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

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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 × 10³/μl; RI 0.800–6.100 × 10³/μl). 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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glands. The right kidney was firmly adhered to the sur-
caudal vena cava. An anomalous bifurcation of the cau-
and polycystic with neovascularization to the aorta and
and explored. The right kidney was severely enlarged
tered beginning on the day of the procedure in conjunc-
q12h). Prednisolone (0.5 mg/kg PO q24h) was adminis-
4 days prior to surgery with ciclosporin (3 mg/kg PO
prior to the procedure. Immunosuppression was initiated
matched to identify a compatible donor cat. An additional
was considered an appropriate candidate for renal trans-
plantation. The cat was administered darbepoetin (1 μg/
kg SC) 8 days prior to surgery, blood typed and cross-
plantation. The cat was administered darbepoetin (1 μg/
within normal limits.
Serum total thyroxine (1.49 μg/dl; RI 1.00–4.00 μg/dl) was
concurrent urine culture was negative for any pathogens.
creatinine ratio (1.32; RI 0–0.5) confirmed proteinuria. A
cystic, the right appeared more severely affected than
of chronic inflammation associated with a cystic or ser-
needle aspirate was performed. Cytology revealed pro-
and severe hypoglycemia (blood glucose 30 mg/dl; RI
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]), hypo
calcemia (calcium 7.3 mg/dl; RI 9.1–11.2 mg/dl) and
hyperphosphatemia (phosphorus 8.2 mg/dl; RI 3.0–6.6
A focal ultrasound of the allograft kidney
revealed venous and arterial Doppler signal throughout
the entire allograft and the allograft renal vein and arter-
ies, 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 adminis-
teried 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 clin-
ical condition continued to progressively decline with
development of marked obtundation and signs of sep-
sis. Hypotension (systolic blood pressure 64 mmHg)
and severe hypoglycemia (blood glucose 30 mg/dl; RI
67.0–168.0 mg/dl) occurred. Hypoglycemia was ini-
tially treated with a dextrose bolus (0.5 g/kg IV) and a
5% dextrose CRI (1 ml/kg/h). Cefazidime (40 mg/kg
IV q6h) and clindamycin (10 mg/kg IV q12h) were also
administered. Hypotension was treated with a norepi-
nephrine (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 neutro-
philia (neutrophils 31.06 × 10^9/μl; RI 2.30–11.60 × 10^9/μl)
with a concurrent left shift (band neutrophils 103/μl).

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

(urate 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 con-
current disease and revealed no abnormalities. On
abdominal ultrasound, multiple variable sized bilateral
renal cysts and hepatic cysts were noted, consistent with
PKD. Pyelecstasy 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 trans-
plantation. The cat was administered darbepoetin (1 μg/
kg SC) 8 days prior to surgery, blood typed and cross-
matched 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 adminis-
tered beginning on the day of the procedure in conjunc-
tion 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 cau-
dal vena cava was observed at the level of the adrenal
glands. The right kidney was firmly adhered to the sur-
rounding tissues, and although both kidneys were poly-
cystic, 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 pro-
teinaceous fluid, a moderate number of macrophages,
re new neutrophils and few small lymphocytes, suggestive
of chronic inflammation associated with a cystic or ser-
omatous mass. No neoplastic cells were observed. A
right nephrectomy was performed prior to transplanta-
tion and the entire native kidney was submitted for
biopsy. Owing to the firm adhesions to the body wall
and surrounding tissues, extensive dissection was neces-
sary to remove the right native kidney. The donor kid-
ned, 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). Although the allograft kid-
ney was observed to be of normal color and firm consist-
cy following transplantation, suggesting adequate
fusion, 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
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cleation and frequent mitotic figures. These histologic


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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 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
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.

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).5,7 Resembling PKD in
It has been speculated that there is a link between ADPKD and RCC. 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. RCC is reported to be approximately 2–3 times more frequent in patients with ADPKD in ESRD vs patients in ESRD alone. 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%. 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. 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.

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 hypercoagulability and TE disease have been established in veterinary medicine, including neoplasia, anemia and sepsis. In cats, primary renal neoplasia such as RCC is extremely rare, only described in a few case reports and surveys. 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

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**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 (*)
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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References
1 Aronson LR and Phillips H. Renal transplant. In: Tobias KM and Johnson SA (eds). Veterinary surgery: small animal. St Louis, MO: Elsevier-Saunders, 2012, pp 2025–2027.
2 Wormser C and Aronson LR. Perioperative morbidity and long-term outcome of unilateral nephrectomy in feline kidney donors: 141 cases (1998–2013). J Am Vet Med Assoc 2016; 248: 275–281.
3 Lyons LA, Biller DS and Erdman CA. Feline polycystic kidney disease mutation identified in PKD1. J Am Soc Nephrol 2004; 15: 2548–2555.
4 Zachary JF and McGavin MD. The urinary system. In: Newman SJ (ed). Pathologic basis of veterinary disease. 5th ed. St Louis, MO: Elsevier, 2012, pp 618–622.
5 Barthez PY, Rivier P and Begon D. Prevalence of polycystic kidney disease in Persian and Persian related cats in France. J Feline Med Surg 2003; 5: 345–347.
6 Wilson PD. Mechanisms of disease: polycystic kidney disease. N Engl J Med 2004; 350: 151–164.
7 Hansen CC, Derrick M, Warrich A, et al. The association between autosomal dominant polycystic kidney disease and renal cell carcinoma. Open J Urol 2015; 5: 84–90.
8 Tan M, Wetersen HI, Chu K, et al. Novel inhibitors of nuclear transport cause cell cycle arrest and decrease cyst growth in ADPKD associated with decreased CDK4 levels. Am J Physiol Renal Physiol 2014; 307: F1179–F1186.
9 Hajj P, Felicott S, Massoud W, et al. Prevalence of renal cell carcinoma in patients with autosomal dominant polycystic kidney disease and chronic renal failure. Urology 2009; 74: 631–634.
10 Fox PR, Petrie JP, Hohenhaus AE, et al. Peripheral vascular disease. In: Ettinger SJ and Feldman EC (eds). Textbook of veterinary internal medicine. 6th ed. St Louis, MO: Elsevier-Saunders, 2007, pp 1145–1148.
11 Bonsebiante F, Benali SL, Trez D, et al. Histological and immunohistochemical characterization of feline renal cell carcinoma: a case series. J Vet Med Sci 2016; 78: 1039–1043.
12 Henry CJ, Turnquist SE, Smith A, et al. Primary renal tumours in cats: 19 cases (1992–1998). J Feline Med Surg 1999; 1: 165–170.
13 Steinberg H and Thomson J. Bilateral renal carcinoma in a cat. Vet Pathol 1994; 31: 704–705.
14 Engle GC and Brodey RS. A retrospective study of 395 feline neoplasms. J Am Anim Hosp Assoc 1969; 5: 21–31.
15 Tan PH, Cheng L, Rioux-Leclercq N, et al. Renal tumors: diagnostic and prognostic markers. Am J Surg Pathol 2011; 35: 1518–1531.
16 Migaki G. Compendium of inherited metabolic diseases in animals. Prog Clin Biol Res 1982; 94: 473–501.