Abbie's Abdomen

A Case Report of Canine Renal Tubular Carcinoma

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Introduction:

Neoplasia of the urinary tract is uncommon and accounts for less than 1% of all neoplasia of domestic animals. Primary renal tumors in particular are extremely rare and account for only 0.3% of all canine neoplasia.[1] Primary renal tumors may arise from the epithelium, the mesenchyma, or have mixed embryonal origin.[2] A study of 54 primary renal tumors in dogs showed a distribution of 85.2% tumors of epithelial origin, 11.1% mesenchymal, and 3.7% of mixed origin.[3] All primary renal tumors tend to present with common non-specific clinical signs including lethargy, anorexia, abdominal pain, cachexia, polyuria/polydipsia, and hematuria.[2,1] Dogs tend to be middle-aged to older when diagnosed and they are often diagnosed late in the course of disease.[2,4] Consequently, pulmonary metastasis has been detected in 18-48% percent of dogs at the time of diagnosis. Additionally, the tumors tend to be quite large at the time of diagnosis with 20-43% of dogs presenting with a palpable abdominal mass.[4]

History and Presentation:

Abbie, an 11 year-old female spayed Labrador retriever, presented to Mississippi State University's College of Veterinary Medicine emergency service the evening of November 6, 2018 for further investigation of a sudden 15% decrease in body weight and an abdominal mass discovered by her referring veterinarian. Approximately 1.5-2 months previously, Abbie's owner noticed that she began to have a change in her respiratory pattern and appeared to be panting, especially at night. She also appeared to be uncomfortable and grunted whenever she changed positions or laid on her right side. Abbie is a hunting dog, and her owner noted that there had been a few sporadic episodes when Abbie did not retrieve decoys as aggressively and seemed "not quite herself." He also reported that she seemed stiff in the morning, most notably in her right shoulder and stifle, but warmed out of it after a few steps. Abbie had been on a weight

management diet over the past month, but her owner reported no other changes to her diet or lifestyle.

Abbie originally presented to her primary care veterinarian on October 31, 2018 for routine blood work due to NSAID use for arthritis and as pre-anesethetic blood work prior to a dental cleaning. At this time her systemic blood work was unremarkable. A dental prophylaxis cleaning was scheduled for November 6, 2018. When Abbie returned for her dental cleaning, her referring veterinarian noted a weight loss of 15%. Physical examination that day also revealed a large, firm, soft tissue mass just caudal the 13th rib on her right side. Abdominal radiographs showed a mass effect in the area of the right kidney. At this time, Abbie was referred to MSU-CVM for further examination and diagnostics.

On presentation to MSU-CVM emergency service, Abbie was anxious however bright, alert, and responsive. Cardiothoracic auscultation revealed no abnormalities. On musculoskeletal evaluation, she was resistant to full extension of both carpi. Mild pain was elicited on palpation of thoracic spine. Her peripheral lymph nodes were small and symmetric on palpation. Abdominal palpation revealed an approximately 9 cm in diameter, round, irregular, firm intra-abdominal mass just caudal to the 13th rib. Abbie showed discomfort when pressure was applied to the mass. No free fluid was noted in the abdomen on brief ultrasound scan. The remainder of her physical exam was unremarkable. Abbie was hospitalized overnight with supportive care, including the anti-emetic maropitant and hydromorphone for pain management.

Diagnostic Approach/Considerations

Abbie was transferred to the MSU-CVM Oncology service the following morning for further diagnostics to aid in characterization of the mass. A renal chemistry panel and urinalysis

were performed due to the suspicion that the mass may be associated with the right kidney. Hematuria is a common urinalysis abnormality with primary renal tumors and occurs in up to 32% of patients.[2,1] Additionally, pyuria, proteinuria, and isosthenuria may be seen.[2] Azotemia is a frequent biochemical change however, renal failure does not commonly occur with canine renal neoplasms.[1,5] The exception to this is with renal cystadenocarcinoma found only in German Shepherd Dogs.[5] The renal chemistry panel and urinalysis for Abbie were within normal limits and showed no kidney function compromise nor overt evidence of a urinary tract infection. Common hematologic abnormalities associated with primary renal tumors include neutrophilia, anemia, and thrombocytopenia.[2] The complete blood count for Abbie from the referring veterinarian was within normal limits. A platelet count was performed to ensure Abbie's platelets were adequate for appropriate hemostasis, and revealed no evidence of thrombocytopenia.

In a study that looked at 82 dogs with primary renal neoplasia, pulmonary metastasis was seen in 16% of dogs at the time of diagnosis. Up to 77% of dogs had evidence of metastasis at the time of death.[2] Abbie's thoracic radiographs showed no evidence of pulmonary metastasis. Abdominal ultrasound showed loss of normal renal architecture within the right kidney, an approximately 9 cm mass confluent with the right kidney, and bilaterally enlarged adrenal glands. Fine needle aspirates of the mass were performed and cytology was suggestive of a carcinoma, however histopathology was recommended.

