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Renal transitional cell carcinoma with bilateral ocular metastasis in a cat

Irit Grader[1], Teresa L Southard[2] and Marjorie H Neaderland[3]

Abstract

Case summary A 4-year-old, spayed female, domestic shorthair cat was presented for evaluation due to a 4 day history of inappetence and lethargy. Physical examination revealed mild dehydration and blindness of the left eye. Abnormal imaging findings included a well-margined soft tissue mass with irregular central cavity located in the dorsal aspect of the caudal lung lobe. Cytological examination of the mass revealed chronic inflammation with hemorrhage. Tests for parasitic and fungal diseases were negative. Ophthalmic examination 17 days after the cat was initially presented revealed severe diffuse pathology of both retinas. Left renomegaly was noted 22 days after the initial presentation, and cytological examination of samples obtained from the right vitreous, left kidney and the pulmonary mass yielded atypical epithelial cells exhibiting malignant changes. Post-mortem examination following euthanasia revealed renal transitional cell carcinoma with metastasis to both eyes, lungs and skeletal muscle. Immunohistochemical evaluation of the neoplastic cells in the eye revealed moderate cytoplasmic reactivity for CK7. CK20 immunohistochemistry was negative.

Relevance and novel information To the best of our knowledge, this is the first report of renal transitional cell carcinoma with ocular metastasis in a cat. In addition, this report describes immunohistochemistry results of transitional cell carcinoma in a cat using CK7 and CK20.

Accepted: 20 June 2016

Introduction

Renal transitional cell carcinoma (TCC) in cats is a rare condition with a frequency of 0.068% reported in a necropsy review.[1] Here we report a case of feline transitional cell carcinoma found in both kidneys with signs of ocular metastases occurring prior to renal abnormalities being detected.

Case description

A 4-year-old, spayed female, domestic shorthair cat was presented with a 4 day history of inappetence and lethargy. On physical examination, the cat weighed 3.8 kg (body condition score 3/5) and was calm, alert and responsive. Rectal temperature was 37.9°C and the cat was determined to be 5% dehydrated, due to tacky mucous membranes and an increase in capillary refill time. Heart and respiration rates were 200 beats/min and 40 breaths/min, respectively, and heart and lungs auscultated normally. The abdomen was soft and no abnormalities were noted by palpation. Evaluation of the left eye revealed dilated pupil and loss of direct pupillary light reflex (PLR). PLR left eye (OS) to right eye (OD) was negative as well. Menace response and dazzle reflex were absent. The left conjunctiva, cornea, sclera, anterior chamber and lens were normal. The vitreous and ocular fundus were visualized with direct ophthalmoscopy (Direct Opththalmoscope; Welch Allyn) and appeared normal. The right eye appeared to be normal and visual. Applanation tonometry (Reichert Tono Pen XL; Medtronic) estimated the intraocular pressure (IOP)

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as 12 mmHg OD and 11 mmHg OS. Systolic arterial blood pressure was 130 mmHg (Doppler method).

Results of feline leukemia virus antigen, feline immunodeficiency virus antibody and feline heartworm antigen testing (SNAP Feline Triple Test; IDEXX Laboratories) were negative. Complete blood count (CBC) results were within normal limits and serum chemistry profile revealed elevated alanine aminotransferase (217 U/l; reference interval [RI] 12–130 U/l), gamma glutamyl transferase (12 U/l; RI 0–4 U/l) and amylase (2169 U/l; RI 500–1500 U/l). Pyuria and increased urine specific gravity (1.053) were noted on urinalysis with no bacterial growth on culture. The inappetence, lethargy and abnormal laboratory results raised suspicion for possible pancreatitis, inflammatory bowel disease, cholangiohepatitis or a combination of these diseases. The cat had never before been vision tested and, accordingly, it was unknown if the blindness was acute or an ongoing problem. The cat was hospitalized for supportive care and blood was collected for evaluation of total thyroxine (T4), feline pancreatic-specific lipase, cobalamin level, trypsin-like immunoreactivity level and folate levels. Test results indicated decreased folate levels (9.38 ng/ml; RI 9.7–21.6 ng/ml); all other test results were within normal limits. Blood was also submitted for evaluation of prothrombin time and partial thromboplastin time to ensure normal clotting in preparation for potential aspiration of the liver during a scheduled abdominal ultrasound.

