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Unilateral primary carcinoma of the kidney with central nervous system invasion and vertebral lysis in a cat

Latasha Ludwig[1], Roman Husnik[2,3], Emily Rätsep[1,4], Janet Beeler-Marfisi[1], Margaret Stalker[5], Geoffrey A Wood[1] and J Paul Woods[3]

Abstract

Case summary A young adult female spayed domestic shorthair cat presented for acute hindlimb weakness and anorexia with a 1-month history of lethargy, hyporexia and weight loss. A mass was palpable in the caudolateral abdomen and the left hindlimb was diffusely edematous. Abdominal ultrasound showed hydronephrosis of the left kidney with suspected hydroureter and heterogeneous tissue in the dorsal abdomen. CT evaluation confirmed a mass extending from the left kidney through the lumbar musculature with hydronephrosis, aortic attenuation, caudal vena caval thrombosis and lysis of vertebrae 4 and 5. Fine-needle aspiration of the mass suggested squamous cell carcinoma. Owing to clinical deterioration, euthanasia was elected. At necropsy, the left kidney was firmly adhered to the lumbar region with tissue that obliterated the musculature and surrounded the aorta and vena cava. There was hydronephrosis of the left kidney. Histopathologic evaluation of the mass revealed islands of neoplastic epithelial cells separated by fibrous connective tissue and areas of gradual keratinization with rare squamous metaplasia. The histologic diagnosis was invasive carcinoma with desmoplasia and vascular invasion.

Relevance and novel information Primary carcinomas of the kidney in cats are rare and this report documents a progression of disease not previously reported in cats. This is the second reported case of a primary carcinoma of renal origin with features of squamous cell carcinoma in a cat, and the first with lumbar and vascular invasion. This is also the first use of kidney injury molecule-1 to help investigate tumor differentiation in cats.

Keywords: Renal; urothelial carcinoma; squamous cell carcinoma; kidney injury molecule-1

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Introduction

Primary renal neoplasia is uncommon in humans and domestic animals, with a reported incidence of 1–1.5% of all neoplasms in dogs and cats.[1–4] Only 12% of neoplasms involving the kidney are of primary renal origin in cats.[5] Renal cell carcinoma is most common in humans, dogs and cats, followed by urothelial carcinoma (UC).[1,2,4–6] Renal squamous cell carcinoma (SCC) is rare in humans, dogs and cats, and most commonly arises from the renal pelvis.[5–11] In cats, renal pelvis-origin SCC has been described in a single case report and in a conference proceeding.[6,7] However, as squamous differentiation may occur in UCs, particularly in cats, the veterinary literature regarding UC vs SCC in the urinary tract may be confounded.[6,7,12]

[1]Department of Pathobiology, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada
[2]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN, USA
[3]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada
[4]Animal Health Laboratory, University of Guelph, Kemptville, ON, Canada
[5]Animal Health Laboratory, University of Guelph, Guelph, ON, Canada

Corresponding author:
Roman Husnik MVDr, PhD, DACVIM (SAIM), Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, 625 Harrison Street, West Lafayette, IN 47907-2050, USA
Email: husnikr@gmail.com

Case description

A young adult female spayed domestic shorthair cat presented to the Ontario Veterinary College's emergency service for acute hindlimb weakness and anorexia. The cat had a 1-month history of progressive lethargy, hyporexia and mild weight loss that progressed in the 48–72 h prior to presentation to complete anorexia, adipsia and weakness leading to collapse. The cat was kept predominantly indoors, was fully vaccinated, feline immunodeficiency virus/feline leukemia virus negative and healthy since being adopted 1 year prior. Ovariohysterectomy had been performed before adoption.