Treatment options for renal tumors and the need for further diagnostics to characterize Abbie's tumor further were discussed with her owner. The decision was made to take Abbie to surgery to perform a nephrectomy and submit the renal mass for histopathologic evaluation. Computed tomography of the abdomen was performed for surgical planning. The CT scan

revealed that the renal mass was occluding and compressing the caudal vena cava. Bilateral enlargement of the adrenal glands previously noted on abdominal ultrasound was confirmed. Additionally, the spleen was noted to be enlarged with irregularly distributed nodular lesions throughout. Blood typing was performed in case excessive hemorrhage occurred during surgery and required a blood transfusion. This revealed type DEA 1.1 positive blood.

Abbie was prepped for surgery and a full abdominal explore was performed. The spleen was found to have numerous nodules, approximately 1-2 cm in diameter distributed throughout. The right kidney was then found to be grossly abnormal and the renal tumor was approximately 9 cm in diameter, irregularly shaped, ulcerated, and highly vascular. Upon further exploration, it was determined that the renal mass did not invade the caudal vena cava but was compressing and nearly occluding it. The mass and the right kidney were bluntly dissected and a ureteronephrectomy was performed. In addition, a splenectomy was performed and liver punch biopsies were taken from the left lateral liver lobe. Histologic sections of the renal mass showed cuboidal to polygonal cells with eosinophilic cytoplasms forming tubular structures indicating that the mass was a renal tubular carcinoma. There were approximately 3-4 mitotic figures per high powered field. Histologic sections of the spleen and liver revealed no evidence of metastasis.

Pathophysiology

Of primary renal tumors, renal cell carcinomas are the most common type, making up 49-65%.[3,2] Renal cell carcinomas originate from the epithelial cells of the distal convoluted tubules of the nephron.[6,7] The gross appearance of these tumors tends to be a large unilateral mass, spanning an entire pole of the kidney.[8] They can be classified by histologic type as papillary, tubular, solid, cystic, or multilocular cystic.[4] Abbie's tumor was consistent with a tubular type

carcinoma. Tubular type tumors are made up of neoplastic cells forming tubules that are separated by fibrovascular stroma. They often contain basophilic material and apoptotic cellular debris.[4] It is reported in the literature, that poorly differentiated tubular tumors tended to have a shorter median survival time. However, patients with predominantly tubular tumors with no vascular invasion and no metastatic disease had the longest survival times. This suggests that histologic type had a significant association with patient outcome.[6]

Cytologic subtypes have also been described for renal cell carcinomas, including chromophobic and clear cell types. Clear cell carcinomas are described as being composed of cells with abundantly vacuolated cytoplasms, while chromophobe carcinomas are described as solid tumors made up of polygonal cells with abundant eosinophilic cytoplasm.[4] Clear cell carcinomas have been reported to have a shorter survival time with a median survival time in one study of 87 days.[1] However, while clear cell carcinomas are the most frequently diagnosed renal cell carcinomas in humans, they are uncommon in dogs. Case reports have suggested that canine renal cell carcinomas appear to be more similar to human chromophobe and collecting duct subtypes.[4] Abbie's tumor was described as being made up of cuboidal to polygonal cells with scant to moderate eosinophilic cytoplasm that was fairly vacuolated. While there were occasional cells throughout the tumor that could be classified as clear cell, the majority of the tumor was made up of chromophobic type cells. Thus Abbie's tumor is classified as a tubular, chromophobic renal cell carcinoma.

Mitotic index, along with nuclear size and pleomorphism, tumor differentiation, invasiveness, clear cell morphology, and Fuhrman nuclear grade have been described in the literature as showing a significant difference in survival times. Mitotic index, however, appears to be the only independent prognostic variable.[4] Mitotic index is determined by the number of

mitotic figures in 10 fields at 400x magnification. The literature reports that a mitotic index greater than 30 correlated with a 187 day median survival. A Mitotic index less than 10 correlated with 1184 day median survival, and a mitotic index between 10 and 30 correlated with a median survival of 452 days.[4,1] Abbie's tumor was described as having 3-4 mitotic figures per high powered field. One may postulate that this corresponds to a mitotic index of greater than 30, however that would assume that the 10 high powered fields are uniform.

Renal cell carcinomas tend to have a moderate metastatic rate at 16-34% at the time of diagnosis. That rate is higher (70-75%) later in the course of the disease. Sites of metastasis include the contralateral kidney, other abdominal organs, the omentum, peritoneum, and lungs.[1] Metastasis to the adrenal gland occurred in 4% of human renal cell carcinoma cases and has been reported once in a canine study. However, local extension into the caudal vena cava occurs more commonly.[2] The literature shows that evidence of metastasis at the time of diagnosis results in shorter survival times. Alternatively, survival times have been reported up to four years following nephrectomy when there was no evidence of metastasis.[1] At the time of diagnosis, Abbie had no evidence of pulmonary metastasis on thoracic radiographs. Additionally, histopathology of the spleen, following splenectomy, and liver punch biopsies showed no evidence of metastasis.

