“Ureter in for a Surprise”

A Case Report of TCC

Kaitlyn M. Havill
Mississippi State University
College of Veterinary Medicine
Class of 2018

Clinicopathological Conference
Advisor: Dr. Hayley Gallaher, DVM
October 27, 2017

Introduction

Urinary tract neoplasms cover approximately 1-2% of all canine neoplastic diseases. [11] Transitional cell carcinoma (TCC) is the most common cancer of the urinary tract in dogs. TCC is most commonly found in the trigone of the bladder. TCC is malignant and highly invasive to surrounding tissues. At the time of diagnosis of TCC, metastasis is approximately 20%.[5] Metastasis occurs at the lungs, regional lymph nodes, prostate and the bone. Risk factors of dogs include obesity, female gender, exposure to older generation flea control products, herbicides and pesticides. Clinical signs on presentation include lower urinary tract signs such as hematuria, stranguria, pollakiuria, and dysuria. Definitive diagnosis of transitional cell carcinoma is made via histopathology.[11] Treatment is palliative, including surgical and medical management.

History

A 12-year-old male neutered Shih-Tzu was referred to Mississippi State University Animal Health Center, Emergency Service on the evening of November 25, 2016 for a 4-day history of lethargy, anorexia, and vomiting.

The patient had been anorexic since November 21st and had progressively become more lethargic and depressed. On November 25th, he was taken to Flowood's AERC. There, an aFAST scan was performed which revealed free fluid in all four quadrants of the abdomen and a large fluid filled structure in the location of the left kidney. Bloodwork revealed a moderate neutrophilia, severe azotemia, moderate hyponatremia, moderate hyperphosphatemia, mild hypoalbuminemia, and a moderately elevated ALP. Due to the extensive problem list, the patient was referred to MSU-CVM for further evaluation and treatment of a suspected hydronephrosis.

Presentation

Upon presentation, the patient appeared lethargic and depressed. He weighed 9.3 kg (20.5 lb) with a body condition score of 6/9. His heart rate was elevated at 164 beats per minute while the rest of his vital parameters were within normal limits (102.1 temperature and 24 respiration). His ECG and blood pressure readings were within normal limits. On abdominal palpation, the patient was found to be painful around the left flank. Again, aFAST revealed a free fluid score of 4/4. The patient was sedated with dexmedetomidine and methadone for an abdominocentesis. Due to the location of bowel within the free fluid, a viable free fluid pocket was not able to be found within the abdomen, therefore a sample was not collected and the patient was reversed with atipamezole.

The patient's mucous membranes were tacky and he was estimated to be approximately 5% dehydrated. A urine sample was obtained prior to starting fluids, and urinalysis revealed bacteria, red and white blood cells. The patient was started on LRS fluid at 35 ml/hr (2x maintenance) and Unasyn (30 mg/kg IV q8h). He was also started on several other medications: pantoprazole (1 mg/kg IV q24h) for a gastroprotectant, maropitant citrate (1 mg/kg IV q24h) for anti-nausea, and methadone for analgesia. A complete blood count showed a moderate neutrophilia with a left shift. The first 24 hours in ICU, the patient was aFAST scanned every 12 hours to look for any increased free fluid present. Once his fluid deficits were corrected and he maintained adequate perfusion, he was placed on maintenance fluids at 23 ml/hr of LRS and continued to be monitored in ICU.

The following day, bloodwork was repeated revealing severe worsening of the neutrophilia with left shift, but had a resolved azotemia. Coagulation profile revealed PT and PTT were within normal limits. An official abdominal ultrasound reported free fluid within the abdomen, a severely enlarged left kidney, and an inflamed pancreas. An abdominocentesis was performed during ultrasound and analysis revealed an exudative fluid. Fluid creatinine and potassium were similar to blood creatinine and potassium and indicated no evidence of uroabdomen. The patient was transferred to MSU-CVM surgery service for an emergency nephrectomy that afternoon due to an increasing neutrophilia.

Abdominal exploratory revealed a dilated left kidney and left ureter. A left nephrectomy and ureterectomy was performed and samples were submitted for histopathology. Multiple raised white nodules, between approximately 0.5-1 cm in size, were present on the ureter, diaphragm, pancreas, and spleen. Differentials for the nodules included abscess formation, granuloma, or metastasis. Postoperatively, thoracic auscultation revealed increased, harsh lung sounds and crackles. Throughout the day, the patient had multiple bouts of respiratory distress within the 36 hours postop. He was placed in the oxygen cage and continuous monitoring was performed. An ultrasound guided right thoracocentesis was performed later in the day and approximately 25 ml of proteinaceous fluid were collected, but a fluid analysis was not performed. Bloodwork was performed daily to assess his CBC and chemistry throughout his hospitalization. Medical management was performed for the following 5 days**.**

Differential Diagnosis

Given the patient's history, physical exam findings and exploratory surgery, our main differential was hydronephrosis with a possible peritonitis due to an ascending infection or

stones. Without further diagnostics and with the results of histopathology from the nephrectomy and urectomy pending, other differentials, including pancreatitis, sterile vs. septic peritonitis, or neoplasia.