On presentation, the cat's body condition score was 2/9, with marked muscle wasting and signs of marked dehydration. The cat was tachycardic with a sinus rhythm. Rectal temperature and peripheral lymph nodes were normal. A firm mass was palpable in the left caudal abdomen. The hindlimbs were warm with strong femoral pulses, but could support only a few steps of ambulation, and the left hindlimb was diffusely edematous. Point-of-care blood gas (ABL90 Flex Plus; Radiometer Canada) evaluation revealed marked hypercalcemia (ionized calcium 2.08 mmol/l; breed-specific reference interval [RI] 1.15–1.34), hyperlactatemia (3.4 mmol/l; RI <2.0) and a packed cell volume of 37% (0.37 l/l; RI 0.28–0.49). A complete blood count (ADVIA 2120 Hematology System; Siemens Healthcare Diagnostics) revealed a stress leukogram (white blood cell count 17.6×10^9/l; RI 4.2–13.0) characterized by neutrophilia (15.66×10^9/l; RI 2.1–8.3), lymphopenia (0.88×10^9/l; RI 1.1–8.1) and monocytosis (0.88×10^9/l; RI 0.0–0.5). The only clinically relevant abnormalities on the serum biochemical profile (Roche cobas 6000 c501 Module; F. Hoffman-La Roche) were hypercalcemia (3.94 mmol/l; RI 2.22–2.78) and mild hyperkalemia (5.3 mmol/l; RI 3.6–5.2), but there was no evidence of azotemia. Analysis of urine collected via cystocentesis after fluid administration showed a urine specific gravity of 1.028, hematuria (1+), proteinuria (1+) and an occasional coarse granular cast.

On abdominal ultrasound the left kidney was subjectively enlarged, although a precise measurement was not obtained. The renal architecture was replaced by a cavitated center surrounded by a thin rim of hyperechoic tissue (hydronephrosis), suggestive of ureteral obstruction. The left ureter was not identified proximally but a distended tubular structure was seen distally along the dorsal abdomen. A 1.5 cm diameter mass of intermediate echogenicity was noted, located immediately ventral to a hyperechoic interface, at approximately the level of the third and fourth lumbar vertebrae. Ultrasonographic findings were corroborated by CT, which also identified that the kidney was confluent with a mass of heterogeneously contrast-enhancing tissue that extended into the dorsomedial abdomen and lumbar musculature, effacing the ventral aspects of the fourth and fifth lumbar vertebral bodies. This mass surrounded and caused marked luminal reduction of the aorta, and effaced a portion of the caudal vena cava. Peritoneal effusion, marked subcutaneous edema of the left hindlimb and inguinal lymphadenopathy, likely secondary to caval obstruction, were also noted.

The appearance of the abdomen on imaging, signalment and history suggested abscessation, but the aggressive behavior of the mass and absence of pyrexia or an inflammatory leukogram were more consistent with neoplasia. An ultrasound-guided fine-needle aspirate preparation of the left epaxial musculature was evaluated. Rare clusters of disorganized cells with intracytoplasmic bridging, a moderate amount of glassy, basophilic cytoplasm and occasional perinuclear vacuolation were observed (Figure 1a). These cells exhibited marked pleomorphism and rare multinucleation. Rare anucleate keratinized cells were present (Figure 1b), as well as areas of necrotic debris and neutrophils. A cytopathologic diagnosis of SCC was made.

The cat was placed on intravenous fluids (Plasma-Lyte A at 4 ml/kg/h), ampicillin (22 mg/kg q8h IV) and a continuous rate infusion of fentanyl (2 µg/kg/h). The left hindlimb edema progressed over 24–48 h and the cat became non-ambulatory; euthanasia was elected.

At necropsy, the left kidney was enlarged, measuring 5.6 cm × 3.0 cm, and there was complete loss and replacement of the parenchyma by turbid yellow fluid encased in a thick fibrous capsule (hydronephrosis). The dorsal aspect of the kidney was firmly adhered to the adjacent body wall by a scirrhous mass. The mass invaded and effaced the lumbar musculature, overlying vertebrae, surrounded the local vasculature and obscured the left ureter. Thus, ureteral obstruction by the mass was presumed as the cause of hydronephrosis.