Treatment and Management

For any primary renal neoplasia, a nephrectomy with complete tumor excision is the primary therapy. However, because of the metastatic rate often associated, adjuvant chemotherapy is recommended. Renal cell carcinomas do however, have a poor response rate to conventional chemotherapy in humans. Because of this, a variety of other treatments have been implemented in human medicine to prolong survival times. Small molecule inhibitors,

antiangiogenic drugs, and immunotherapies have proven to have some efficacy in prolonging survival times in humans with renal cell carcinomas. Today, immunotherapy with interleukin-2 and interferon are mainstays of therapy in human medicine.[2] Additionally, the use of tyrosine kinase inhibitors has significantly increased survival times in human patients. Cox-2 inhibitors have also been used in the treatment of human renal cell carcinoma with some success as Cyclooxygenases are involved in cancer development by inhibiting apoptosis, supporting cellular proliferation, increasing angiogenesis, and decreasing immunity.[6]

Canine studies have not yet shown a statistical difference in survival times for dogs who undergo chemotherapy.[2,4] While there is no standard chemotherapy protocol set for renal carcinomas, the literature reports the use of single-agent and combination chemotherapy protocols including doxorubicin, cyclophosphamide, carboplatin, mitoxantrone, or paclitaxel.[2] One study that looked at twenty-seven dogs who received adjuvant chemotherapy, reported that the longest median survival time appeared to be associated with the use of mitoxantrone followed by carboplatin, however there was still no statistically significant difference in overall survival times among this group.[6] The literature also suggests the small molecule inhibitor toceranib phosphate, a tyrosine kinase inhibitor, may have some efficacy in prolonging survival times in the canine patient.[1] This is because mutations in the transmembrane tyrosine kinase growth factor receptor, c-Kit, may play a role in the pathogenesis of renal cell carcinomas by causing apoptosis resistance and cellular proliferation.[7] Chemotherapeutic options discussed with Abbie's owner included intravenous carboplatin or the oral chemotherapeutic Palladia (toceranib), a tyrosine kinase inhibitor. The third option discussed with Abbie's owner, was the option to not pursue chemotherapy and instead monitor Abbie for evidence of local recurrence or

metastasis. It was made known, however, that by the time metastasis was detectable it is often too late for chemotherapy to be effective.

Case Outcomes:

At this time, Abbie's owner elected to not proceed with chemotherapy and instead monitor her for signs of local recurrence or metastasis. Instruction was given to monitor for abdominal pain, discomfort, lethargy, increased respiratory rate or effort, vomiting, inappetence, stranguria, or polyuria. In addition, due to the bilateral adrenomegaly noted on abdominal ultrasound and CT, Abbie's owner was instructed to monitor for signs associated with hyperadrenocorticism such as alopecia, increased panting, polyuria/polydipsia, or a pot-bellied appearance. During a recent client communication with Abbie's owner, it was mentioned that she is continuing to pant excessively but has developed no other overt signs of Hyperadrenocorticism. Her owner informed us that he would like to pursue further diagnostics for the disease and that he was deciding whether or not he would like to pursue chemotherapy. The case has since been lost to follow-up.

References:

1. Burgess K, DeRegis C. Urologic Oncology. Vet Clin Small Anim 2018; 49:311-323.
2. Bryan J, Henry J, Turnquist S, et al. Primary Renal Neoplasia of Dogs. J Vet Intern Med 2006; 20:1155-1160.
3. Baba AI, Câtoi C. Urinary Tract Tumors In: Comparative Oncology. Bucharest: The Publishing House of the Romanian Academy; 2007; Chapter 13. Available at: https://www.ncbi.nlm.nih.gov/books/NBK9544/. Accessed Feb 14, 2019.
4. Edmondson E, Hess A, Powers B. Prognostic Significance of Histologic Features in Canine Renal Cell Carcinomas: 70 Nephrectomies. Veterinary Pathology 2015; 52(2):260-268.
5. Saridomichelakis M, Koutinas C, Souftas V, et al. Extensive caudal vena cava thrombosis secondary to unilateral renal tubular cell carcinoma in a dog. Journal of Small Animal Practice 2004; 45:108-112.
6. Carvalho S, Stoll A, Priestnall S, et al. Retrospective evaluation of COX-2 expression, histological and clinical factors as prognostic indicators in dogs with renal cell carcinomas undergoing nephrectomy. Veterinary and Comparative Oncology 2016; 15(4):1280-1294.
7. Gil da Costa R, Oliveira J, Saraiva A, et al. Immunohistochemical Characterization of 13 Canine Renal Cell Carcinomas. Veterinary Pathology 2011; 48(2):427-432.
8. Lucke V, Kelly D. Renal Carcinoma in the Dog. Vet Pathol 1976; 13:264-276.