The following day, the cat was sedated with a combination of butorphanol tartrate (0.2 mg/kg SC [Dolorex; Merck Animal Health]) and midazolam (0.2 mg/kg SC [Midazolam; Akorn]) to decrease pain and discomfort during imaging procedures. A veterinarian with advanced training in ultrasonography performed abdominal ultrasound (Ultrasound System t3000; Terason) and an ultrasound-guided aspiration of bile for culture due to suspicion of cholangiohepatitis. Results were negative for bacterial growth. No abnormalities were found on the abdominal ultrasound (Figure 1), and abdominal radiographs (Radiology imaging system DXE 325; General Electric). Thoracic radiographs showed a well-marginated soft tissue mass with a central cavity, in addition to small mineral-to-soft-tissue opacities in the fourth rib costochondral junction and at the ventral aspect of the seventh intercostal space (Figure 2). Cryptococcus antigen test results were negative. Results of an ultrasound-guided fine-needle aspiration of the pulmonary mass revealed chronic inflammation with hemorrhage. The lethargy and inappetence improved after 36 h of hospitalization and supportive care with fluids (10 ml/h IV [Lactated Ringer's Solution; Hospira]), maropitant citrate (1 mg/kg q24h SC [Cerenia; Zoetis]) and famotidine (0.5 mg/kg q12h SC [Famotidine; West Ward]). As some of the laboratory results were still pending at the time of discharge, the cat was sent home with medication supporting potential gastrointestinal abnormalities, including cyproheptadine (0.5 mg/kg q12h PO for 5 days [Cyproheptadine; Cypress Pharmaceutical]), maropitant citrate (1 mg/kg q24h PO for 8 days [Cerenia; Zoetis]), metronidazole (7.5 mg/kg q12h PO for 5 days [Metronidazole Benz; Roadrunner Pharmacy]) and amoxicillin (13 mg/kg q12h PO for 7 days [Biomox; Virbac]).

Four days after the cat was initially presented, the owners reported that she was eating well and was more active. No abnormalities were noted on complete physical examination. Examination of both eyes revealed no change from the findings noted on the first day on which the cat was presented. The owners were advised of the possibility that primary or metastatic neoplasia or an infectious agent was the likely cause of the blindness and pulmonary mass, and referral for consultation with an ophthalmologist and a neurologist was recommended.

Nine days after the cat was initially presented, the owners reported that her appetite and activity continued to improve. However, on physical examination, the cat appeared blind in both eyes. Both pupils were dilated

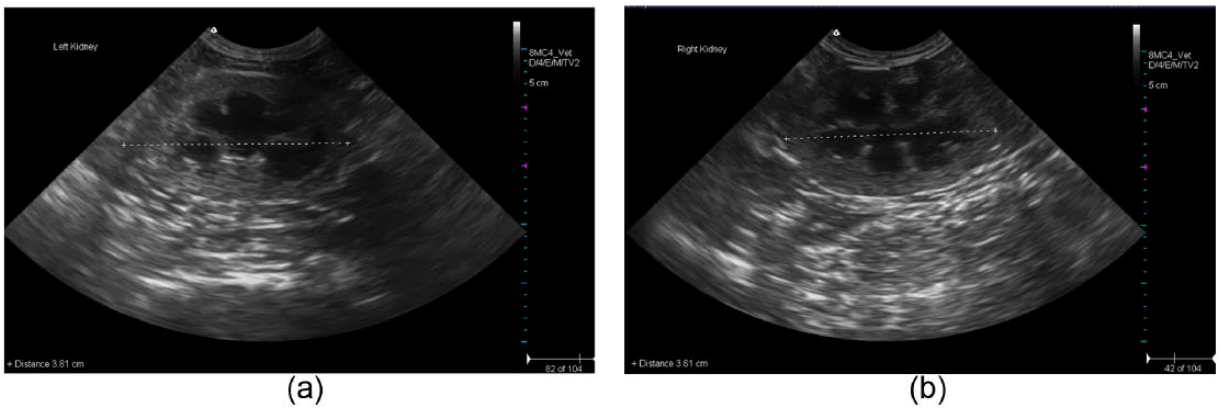

Figure 1 Renal sonograms. (a) Left and (b) right sonogram images of the kidneys taken 24 h after hospitalization and fluid therapy