On histologic examination, the sublumbar mass was composed of neoplastic epithelial cells arranged in islands separated by fibrous connective tissue (Figure 2a). There were frequent central areas of necrosis, and marked anisocytosis and anisokaryosis. In some areas the neoplastic cells underwent gradual inward keratinization with rare islands containing a central aggregate of brightly eosinophilic keratin, consistent with squamous metaplasia (Figure 2b,c). Vascular invasion of a large vein was observed. The neoplasm effaced the ventral portion of the vertebrae (Figure 3a) and neoplastic cells tracked along the ventral nerve root, protruded into the spinal canal and entered the dura mater (Figure 3b). Only a fibrous capsule with small aggregates of neoplastic cells remained of the left kidney. The histologic diagnosis was invasive carcinoma with desmoplasia and vascular invasion.

Immunohistochemistry (IHC) was performed to determine the origin of the neoplastic cells. Cytokeratin (CK) AE1/AE3, CK7, CK20, uroplakin-III and vimentin stains were performed using standard protocols. Kidney injury molecule-1 (KIM-1) IHC was performed as previously

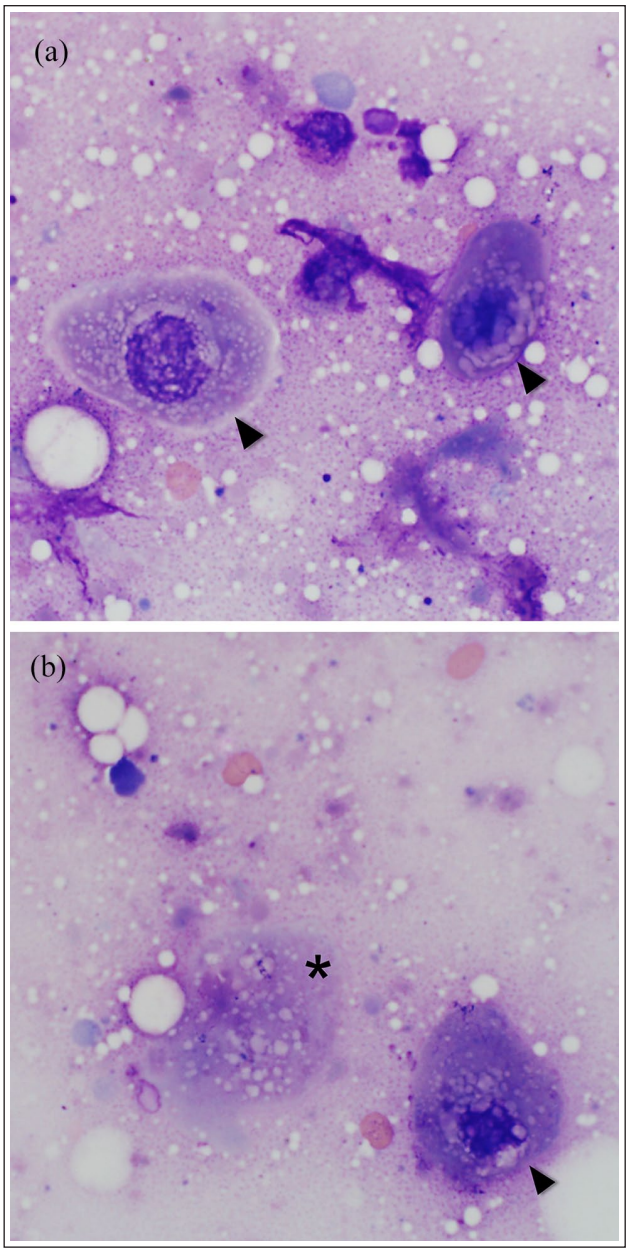

Figure 1 Fine-needle aspiration preparation from abnormal left caudal epaxial musculature in a young adult female spayed domestic shorthair cat (modified Wright's stain, × 1000). (a) Rare neoplastic epithelial-origin cells (arrowheads) are present on a background of necrotic debris with scant hemorrhage. Neoplastic cells have a moderate amount of glassy, variably basophilic cytoplasm and perinuclear vacuolation, and (b) rare anucleate keratinized cells are present (*)

