identify a compatible donor cat. An additional dose of darbepoetin (1 µg/kg SC) was administered 1 day prior to the procedure. Immunosuppression was initiated 4 days prior to surgery with ciclosporin (3 mg/kg PO q12h). Prednisolone (0.5 mg/kg PO q24h) was administered beginning on the day of the procedure in conjunction with ciclosporin for further immunosuppression.

During surgery, the abdomen was routinely entered and explored. The right kidney was severely enlarged and polycystic with neovascularization to the aorta and caudal vena cava. An anomalous bifurcation of the caudal vena cava was observed at the level of the adrenal glands. The right kidney was firmly adhered to the surrounding tissues, and although both kidneys were polycystic, the right appeared more severely affected than the left. Because of how grossly diseased and enlarged the right native kidney appeared, an intraoperative fine-needle aspirate was performed. Cytology revealed proteinaceous fluid, a moderate number of macrophages, rare neutrophils and few small lymphocytes, suggestive of chronic inflammation associated with a cystic or seromatous mass. No neoplastic cells were observed. A right nephrectomy was performed prior to transplantation and the entire native kidney was submitted for biopsy. Owing to the firm adhesions to the body wall and surrounding tissues, extensive dissection was necessary to remove the right native kidney. The donor kidney, provided by a cat in the MJR-VHUP renal transplant colony, was harvested and transplanted as previously described following removal of the right native kidney (supplementary material).[1,2] Although the allograft kidney was observed to be of normal color and firm consistency following transplantation, suggesting adequate perfusion, no urine production was identified.

Postoperatively, the cat was maintained on a fentanyl continuous rate infusion (CRI; 2–3.5 µg/kg/h). The morning after the procedure, the cat appeared bright, was ambulatory and readily ate and drank small amounts. However, throughout the day the cat's appetite began to decline. Owing to the decreased appetite, the ciclosporin dosage was decreased accordingly (2.5 mg/kg PO q12h), and ondansetron (0.2 mg/kg IV q8h) and pantoprazole (1 mg/kg IV q24h) were administered. Serum biochemical analysis revealed azotemia (BUN 70 mg/dl [RI 15–32 mg/dl], creatinine 2.4 mg/dl [RI 1.0–2.0 mg/dl]), hypocalcemia (calcium 7.3 mg/dl; RI 9.1–11.2 mg/dl) and hyperphosphatemia (phosphorus 8.2 mg/dl; RI 3.0–6.6 mg/dl). A focal ultrasound of the allograft kidney revealed venous and arterial Doppler signal throughout the entire allograft and the allograft renal vein and arteries, indicating adequate blood flow. No evidence of obstruction was observed. Despite a prior intraoperative transfusion of packed red blood cells, the cat remained anemic (hematocrit 22%; RI 31.70–48.00%) so another unit of packed red blood cells was administered.

Two days following the procedure, the cat developed watery, mucoid diarrhea, which appeared to be causing irritation of the perineum. Foci of erythema and erosions were also appreciated in the inguinal and medial thigh regions. Metronidazole (10 mg/kg IV q12h) was administered in addition to the cat's other medications. Fentanyl CRI was discontinued and buprenorphine (0.01–0.015 mg/kg IV q8h) was administered for further analgesia.

Anorexia continued and a nasoesophageal feeding tube was placed 4 days postoperatively. The cat's clinical condition continued to progressively decline with development of marked obtundation and signs of sepsis. Hypotension (systolic blood pressure 64 mmHg) and severe hypoglycemia (blood glucose 30 mg/dl; RI 67.0–168.0 mg/dl) occurred. Hypoglycemia was initially treated with a dextrose bolus (0.5 g/kg IV) and a 5% dextrose CRI (1 ml/kg/h). Ceftazidime (40 mg/kg IV q6h) and clindamycin (10 mg/kg IV q12h) were also administered. Hypotension was treated with a norepinephrine (0.5 µg/kg/min) CRI, a vasopressin (0.5 mIU/kg/min) CRI and a whole blood transfusion (40 ml total). Hematologic analysis revealed a marked neutrophilia (neutrophils 31.06 $\times 10^3$/µl; RI 2.30–11.60 $\times 10^3$/µl) with a concurrent left shift (band neutrophils 6.21 $\times 10^3$/µl; RI 0.00–0.10 $\times 10^3$/µl).