Pathophysiology

Transitional cell carcinoma is a malignant tumor that typically invades the bladder and other urogenital sources. As the cells proliferate, the urinary system may become blocked. With an obstruction, fluid will increase in the urinary system and there will become an increase in pressure, therefore backing up the system cranial to the obstruction.[7] An obstruction in the ureter builds up pressure to the kidney, causing a hydronephrosis. Hydronephrosis can be seen from many different etiologies: ectopic ureters, ascending infection, stones, parasites (*D. renale*), neoplasia, and spay granulomas.[11] With pressure building from an obstruction, the diameter of the kidney increases, therefore decreasing the capsule wall thickness. In the case of this patient, the TCC originated in the left ureter causing an obstruction and decreased outflow of urine. Continuous urine production caused backflow into the left kidney, dilating and decreasing the capsular wall thickness.

Diagnostic Approach/Considerations

For our patient, a complete blood count, biochemistry profile, and urinalysis were obtained. The most concerning abnormality was the increasing neutrophilia with a left shift. In most literature on TCC, complete blood cell count has not shown a significant correlation with neoplasia. Neutrophilia has been the most common reported abnormality, but has not been

shown to be statistically significant. However, with a neutrophilia greater than 40,000 cells/uL, paraneoplastic syndrome could not be ruled out.[4]

Patients that are ultimately diagnosed with transitional cell carcinoma typically present with signs of hematuria, stranguria, or pollakiuria.[7]Diagnostic tools used in research to determine transitional cell neoplasia include urine sediment, fine needle aspiration, biopsy via abdominal exploratory, cystoscopy, or traumatic catheterization. The gold standard for diagnosis of transitional cell carcinoma requires a biopsy of the tissue and histopathology.

According to Knapp et. al, 30% of dogs with TCC had neoplastic cells identified in the urine sediment in a study performed in 2013. Recently, a urine antigen dipstick test has been used to identify transitional cells, but false positives have kept it from being truly reliable for ruling out TCC.[3]

Due to recent studies showing metastasis of approximately 20% of TCC patients at diagnosis, it is imperative to further investigate spread to other organs.[9] Thoracic radiographs, abdominal ultrasound, lameness examination for any source of bone metastasis and further investigation with radiographs or scintigraphy are all recommended in a full work up for a metastatic disease.

Treatment & Management

Unfortunately, there is no cure for TCC. Palliative treatment includes surgical and medical therapy. The purpose of management for a patient with TCC is to decrease clinical signs and prolong short-term survival.

Surgical intervention includes debulking the tumor via blunt dissection or laser. Laser therapy has been recently published in the literature[1], but the risk of bladder perforation has limited widespread use. Surgical excision is possible if the tumor is in the upper urinary system and unilateral, or is in an area of the bladder that is resectable (body and neck). As previously mentioned, TCC in the bladder typically affects the trigone, which unfortunately renders it unresectable. Abdominal exploratory is useful when having a gross visualization of the tumor, collecting full biopsies, or placing stents to resolve any obstructions.

Chemotherapy can be used as a palliative treatment, therefore decreasing clinical signs and prolonging short-term survival (approximately 130-300 days)[5]. Several different chemotherapeutic agents have been used as single agents, or in combination with COX-specific inhibitors. Medical therapy for TCC also includes use of COX inhibitors on their own. A COX-2 inhibitor, with piroxicam being the most well studied, has the best single agent efficacy, with a reduction in tumor size of >50% in about 30% of dogs as well as improvement of clinical signs of TCC patients.[6] The most effective protocols to date incorporate an injectable chemotherapy, mitoxantrone, with piroxicam. In one study, this regimen resulted in an overall 35% response rate in the measured size of the tumors in 48 dogs.[6] More importantly, symptomatic improvement occurred in 75% of the dogs.[6] The average survival time in this study was 10 months, compared with 6 months with piroxicam alone.[6] Other combinations, such as cisplatin and piroxicam, led to impressive remission rates (50–71%), but renal, gastrointestinal, and bone marrow toxicities limit the use of this protocol.[5]

Additional medical therapy which should be considered for use in TCC patients include antibiotics. As urinary tract infections are commonly seen with TCC, appropriate urine culture and antibiotic therapy are recommended.[1]

Radiation therapy of TCC has been a recent development. In a more recent report of 10 dogs, weekly coarse fraction external-beam RT combined with mitoxantrone and piroxicam was tolerated, but results were no better than medical therapy alone.[10]