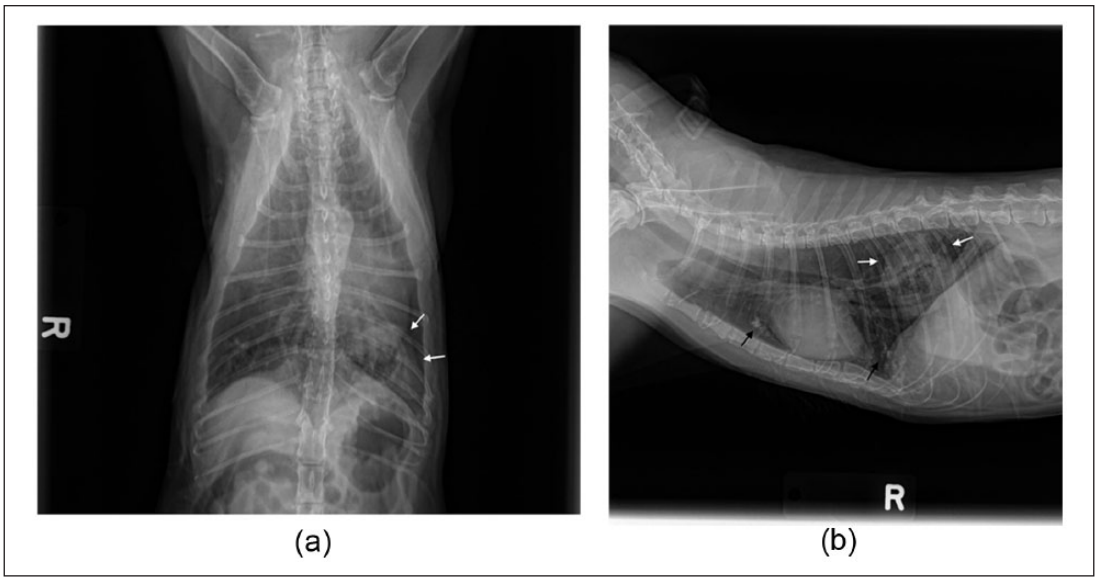

Figure 2 Thoracic radiographs. (a) Ventrodorsal and (b) lateral radiographic views of the thorax. A well-marginated soft tissue mass with a central cavity was noted in the dorsal aspect of the left caudal lung lobe (white arrows). Small mineral-to-soft tissue opacities were noted in the fourth rib costochondral junction and at the ventral aspect of the seventh intercostal space (black arrows)

and direct PLR and menace response were absent in both eyes. No other abnormalities were noted during physical examination. Again, a referral to a specialist was recommended to the owners. Fourteen days after the initial presentation, the cat was evaluated by a neurologist and underwent MRI which revealed normal brain parenchyma and ventricular system, and a slightly enlarged pituitary gland. Ophthalmic examination 17 days after the initial presentation confirmed blindness and dilated non-responsive pupils in both eyes (OU). Ocular abnormalities were limited to the fundus OU. The tapetal fundus of the left eye had a homogenous tan appearance with an infiltrate that almost completely obscured the tapetum and variably obscured the retinal vessels resulting in apparent absence or thinning of many retinal vessels, and a beaded appearance to others (Figure 3). The optic nerve was not clearly visible but was hemorrhagic. In the right eye there was nearly complete bullous retinal detachment (Figure 4). The detached retina appeared thickened with multifocal hemorrhages. The optic nerve was obscured by the detached retina. Applanation tonometry (Reichert Tono Pen XL; Medtronic) estimated the IOP as 16 mmHg OD and 12 mmHg OS. Aspiration of the lung mass and vitreous was recommended due to suspicion of metastatic neoplasia or systemic infection.

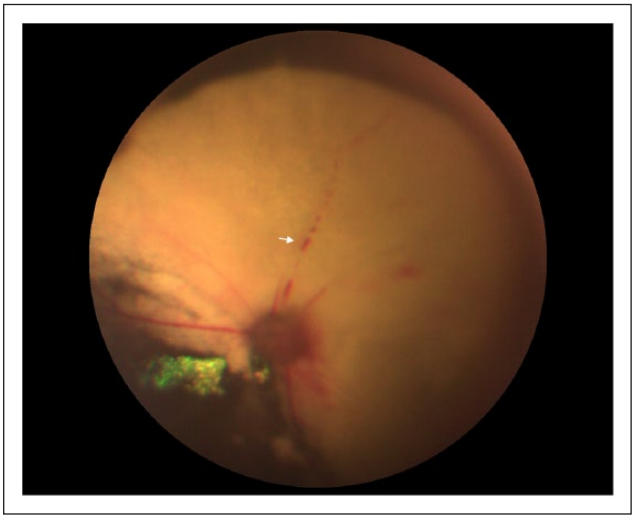

Figure 3 Left eye, fundus. Fundic photograph of the left eye on day 17 following initial presentation. A diffuse tan subretinal and/or intraretinal infiltrate almost completely obscured the tapetum and many retinal blood vessels causing them to be inapparent, inconsistently thinned and sometimes to appear beaded (arrow). A small area of tapetum was visible ventromedial to the optic nerve head. Peripapillary retinal hemorrhages were present dorsolaterally and in the dorsolateral mid-peripheral fundus. The optic nerve was not clearly visible but was hemorrhagic

Twenty-two days after the cat was initially presented the owner reported that her appetite had decreased again but activity was improving. On physical examination, the cat had lost approximately 15% of its body weight (3.2 kg) and was now estimated to have a body condition score of 2/5. The cat was calm, alert and responsive, and rectal temperature was 38.3°C. The heart rate and respiration rate were 200 beats/min and 40 breaths/min, respectively, and both heart and lungs auscultated normally. Both pupils were dilated and vision was absent. The right vitreous appeared hemorrhagic. The vessels of the left retina were difficult to visualize. Abdominal palpation revealed an enlarged and apparently non-painful left kidney. Abdominal radiographs confirmed

left renomegaly (Figure 5), and on thoracic radiographs the mass in the dorsal aspect of the left caudal lung lobe remained the same and had not increased in size. CBC results included mature neutrophilia (24,752/µl; RI 2500–8500/µl) and mild monocytosis (816/µl; RI–600/µl). Serum chemistry profile findings included hypercalcemia (13.0 mg/dl; RI 8.2–10.8 mg/dl), increased amylase (2232 U/l; RI 100–1200 U/l) and lipase (210 U/l; RI 0–205 U/l). Urine specific gravity was 1.036 and urinalysis revealed hematuria and proteinuria. *Blastomyces dermatitidis* antigens were not detected in serum and urine. Serum *Toxoplasma gondii* IgM titers and IgG titers were negative and 1:256, respectively.