Five days following surgery, the cat began to show neurologic signs consisting of anisocoria, delayed-to-absent palpebral reflexes and menace response bilaterally and intractable seizures. At this time, biopsy results of the right native kidney removed at surgery were received and histopathology showed an infiltrative epithelial neoplasm composed of tubules of polygonal-to-cuboidal cells separated by a desmoplastic stroma. The neoplastic cells exhibited marked anisocytosis and anisokaryosis with prominent nucleoli, occasional binucleation and frequent mitotic figures. These histologic

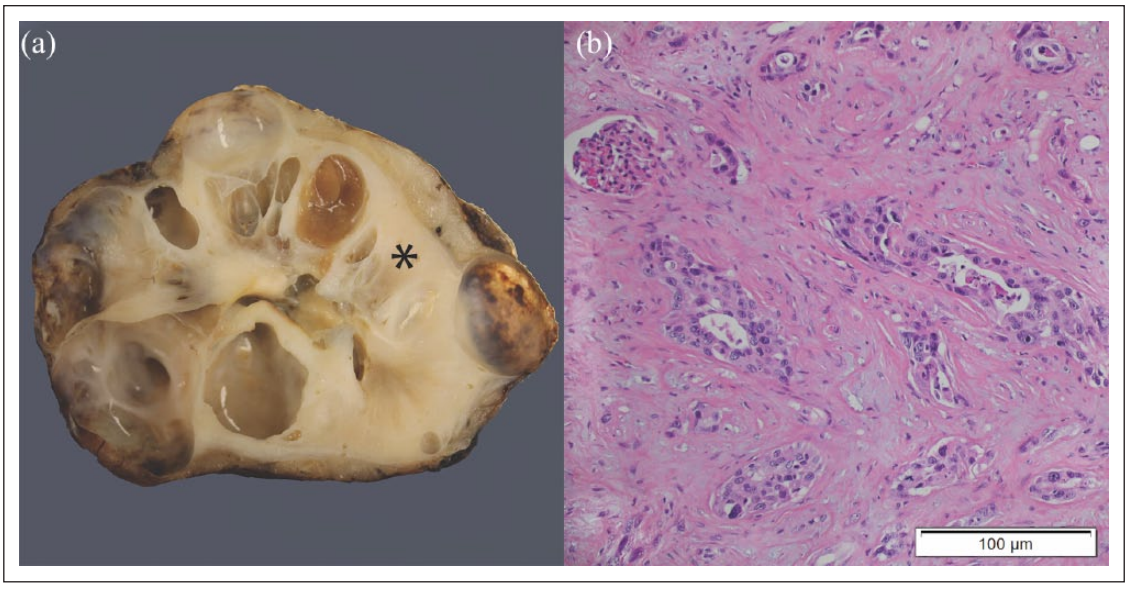

Figure 1 Native right kidney, removed at the time of transplantation. (a) The kidney was enlarged with an irregular cortical surface and numerous, variable sized fluid-filled cysts. The cysts were compatible with polycystic kidney disease. Although no distinct neoplastic masses were identified grossly, abundant firm, white–tan tissue separated the cysts and regionally replaced the renal parenchyma (*). (b) Despite intraoperative cytology suggestive of inflammation, histology of the renal parenchyma identified an infiltrative neoplasm composed of tubules and small islands of neoplastic epithelial cells amid an abundant desmoplastic stroma. Cellular and nuclear pleomorphism was marked, and mitoses were frequent. These features were consistent with a renal cell carcinoma in the right native kidney