Expected Outcome/Prognosis

Transitional cell carcinoma is a malignant neoplasm. These tumors have a poor prognosis, although multimodal treatment therapies may extend the survival period. Fulkerson and Knapp at Purdue University report obtaining baseline measurements of the TCC masses, initiating treatment, monitoring the response to that treatment at 4- to 8-week intervals, and continuing that treatment as long as the TCC is controlled, the side effects are absent or acceptable, and the quality of life is good.[5] When using this protocol, TCC growth can be controlled in approximately 75% of dogs, quality of life is usually very good, and median survival times can extend well beyond a year.[5] Cancers of the transitional epithelium represent a very rare finding in the renal pelvis, due to arising in other areas of the urinary tract. Unfortunately, literature review reports less than 20 cases of renal pelvic tumors in canine species.[2] With this uncommon type of transitional carcinoma, very little is truly known on the prognosis. Baskin et al, report that 4/48 (8%) dogs on a military base were diagnosed at necropsy with a transitional cell carcinoma of the upper urinary tract. On gross presentation, all were presented with a unilateral hydronephrosis.[1]

In conclusion, the main issue with transitional cell carcinoma is from the tumor causing an obstruction of the urinary tract. When there is an obstruction, this compromises the animal's health and well-being. When treatment is not an option, euthanasia is warranted. At the time of death, metastasis has been shown to have occurred in 50-70% of patients in several studies.[4,5]

Case Outcome

After recovery from surgery, the patient had an increasingly severe leukocytosis with a left shift. The bloodwork did not improve despite the 4-quadrant antibiotic coverage. Creatinine and alkaline phosphatase enzymes continued to increase. Several days post nephrectomy, the patient was having respiratory difficulty despite being placed in the oxygen cage. Medications were added to aid in his respiratory effort as well as keeping him comfortable: terbutaline (0.01 mg/kg SQ q8), albuterol (puffs PRN), ondansetron (0.93 mg/kg IV q8), meropenem (12 mg/kg IV q8), methylprednisolone (0.2 mg/kg IV q6). Despite continuing efforts, the patient continued to decline. During this time, histopathology of the left kidney, left ureter and of the liver read out as transitional cell carcinoma of ureteral origin with intra-abdominal and pulmonary metastasis.

Due to the grave prognosis, the owner elected to humanely euthanize on 12/2/16. Unfortunately, a necropsy was not selected, and his body was returned to his owner.

References

1. Baskin, G., Paoli, A. (1977). *Primary Renal Neoplasms of the Dog*. Veterinary Pathology. 14: 591-605.

2. Bazzo, R., Bevilacqua, B., Militerno, G., et. al. (2003). *Transitional Cell Carcinoma of the Renal Pelvis in Two Dogs*. J. Vet. Med. A 50, 457-459.

3. Borjesson, D. L., Christopher, M. M. and Ling, G. V. (1999), *Detection of Canine Transitional Cell Carcinoma Using a Bladder Tumor Antigen Urine Dipstick Test*. Veterinary Clinical Pathology, 28: 33–38.

4. Bryan, J., Henry, C., Turnquist, S., et. al. (2006). *Primary Renal Neoplasia of Dogs*. J Vet Intern Med 2006;20:1155–1160.

5. Fulkerson, C., Knapp, D. (2015). *Management of Transitional Cell Carcinoma of the Urinary Bladder in Dogs: A Review*. The Veterinary Journal 205 (2015) 217-225.

6. Henry et al. (2006). *Managing the Canine Cancer Patient*. Veterinary Learning Systems. Clin Cancer Res 9:906–911, 2003.

7. Knapp, D.W., McMillan, S.K., 2013. *Tumors of the urinary system.* Withrow and MacEwen's Small Animal Clinical Oncology, Fifth Ed. Elsevier-Saunders, St. Louis, MO, USA, pp. 572–582.

8. Laing, E., Norris, A., Valli, V., et. al. (1992). *Canine Bladder and Urethral Tumors: A Retrospective Study of 115 Cases (1980-1985).* Journal of Veterinary Internal Medicine; 6:145-153.

9. Mutsaers, A. J., Widmer, W. R. and Knapp, D. W. (2003), *Canine Transitional Cell Carcinoma*. Journal of Veterinary Internal Medicine, 17: 136–144. doi:10.1111/j.1939-1676.2003.tb02424.

10. Poirier, VJ., Vail, DM. et al. (2004). Piroxicam, Mitroxantrone, and Coarse Fraction Radiotherapy for the Treatment of Transitional Cell Carcinoma of the Bladder in 10 Dogs, a Pilot Study. Journal of American Animal Hospital Association. 2004 Mar-Apr; 40(2):131-6.

11. Rosenthal, R., Shell, L. (2015). *Transitional Cell Carcinoma*. Associate Database, Veterinary Information Network. Web. August 6, 2017.