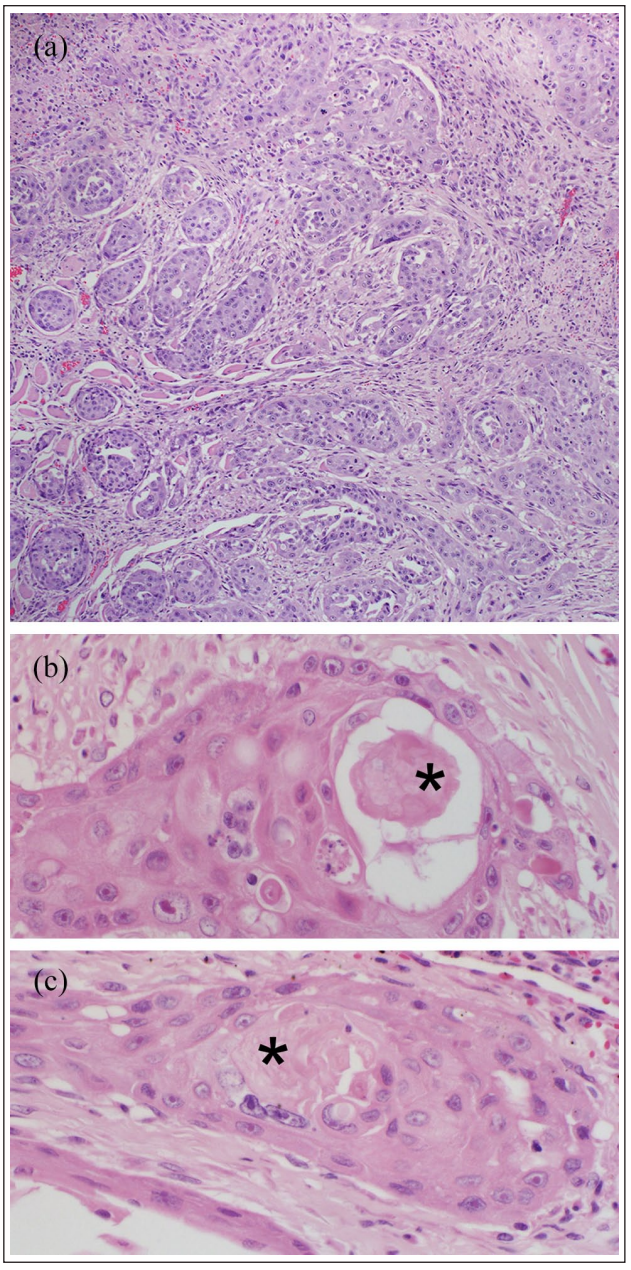

Figure 2 Sublumbar mass (hematoxylin and eosin): (a) neoplastic epithelial cells are arranged in variably sized islands, separated by fibrous connective tissue (× 100) and (b,c) rare islands of neoplastic cells show inward keratinization with a central aggregate of brightly eosinophilic keratin (*) consistent with squamous metaplasia (× 400)

described by Bland et al.[13] All IHC was performed by the Animal Health Laboratory, University of Guelph. Neoplastic cells had cytoplasmic immunoreactivity for CK AE1/AE3 (Figure 4a), and most of the basally located neoplastic cells also had cytoplasmic vimentin immunoreactivity (not shown). Uroplakin-III was negative (Figure 4b), while approximately 5% of neoplastic cells had cytoplasmic immunoreactivity for CK7 (not shown) and rare neoplastic cells had cytoplasmic immunoreactivity for CK20 (Figure 4c). Approximately 10–15% of apically or centrally located neoplastic cells had cytoplasmic immunoreactivity for KIM-1 (Figure 4d).

Discussion

Primary renal neoplasms are rare and the presumed young age of the patient, rapid growth and aggressive