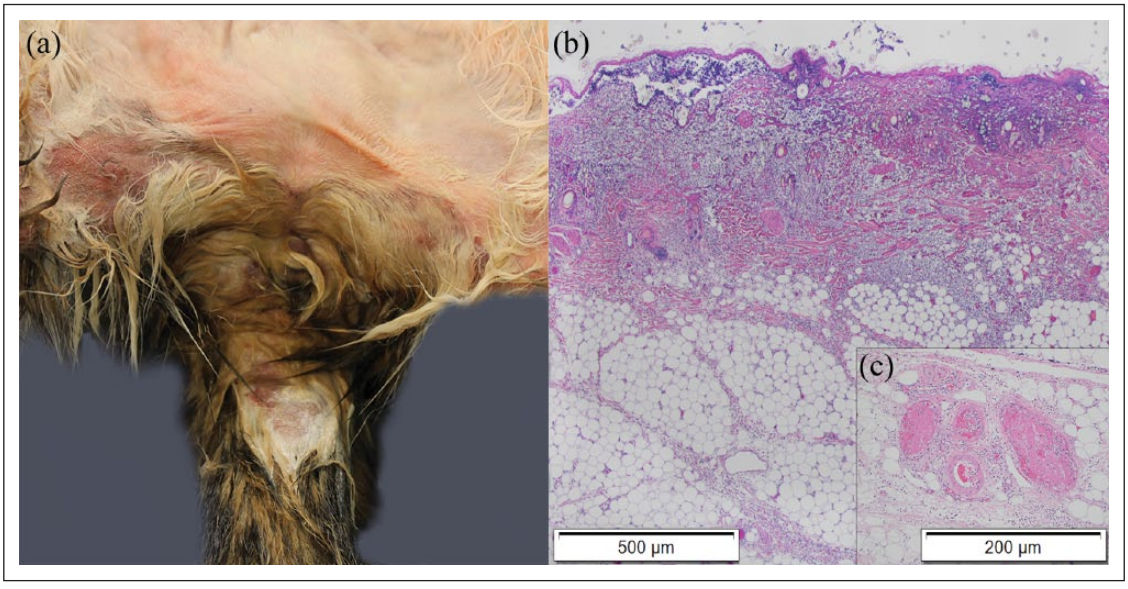

Figure 2 Inguinal and perineal skin. (a) The skin was erythematous with multifocal erosions and ulcers. (b) Histologically, there were large areas of epidermal and dermal necrosis with suppurative inflammation extending throughout the dermis into the subcutis. (c) Dermal and subcutaneous blood vessels frequently contained fibrin thrombi

features were consistent with a renal cell carcinoma (RCC) (Figure 1a,b). Owing to the cat's declining clinical condition and the diagnosis of RCC, humane euthanasia was elected 6 days postoperatively.

Post-mortem histologic evaluation of the erosive skin lesions in the inguinal and perineal regions demonstrated severe regional epidermal and dermal necrosis with a suppurative dermatitis and panniculitis. Blood vessels in

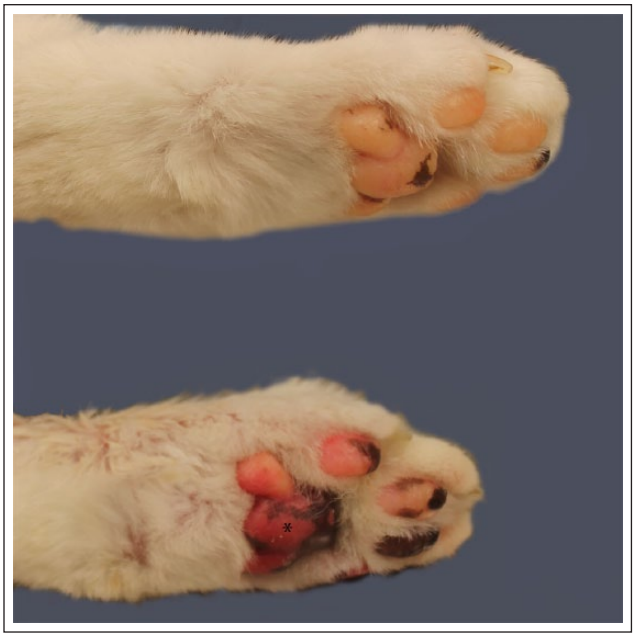

Figure 3 The digital and metatarsal pads of the left pelvic limb were erythematous (*) and the skin distal to the tarsus was hyperemic