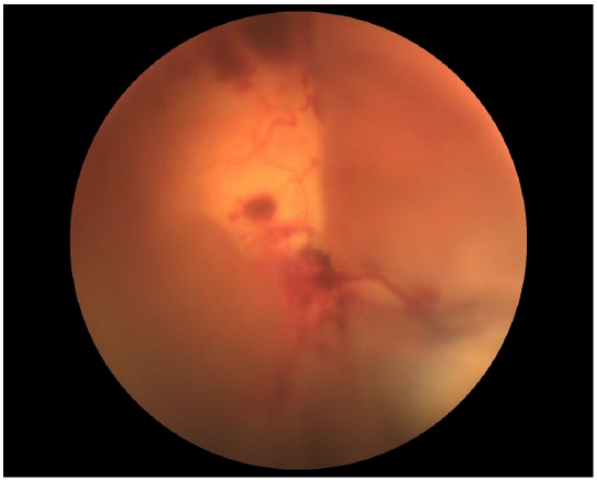

Figure 4 Right eye, fundus. Fundic photograph of the right eye on day 17 following initial presentation. Note the bullous detachment of all but the dorsolateral retina, and retinal hemorrhages located adjacent to the optic nerve, alongside retinal vessels and in the dorsolateral peripheral fundus

Due to lack of evidence supporting an infectious etiology, the results obtained on the initial fine-needle aspiration of the pulmonary mass, and the strong suspicion of a neoplasm, it was decided to perform vitreocentesis, ultrasound-guided aspiration of the left kidney and repeat the aspiration of the pulmonary mass.

Ophthalmic examination of the right eye immediately prior to vitreocentesis revealed normal periocular skin, eyelids, third eyelid and sclera. There was evidence of anterior uveitis with mild conjunctival injection, keratic precipitates ventrally, fibrin on the anterior lens capsule and thickened iris along with moderate rubeosis iridis. Indirect ophthalmoscopy OD revealed a complete bullous retinal detachment with multifocal retinal hemorrhages. The optic nerve was hemorrhagic. The findings OS were unchanged. Applanation tonometry estimated the IOP at 12 mmHg OD and 13 mmHg OS. Vitreocentesis was performed OD as that eye had more advanced disease and was irreversibly blind. Vitreocentesis was performed 5 mm posterior to the dorsomedial limbus aspirating cellular material under direct observation through the dilated pupil. Cytological evaluation of the aspirated right vitreous revealed a malignant epithelial neoplasm with moderate histiocytic and neutrophilic inflammation. Cytological evaluation of the aspirated samples taken from the left kidney and pulmonary mass revealed atypical epithelial cells suggestive of carcinoma, mixed inflammation, necrosis, and recent and chronic hemorrhage.

The cat was euthanized 28 days after she was initially presented, due to poor prognosis. On post-mortem examination, the capsular surface of both kidneys was