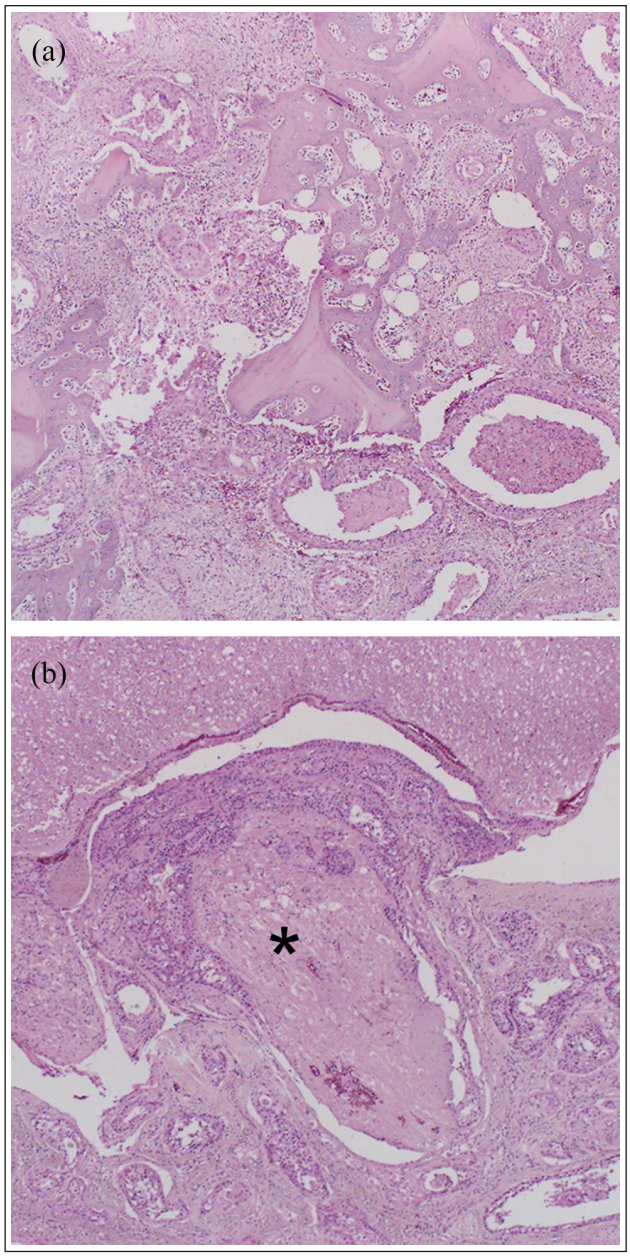

Figure 3 Vertebrae and spinal cord, cat (H&E): (a) islands of neoplastic epithelial cells efface a vertebral body resulting in bone resorption, (× 40) and (b) neoplastic cells invade around and within a ventral nerve root (*) into the intradural space (× 40)

behavior of this neoplasm are also unusual.[2,3,5,6] A single case of aggressive unilateral SCC in a cat with a similar clinical presentation, including hydronephrosis, but with omental metastases was reported.[7] Invasion of adjacent structures and hydronephrosis have also been reported in humans and dogs with renal SCCs.[4,8,14–18] However, this is the first report of a carcinoma of primary renal origin with vascular invasion and bone lysis in a cat.

A range of non-specific clinical signs and diagnostic findings have been described in cats with primary renal neoplasia, with weight loss and hematuria being the most common.[2,5,6] Although anemia is common, polycythemia is also reported, presumably due to excessive erythropoietin production; neither were present in this case.[2,6,19] Hematuria and proteinuria are common, as was seen in this case.[2] Our case also had marked hypercalcemia confirmed by increased ionized calcium. Although hypercalcemia is uncommon in cats, SCC and lymphoma are reported as frequent causes.[20–22] Hypercalcemia related to SCC generally involves tumoral destruction of bone, but there are also reports without obvious bone involvement.[21,23,24] While there are limited studies describing treatment and survival of primary renal tumors in cats, metastatic disease appears common but was not identified in this case.[2,6,25]

Before IHC, our differential diagnoses included SCC and UC, as cells with features of SCC were noted on cytologic evaluation. Renal pelvis SCC is aggressive, with vascular, lymphatic and/or local invasion, including the vertebrae in humans, dogs and a cat.[4,7,8,14–18] In this report, the cytologic appearance, behavior of the neoplasm, hypercalcemia (presumably from bone lysis) and some of the histologic characteristics, including inward keratinization (Figure 2b,c), provided support for a diagnosis of SCC of renal origin. However, histopathology was unable to definitively diagnose SCC, since squamous metaplasia/differentiation is common in feline urinary bladder UCs.[12] The literature suggests that SCC should not be diagnosed if areas of urothelial cells are present.[26] Furthermore, as no renal tissue remained of the affected kidney, a renal pelvic origin was impossible to prove.