these sections often contained fibrin thrombi, exhibited fibrinoid vascular necrosis and occasionally necrotizing vasculitis (Figure 2a–c). Although definitive evidence of bacteremia was not identified, the clinical signs and post-mortem lesions were highly suggestive of an acute inflammatory response. Given the histologic lesions in the skin, ischemic dermal necrosis secondary to thromboembolic (TE) disease with subsequent bacterial invasion was suspected. Similar lesions were identified in the digital and metatarsal pads of the left pelvic limb during necropsy (Figure 3). Primary necrotizing dermatitis due to diarrhea and urine scalding seemed much less likely based on the vascular changes noted on histology but could not be definitively ruled out. Further supporting TE disease, multifocal acute intravascular fibrin thrombi were distributed throughout multiple other tissues, including the allograft kidney, heart, right adrenal gland and one of the anomalous branches of the caudal vena cava (Figure 4). The allograft kidney had multiple fibrin thrombi within the vessels of the renal cortex and corticomedullary junction and foci of segmental acute tubular necrosis with tubular casts (Figure 5a,b). No evidence of inflammation suggesting rejection was found within the allograft or at the vascular anastomoses. No lesions were found in histologic sections of the brain; however, focal vascular lesions or peracute ischemic events without appreciable histomorphologic changes could not be excluded as possible causes of the cat's neurologic signs. Metabolic derangements could have also contributed. Cysts found in the left native kidney, liver and pancreas were consistent with PKD.

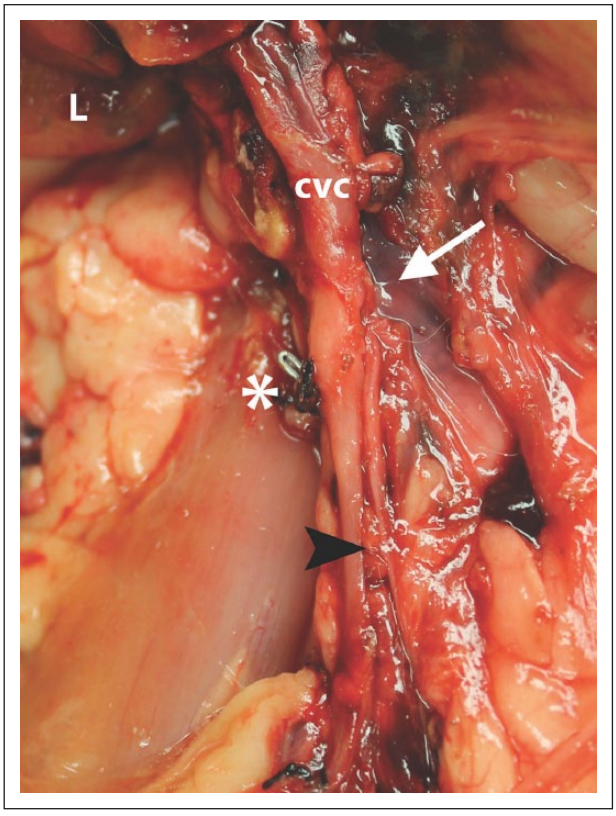

Figure 4 Caudal to the liver (L), there was an anomalous bifurcation (white arrow) of the caudal vena cava (CVC) at the level of the adrenal glands. Distal to the bifurcation, the right branch of the caudal vena cava was regionally thickened and contained a luminal fibrin thrombus (black arrowhead) at post-mortem examination. Hemoclips and sutures surrounded the right renal vein, artery and anastomosing vessels at the site of nephrectomy of the right native kidney (*)