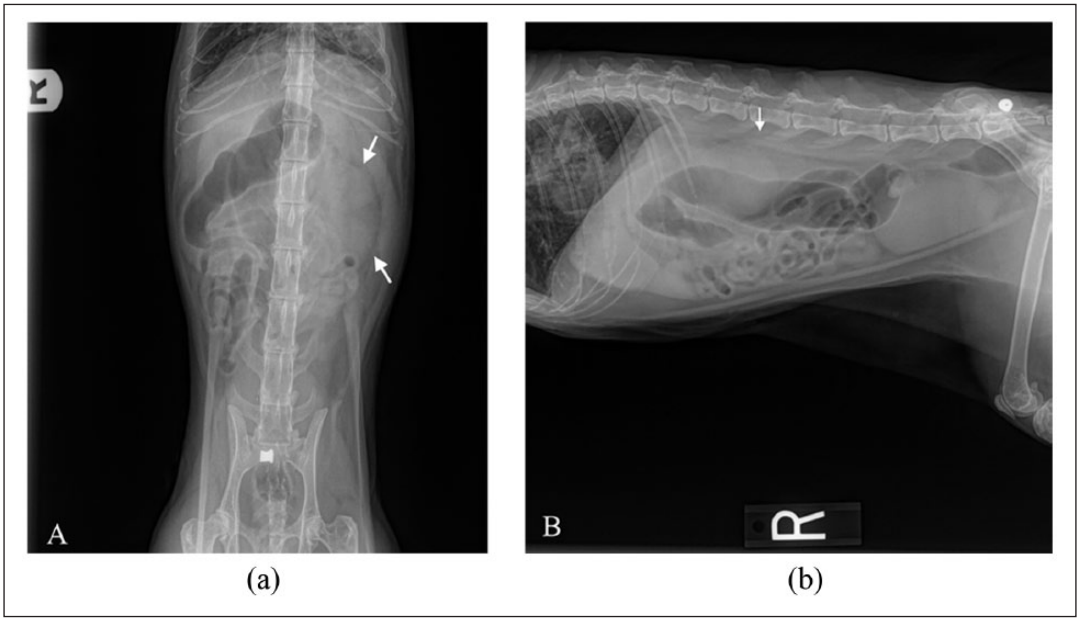

Figure 5 Abdominal radiographs. (a) Ventrodorsal and (b) lateral radiographic views of the abdomen taken on day 22 following initial presentation. Enlargement of the left kidney was noted (arrows). The mass in the dorsal aspect of the left caudal lung lobe remained the same and had not increased in size

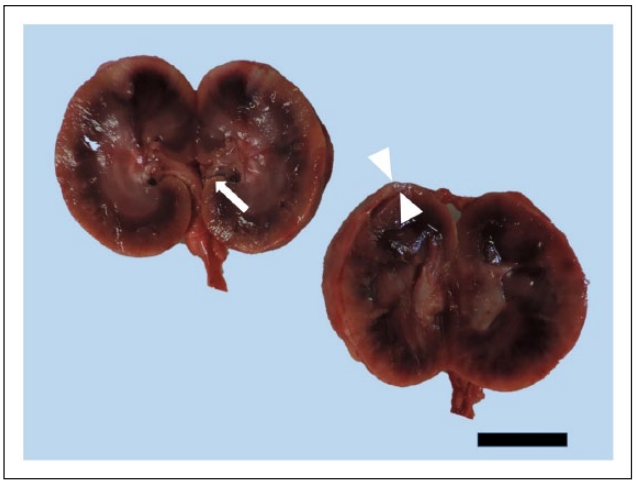

Figure 6 Kidneys, longitudinally sectioned, gross. The capsules were thickened (arrowheads) and the corticomedullary junction was irregular. The renal cortex was multifocally replaced by wedge-shaped tan infiltrates. The contour of the renal pelvices is irregular (arrow). Bar = 1 cm

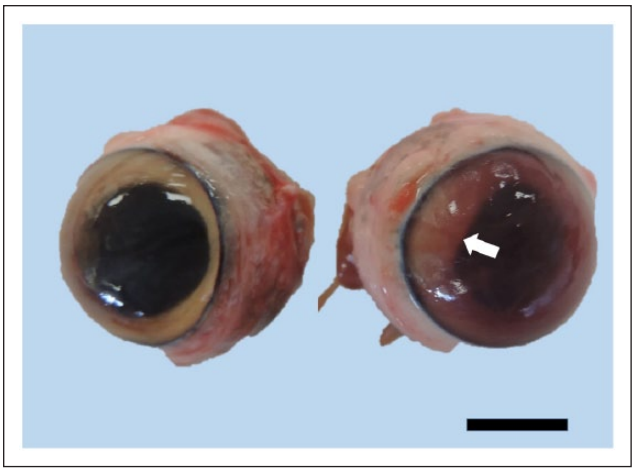

Figure 7 Eyes, gross. The aqueous humor was bilaterally cloudy. In the left eye, the iris was pale tan and thickened (arrow). Bar = 1 cm

irregular, opaque and thickened. On cut sections, both kidneys had an irregular corticomedullary junction, with multifocal, poorly demarcated tan masses expanding the cortex (Figure 6). The largest mass was in the left kidney and measured 1 × 1 × 0.4 mm. In the right kidney a wedge-shaped red area adjacent to a tan mass was suggestive of an infarct. In the left caudal lung lobe, a firm, tan, cavitated mass (2 cm diameter) was identified, and smaller masses were scattered throughout the other lung lobes. In the brain, a 4 mm diameter depressed area was located on the ventral aspect of the left temporal lobe. The aqueous humor of both eyes was cloudy and red tinged, partly owing to post-mortem changes, but disease progression was also possible (Figure 7). Finally, examination of the muscles revealed a firm, tan, poorly demarcated, cavitated mass in the skeletal muscle of the right caudal thigh.