To differentiate between SCC and UC, IHC was pursued. Widespread positivity for CK AE1/AE3 (Figure 4a) supported a diagnosis of carcinoma. Vimentin positivity in human and some canine tumors is related to epithelial–mesenchymal transition and metastatic potential, and was noted in the basal layer of this neoplasm.[27,28] The traditional urothelial IHC markers CK7, CK20 and uroplakin-III did not meet the canine-derived threshold for positivity, arguing against a neoplasm of urothelial origin, but a different threshold may be warranted in cats.[29–32] Since these markers were negative, we pursued KIM-1 IHC. Although this marker has not previously been used to investigate tumor differentiation in feline samples, KIM-1 is expressed in human, mouse and feline proximal convoluted tubules that have been injured, dedifferentiated or undergone replication.[33,34] In humans, KIM-1 was also positive in 67% and 69% of papillary and clear cell renal carcinomas, respectively.[35] To support the use of KIM-1 in suggesting a renal origin, KIM-1 expression was investigated in feline urinary bladder or urethral (n = 10) UCs diagnosed with hematoxylin and eosin. Seven of 10 UCs had >1% of neoplastic cells with cytoplasmic to membranous immunoreactivity, and 3/10 cases had >15% of neoplastic cells positive for KIM-1 (Figure 5). These preliminary results supported our suspicion of a primary renal UC; however,

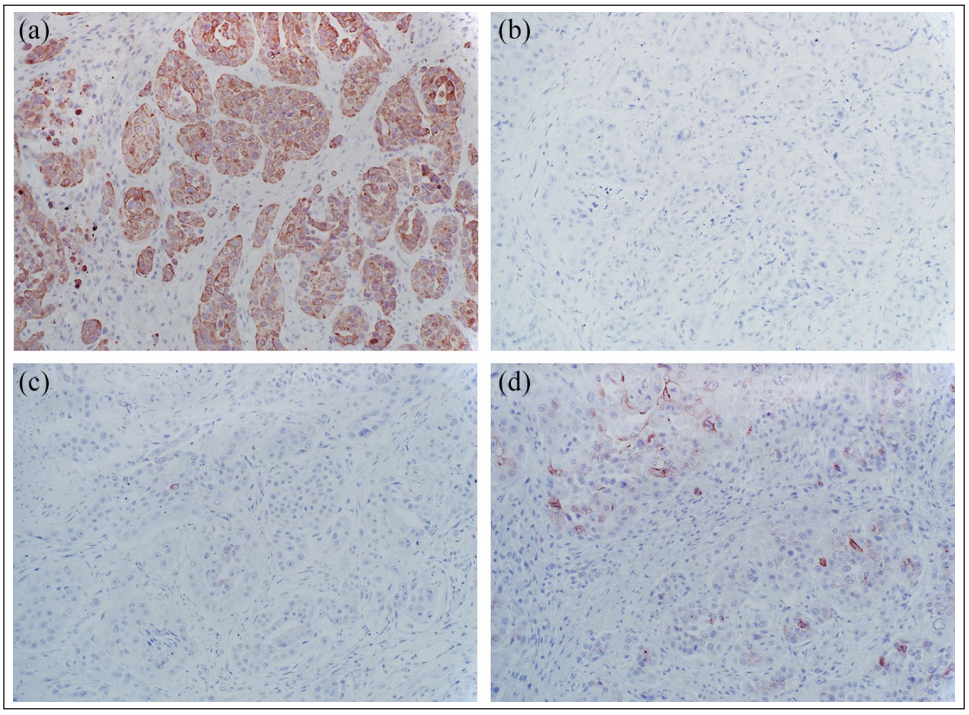

Figure 4 Immunohistochemistry performed on the sublumbar mass (× 200): (a) all neoplastic cells showed widespread immunoreactivity for cytokeratin AE1/AE3; (b) no neoplastic cells showed immunoreactivity for uroplakin-III; (c) rare neoplastic cells showed immunoreactivity for cytokeratin 20; and (d) approximately 10–15% of neoplastic cells, mainly those most apical/central, had cytoplasmic immunoreactivity for kidney injury molecule-1