Discussion

This report describes the diagnosis of RCC in a cat with PKD that was presented for renal transplantation. PKD is an autosomal dominant inherited disease affecting approximately 38% of Persian cats and related breeds. Mutations in the genes polycystin-1 (*PKD1*) and polycystin-2 (*PKD2*) cause the development of renal, hepatic and pancreatic cysts.[3,4] In affected cats, cysts result in renal insufficiency and progressive CKD. PKD is irreversible, with renal transplantation being the only true form of treatment aside from conservative management of the associated CKD or hemodialysis.[5] In a recent review at our practice, CKD secondary to PKD occurred in approximately 6% (n = 10/164) of patients presenting for renal transplantation (LR Aronson, 2017, personal communication). Similarly, in people, autosomal dominant polycystic kidney disease (ADPKD) is a common inherited cystic kidney disease affecting approximately six million people worldwide and is a prominent cause of end-stage renal disease (ESRD).[6,7] Resembling PKD in

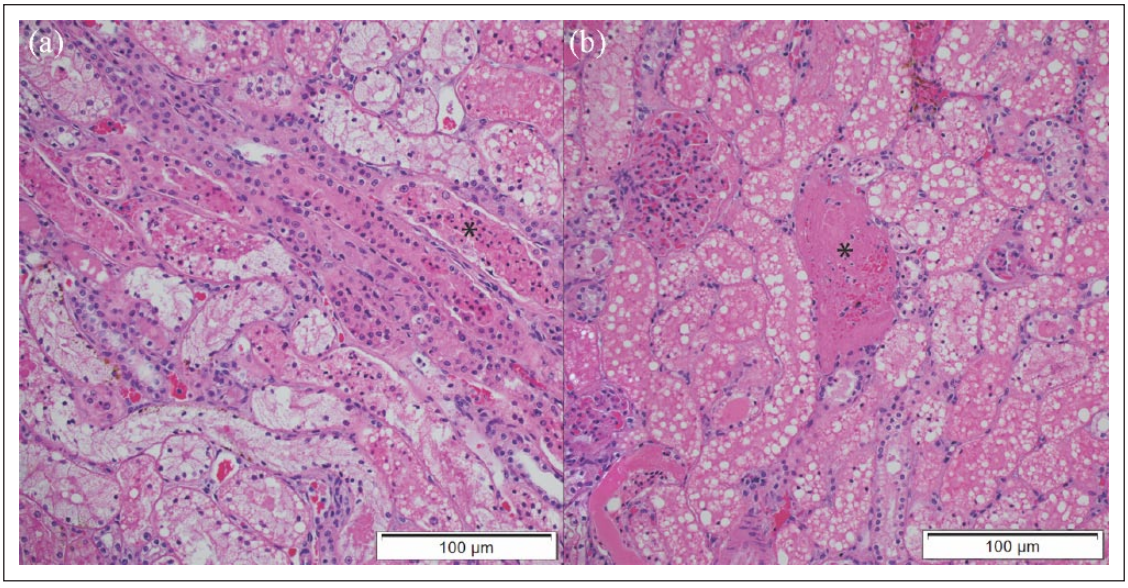

Figure 5 Left allograft kidney. (a) Multiple tubules were lined by necrotic epithelial cells, which were often sloughed into the tubular lumen (*). (b) Multifocally, blood vessels contained fibrin thrombi (*)

cats, ADPKD is due to mutations of either *PKD1* in 85% of cases or *PKD2* in the remaining 15%.[6]