On histologic examination, the pelvis of the kidneys was lined with polygonal neoplastic cells which multifocally invaded the submucosa to form islands and acinar structures (Figure 8). The neoplastic cells demonstrated moderate anisocytosis and anisokaryosis and had moderate amounts of granular, often vacuolated, eosinophilic cytoplasm, round-to-oval nuclei with finally stippled chromatin, and 1–3 magenta nucleoli. Nodules of similar cells multifocally expanded the renal parenchyma and were surrounded by proliferative spindle cells (scirrhous response). Bilaterally, the renal capsule was severely expanded by fibrous connective tissue infiltrated by neutrophils, macrophages and lymphocytes. The histologic appearance of the neoplastic cells was consistent with transitional cell carcinoma. The left optic nerve, perineurium and uveal tract were multifocally infiltrated by clusters of neoplastic cells similar to those in

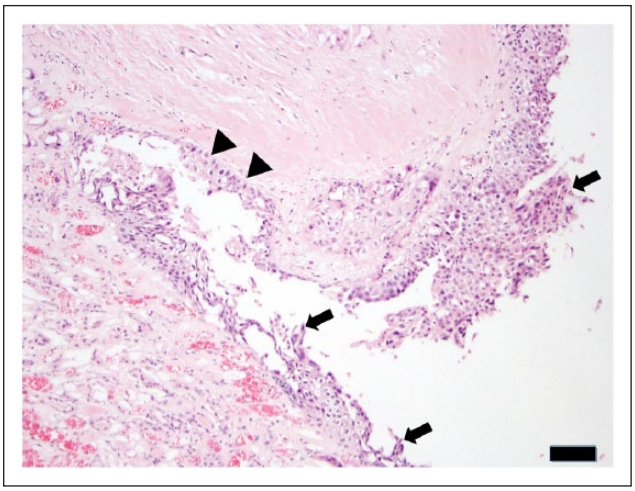

Figure 8 Renal pelvis, histopathology. The renal pelvis was lined by proliferative neoplastic cells forming irregular plaques (arrowheads) and papillary structures (arrows) that were multifocally invading the submucosa. Hematoxylin and eosin stain. Bar = 50 µm

the kidney, consistent with metastatic transitional cell carcinoma. These cells lined the anterior and posterior face of the iris, and the vitreous chamber where they replaced the retina (Figure 9). Extensive hemorrhage was noted in the choroid. Changes in the right eye included a neoplastic infiltrate in the choroid and ciliary body and diffuse retinal detachment, and atrophy. Masses in the lungs, thigh muscle and cerebral cortex were composed of neoplastic cells similar to those described in the kidney. The neoplastic population in the left eye showed moderate immunoreactivity to CK7 (Figure 10). The cells were not reactive with antibodies for CK20 (Figure 11). Gross and microscopic examination of the urinary bladder was unremarkable.

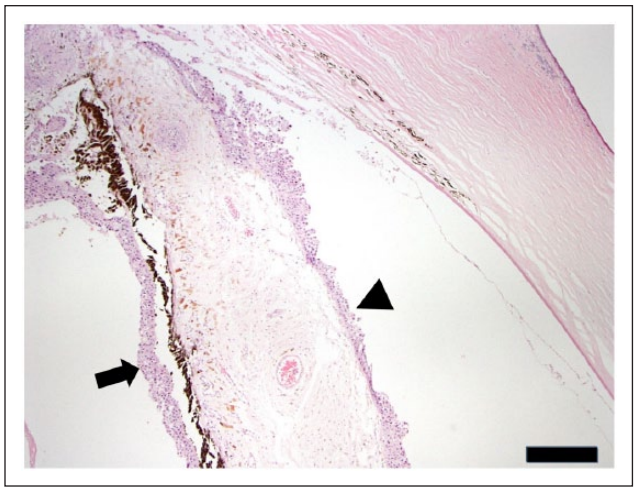

Figure 9 Left eye, iridocorneal angle, histopathology. The anterior (arrowhead) and posterior surfaces (arrow) of the iris were lined by neoplastic cells forming plaques and small papillary structures that multifocally invaded the underlying tissue. Hematoxylin and eosin stain. Bar = 200 µm

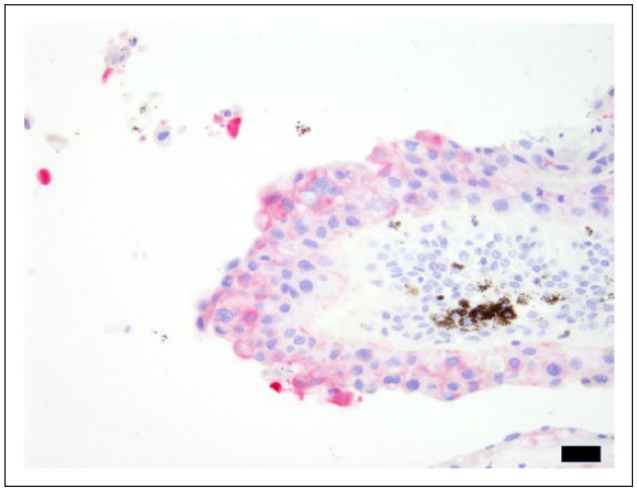

Figure 10 Left eye, ciliary body, CK7 immunohistochemistry. Neoplastic cells showed moderate-to-strong immunoreactivity for CK7. Bar = 20 µm