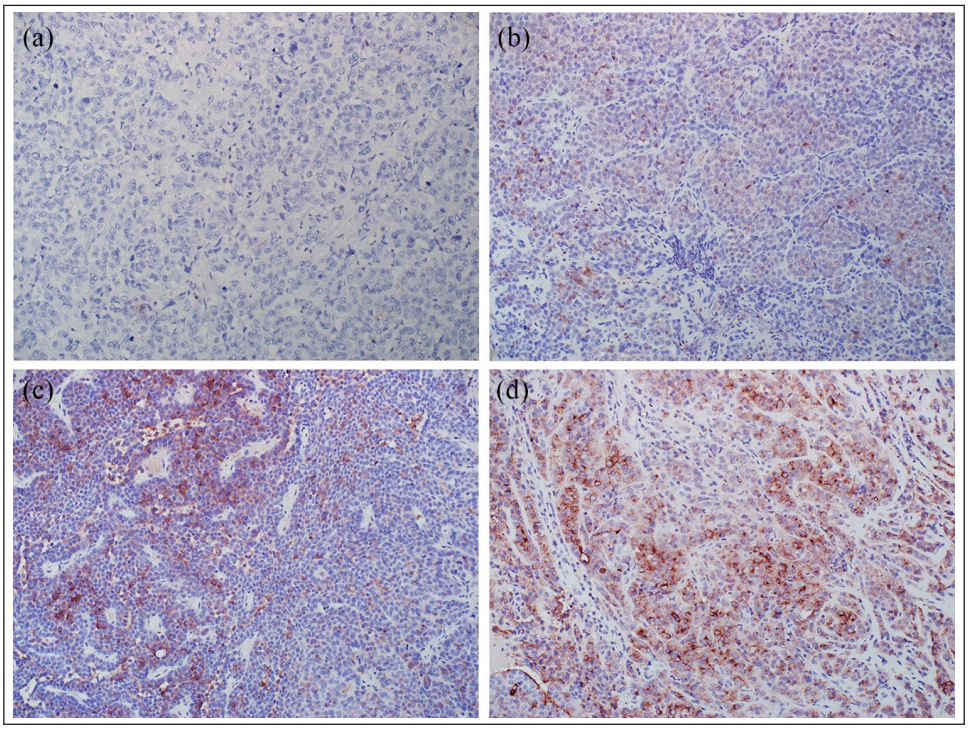

Figure 5 Immunohistochemistry for kidney injury molecule-1 performed on feline urothelial carcinomas (× 200): (a) no neoplastic cells have cytoplasmic immunoreactivity; (b) <5% of the neoplastic cells have strong cytoplasmic immunoreactivity; (c) approximately 15% of the neoplastic cells have strong cytoplasmic immunoreactivity, particularly the apical portion; and (d) >50% of the neoplastic cells have strong cytoplasmic immunoreactivity

we strongly recommend further investigation into KIM-1 as a marker for UC in cats, as associated kidney injury, particularly in renal tumors, may influence the results.

Although urothelial-origin IHC markers were largely negative and the appearance of the cells with inward keratinization and rare areas of squamous metaplasia could suggest SCC, the greater proportion of KIM-1-positive cells in our case (Figure 4d), in conjunction with our preliminary results, and common occurrence of squamous differentiation in UCs in cats led us to a final diagnosis of UC.[12] The poorly differentiated nature of the tumor, advanced stage at diagnosis and limited data due to tumor rarity make a location of origin difficult to prove.

Conclusions

This is the first report of lumbar and vascular invasion by a primary renal tumor in a cat, and the first use of KIM-1 to help investigate tumor differentiation in cats.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iD Roman Husnik https://orcid.org/0000-0003-1646-2421
Geoffrey A Wood https://orcid.org/0000-0003-1756-8607

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