It has been speculated that there is a link between ADPKD and RCC.[6] In people, RCC is a relatively rare form of cancer affecting 10–20 per 100,000 people. Patients with ADPKD are shown to have up-regulated signaling proteins that have been associated with the development of cancer.[8] RCC is reported to be approximately 2–3 times more frequent in patients with ADPKD in ESRD vs patients in ESRD alone.[9] Numerous cases of RCC diagnosed in patients with ADPKD have been reported, with the prevalence of RCC in these patients estimated to be as high as 18%.[7] Some argue that the true prevalence of RCC in patients with ADPKD is actually much higher and that the diagnosis of RCC is often missed owing to the distortion of kidney architecture by multiple cysts. ADPKD interferes with advanced imaging studies commonly used to diagnose RCC and it can present as small, multifocal clusters of cells, making it easy to be overlooked on histopathologic review.[7,9] Despite the current reports, the association of the two diseases remains controversial and the true relationship between RCC and ADPKD has not been determined owing to an insufficient volume of data. Nevertheless, some still consider ADPKD to be a risk factor for RCC.[7]

The declining clinical status postoperatively and the resulting euthanasia of the cat in this report was suspected to be due to TE disease. The authors consider the RCC found in the removed right native kidney and its surgical manipulation during nephrectomy to be the cause of hypercoagulability resulting in the subsequent TE disease, along with other contributing factors such as anemia and sepsis. Several causes of hypercoaguability and TE disease have been established in veterinary medicine, including neoplasia, anemia and sepsis.[10] In cats, primary renal neoplasia such as RCC is extremely rare, only described in a few case reports and surveys.[11–14] Of the reported cases, RCC typically affects older cats, occurs unilaterally and readily metastasizes. In most cases metastasis has already occurred at the time of diagnosis; however, no evidence of metastasis was found in the cat described in this report during its initial work-up for transplantation, at the time of surgery or on post-mortem examination.[15]

Unlike in people, an association between RCC and PKD has not been reported in cats. To our knowledge, the current report is the first case of RCC diagnosed in a cat with PKD. Considering the similarities in mutations and pathogenesis of PKD and ADPKD, it is plausible that there is an association between PKD and RCC in cats analogous to the association that has been reported in the human literature. However, as in the human literature, the data supporting such an association are lacking. This is likely owing to the inherent nature of the rarity of RCC diagnoses and reported cases in cats.[11] The same challenges of diagnosing RCC in patients with ADPKD in human medicine outlined above may also interfere with the diagnosis of RCC in cats with PKD, further contributing to the lack of data. Moreover, the diagnosis of RCC in cats with PKD may be missed owing to clients electing to pursue conservative management of their cats' kidney disease, rather than a more thorough work-up and invasive diagnostics, such as biopsy.

In the cat of this report, although neoplasia was a concern based on the gross appearance of the right native kidney, an aspirate performed at the time of surgery only revealed proteinaceous fluid and signs of chronic inflammation. Definitive diagnosis of RCC in the right native kidney was not made until histopathologic examination was performed following nephrectomy. Preoperative diagnosis of neoplasia, such as RCC, in renal transplant candidates is

ideal. While advanced imaging is commonly used to diagnose RCC in people, CT has not been appended to the pre-transplant protocol as a screening method for neoplasia in transplant candidates at our practice. Given the challenges of diagnosing RCC in patients with PKD via advanced imaging as described in the human literature, the unknown prevalence of RCC in patients with PKD and the added cost of imaging, CT likely offers little utility as a screening option for cats with PKD at this time.[2,3] Pre-transplant screening protocols for PKD patients could be modified as the possible association of the two diseases is further explored.

Conclusions

Cats serve as a valuable model for human disease processes, having numerous hereditary conditions in common, such as PKD and ADPKD.[16] An association between RCC and ADPKD has been reported in human medicine; however, this case represents the first report of RCC in a cat with PKD. While further data are necessary to make any link between RCC and PKD in cats, this case could be the first to show such an association of the two diseases in veterinary medicine. Characterization of a potential relationship between PKD and RCC could prompt changes in the management of cats with PKD in the future.

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Supplementary material Information about harvesting the donor kidney.

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