Discussion

Renal TCC occurs as a result of neoplastic changes to the transitional epithelial layer that lines the pelvis of the kidney. Feline renal TCC has been reported in several case studies.[2–4] In two case series, feline renal TCC was found to affect nearly 16% and 42%, respectively, of cats evaluated for primary renal tumors (excluding lymphoma).[5,6] Other reported primary renal neoplasms in cats include renal cell carcinoma, nephroblastoma, squamous cell carcinoma, tubulopapillary carcinoma, hemangiosarcoma, tubular carcinoma and adenomas,[5,6] with lymphoma being the most common tumor affecting the feline kidney.[7]

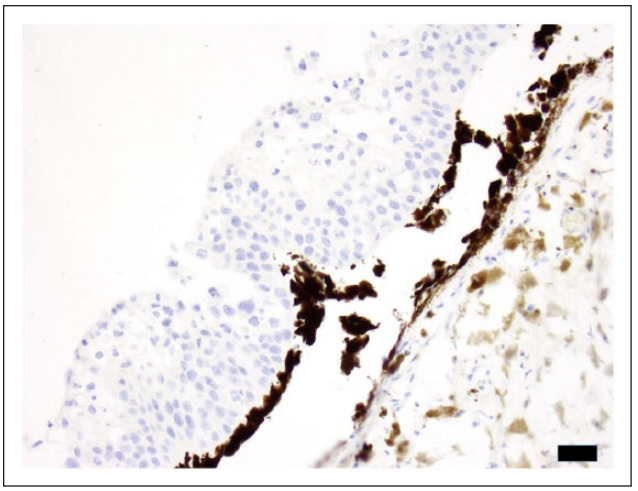

Figure 11 Left eye, ciliary body, CK20 immunohistochemistry. Neoplastic cells were not reactive with antibodies to CK20. Bar = 20 µm

The age of cats affected by renal TCC ranges from 4–15 years, with an average of 11.8 years.[2,6] Affected breeds include domestic longhair,[3] domestic shorthair,[2,3,5] Burmese[4] and Siamese.[6] Of the 14 cats reported to have renal TCC four were neutered males,[3–5] three were spayed females[2,5] and no sex was reported for the additional eight cases.[6] Owing to the small number of cases reported it is difficult to determine if there is a statistically significant breed predisposition or sex predilection in cats.

The clinical signs associated with renal TCC and other primary renal tumors are often non-specific and not directly associated with the renal system. The most commonly reported clinical signs are anorexia, weight loss, depression and lethargy.[2,5,6] It is possible that by the time owners seek medical attention the tumor has already metastasized or has elaborated enough inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1beta and interleukin-6, which promote anorexia, increased energy metabolism and accelerated loss of lean body mass.[8,9] CBC and serum chemistry profile do not show specific changes associated with primary renal neoplasia. Henry et al[5] found that of 10 cats with serum chemistry profile results available, eight cats demonstrated azotemia; Carpenter et al[6] found that azotemia was present only when the unaffected kidney had severe, chronic inflammation. As renal TCC tends to affect older cats it is possible that the presence of azotemia is associated with chronic renal disease. A causative relationship between chronic renal disease and renal TCC in cats has been proposed but not established.[3] The urine specific gravity of cats with renal TCC and other primary renal neoplasia has been reported to range from 1.010–1.042.[2–5] This variability could be due to underlying chronic renal disease or dehydration accompanying inappetence. Hematuria was found in 6/9 cases,[5] and might be a

useful indicator of renal neoplasia, once other causes of hematuria are excluded. In the cat of the present report, non-specific clinical signs were first thought to be associated with gastrointestinal-related disease such as pancreatitis, inflammatory bowel disease or cholangiohepatitis. Renal neoplasia was suspected only after renomegaly was noted later in the course of the disease.

Renal TCC in cats has a unilateral presentation in most cases, unlike renal lymphoma, which tends to be mostly bilateral.[10] Unilateral involvement was noted in 85.7% of cases of feline renal TCC reviewed,[2–6] while one case of renal TCC originated in the left kidney and metastasized to the right kidney.[6] There has been only one report in cats of bilateral de novo renal TCC and the diagnosis was supported by the absence of renal vascular invasion and lack of distant metastasis.[3] In the cat of the present report, the pelvis of both kidneys was affected; however, as metastasis was evident and vascular invasion was noted, it is difficult to determine from which kidney the tumor originated or if it was a bilateral independent neoplasm.

On gross pathologic examination, kidneys affected by TCC may be firm and slightly enlarged or irregularly shaped.[1,6] However, minimal or no gross changes can result in normal palpation and ultrasonographic findings, as in this case and one previously reported case.[3] Renal TCC seems to be especially aggressive in cats and dogs and has been documented to metastasize to multiple sites, including lungs, ureter, liver, mesentery, peritoneum, meninges, perirenal soft tissue, adrenals, lymph nodes, skeletal muscles, spleen, pleura and the heart.[3,5,6,11,12]

Several tumor types have been shown to metastasize to the eyes of cats and dogs; for example, lymphoma, carcinomas, transmissible venereal tumor and hemangiosarcoma.[13–16] Ocular metastases of carcinomas are uncommon in cats. Only 2/75 (2.6%) feline eyes with intraocular neoplasia yielded a diagnosis of metastatic carcinoma.[13] In people, the occurrence of intraocular metastasis has been documented to range from 4.2–8.5% of patients with cancer, depending on the origin of the carcinoma.[17,18] Breast and lung carcinomas were found to be the leading causes of uveal metastasis and represent more than two-thirds of the primary tumor sites found in people.[19]

Intraocular metastasis occurs when neoplastic cells spread via blood to the eye. Metastasis typically affects the choroid owing to its high degree of vascularity. Infiltration of neoplastic cells occurs through the short and long posterior ciliary arteries and, to a lesser extent, through the anterior ciliary arteries.[20] In people, metastasis to the choroid was documented in 88% of cases of uveal metastasis.[19] TCC rarely results in ocular metastasis. There are isolated case reports of TCC originating in the bladder, urethra and ovary with orbital and intraocular metastasis in human beings, dogs and a collared peccary.[21–28] Intraocular metastasis of TCC originating in the kidneys has been reported only once in people,[29] and to the best of our knowledge the current case is the first reported renal TCC with ocular metastasis in cats. It is possible that ocular abnormalities manifested before the renal abnormalities in the cat of the present report because TCC tends to grow along surfaces. As it did so over the choroid, retina and renal pelvices, blindness due to loss of retinal function may have been more obvious to the owners than loss of kidney function.

Immunohistochemistry using antibodies to CK7 and CK20 can help characterize urothelial tumors and assist in distinguishing them from other types of carcinomas. Of four reported feline TCC tumors, three were positive for CK7 and CK20, and one was negative for both antibodies.[30] In the cat of the present case, both the primary renal tumor and the ocular metastases showed moderate-to-strong cytoplasmic immunoreactivity to CK7 and the ocular metastases showed negative immunoreactivity to CK20. Examination of more feline TCC tumors with immunohistochemistry to CK7 and CK20 is required to determine the most common pattern of immunoreactivity.

The prognosis for renal TCC is poor and tumors often have metastasized by the time of diagnosis. Nephrectomy of the affected kidney can be considered if there is no evidence of metastasis and if the other kidney is determined to be functional.[5,6,8]

Analysis of the medical management of the case in this report provides an opportunity to explore the decision-making process in veterinary medicine. Clinical decision making is a cognitive process that occurs in both the conscious and subconscious levels.[31,32] Decision making may be accomplished by the operation of two different cognitive systems. Briefly, system 1 is largely intuitive and allows clinicians to identify a disease based on a familiar pattern (pattern recognition). System 1 requires less mental energy and operates fast but is more prone to mistakes owing to different cognitive biases, heuristics ('rules of thumb') and affective states.[31–35] System 2, however, is more analytical and problem-oriented, operating more slowly and deliberately, requiring more time and mental effort.[31–33] Different strategies have been recommended to minimize cognitive error that originates in cognitive biases afflicting the decision making process, particularly in system 1. Metacognition, applications of checklists, diagnostic algorithms and slowing down while going through the diagnostic process are a few of the recommended strategies.[31,35,36]

The reported clinical signs of inappetence and lethargy in conjunction with the young age of the cat in the present report were intuitively thought of as gastrointestinal in origin. In the present case, system 1 – which was influenced by different cognitive biases such as confirmation

bias, anchoring bias and over-confidence bias, in addition to familiarity/recognition heuristics – led to focusing on the inappetence and lethargy, giving them greater emphasis in the diagnostic plan and not recognizing that the blindness found on the physical examination was a key element in reaching a more accurate diagnosis. In the present case, the blindness should have been addressed much earlier than it was with a referral to an ophthalmologist. In addition, performing an ocular ultrasound at the same time of the abdominal ultrasound could have provided useful information regarding the ocular fundus, potentially detecting retinal detachment and/or choridial thickening which would have localized the disease process to the eye and not to the brain. As a result of confirmation bias, the tests that were initially ordered intended mainly to confirm a gastrointestinal related diagnosis. If thoracic radiographs were taken before more specialized tests were pursued the differential diagnosis would have expended earlier in the diagnostic process and the cat could have been managed differently and more humanely, avoiding unnecessary imaging tests, laboratory tests and medications, and at a more reasonable cost to the owners. A more active and trained system 2 in addition to metacognition would have provided more safeguards against cognitive biases and could have decreased the likelihood of cognitive error.

Conclusions

In spite of the rare occurrence of renal TCC, clinicians should consider the condition, especially in older cats presenting with anorexia, weight loss, depression and lethargy. All patients presented for blindness and mydriasis or noted to have ocular signs during a general physical examination should undergo a complete ophthalmic examination before expensive and higher risk procedures are performed. Clinicians should familiarize themselves with the intricate cognitive process and cognitive biases that take place during diagnosis and management of patients. Metacognition and other cognitive forcing strategies should be learned and incorporated into the diagnostic process to safeguard and decrease the chances of cognitive error and increase the chances of accurate and timely diagnosis.

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