All-Ye Need is One (Kidney)

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Meghan P. Courey

Mississippi State University

College of Veterinary Medicine

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Advisor:

Taya Marquardt DVM, DACVIM (Oncology)

Co-Advisor:

Seth Kettleman, DVM

Introduction

Renal neoplasia is relatively uncommon in domestic animals. When combining primary renal tumors with bladder and urethral tumors, they account for less than 1% of all neoplastic conditions[7]. The most commonly reported bladder tumor in canines, is a transitional cell carcinoma (TCC), which is now formally referred to as invasive urothelial carcinoma (UE) based off of the human nomenclature[7,13]. TCC is a malignant tumor that commonly arises at the trigone of the bladder, urethra, or prostate and often initially presents as nonspecific lower urinary tract signs[7,13]. It can, however, develop anywhere there are transitional cells, which includes the entirety of the urinary tract. TCC is an epithelial tissue derived tumor, making the tumor cells appear cohesive on cytology, and spreads via lymphatics[13]. Due to the non-specific lower urinary signs of stranguria, hematuria, pollakiuria, and tenesmus, TCC often goes undiagnosed until late in the disease process[7]. TCC can also be masked by transient response to antibiotic or anti-inflammatory administration further delaying definitive diagnosis[7,13]. Prognosis of TCC varies based on location, surgical complications, histopathology findings, local invasion, and presence of distant metastasis[5]. Most commonly, patients succumb to the effects of local disease from TCC, and not from distant metastasis[13]. The following case report will outline current literature in the context of an unusual presentation of TCC with important clinical correlates for the practicing veterinarian.

Signalment and History

Allye is an approximately 10-year-old female spayed mixed breed dog that presented to MSU-CVM Internal Medicine Service on September 4, 2020, for lethargy, inappetence, vomiting, pain, and a distended abdomen. Allye had a previous history of a complicated

ovariohysterectomy (OHE) due to a suspected left-sided penetrating wound trauma to the abdomen evidenced by scar tissue present at the time of surgery.

Upon presentation to MSU-CVM, Allye was dull, quiet, but responsive. Her vital parameters included a heart rate of 120 beats per minute (normal 60-120 beats per minute), a respiratory rate of 60 breaths per minute (normal 10-30 breaths per minute), a temperature of 99.9°F (normal 98.0-102.5°F), with pink and tacky mucous membranes, and capillary refill time of less than two seconds. She had a body condition score of 7/9 indicating she was overweight, with 5/9 being ideal. Through the Internal Medicine service Allye underwent a full diagnostic work up including a complete blood count, chemistry panel, abdominal and thoracic radiographs, and an abdominal ultrasound. The findings revealed a suspected hydronephrosis of her left kidney and Allye was transferred to the surgery service for further intervention.

Diagnostic Approach

It was noted in Allye's history, that she experienced a "traumatic spay" when she was a puppy. This clinical clue proved valuable as neutered animals, both male and female, are reported to have approximately four times the risk of developing TCC[7]. Obesity, is also an important risk factor which may have contributed to the development of TCC[2,7]. Another common risk factor, is exposure to chemicals, including topical flea therapy, tick dips, lawn herbicides, and insecticides[2]. It is postulated that the risk of TCC from lawn herbicides is associated with ingestion and then excretion in the urine directly exposing the urothelium to the carcinogen[2]. Allye's history and presentation make this an unlikely risk factor, but it is an important reminder to always include these questions in your history gathering. In Allye's case, it is likely a combination of underlying inflammation, obesity, and her status as a spayed female that contributed in the development of her TCC.

Considering TCC is the most common neoplasm affecting the urinary bladder in dogs, it is important to make a definitive diagnosis if it is suspected[2,9]. Allye's bloodwork showed an elevated blood urea nitrogen (BUN), which can be indicative of renal malfunction. Using a combination of abdominal radiographs, ultrasound, and baseline bloodwork, an abnormality in the urinary tract suspicious of TCC moves higher on the differential list, but definitive diagnosis of TCC requires biopsy and histopathology. A combination of fine needle aspirate (FNA) cytology and a BRAF urine test can be used to make a suspected diagnosis as well, but percutaneous aspirates of a suspect TCC are often avoided for the risk of tumor seeding[2].

Based on Allye's abdominal radiographs, it was noted that there was decreased abdominal serosal detail and a normal left kidney was unable to be clearly identified. There was a smoothly marginated mass noted in the left half of the abdomen which was displacing the intestines to the right. Allye's abdominal ultrasound supported the radiographic findings with evidence of a severely dilated left kidney and echogenic fluid replacing the parenchyma. There was minimal evidence of any residual renal cortical parenchyma remaining suggesting renal atrophy secondary to hydronephrosis. There was significant hyperechoic material noted in the left renal pelvis, which may be the causative etiology leading to the hydronephrosis and hydroureter. The majority of the left ureter was moderately dilated and measured 4.8mm in diameter. The right kidney had hyperechoic punctate foci within the renal cortex. Based on these findings, it was suspected that Allye had left hydronephrosis and hydroureter as well as chronic kidney disease in the right kidney. Significant peritoneal effusion was also appreciated but could not be distinguished as urine, hemorrhage, or a modified transudate. Due to the unknown etiology causing the hydroureter, abdominal effusion, and hydronephrosis, Allye was immediately prepared for emergency surgery.

Surgical Approach

On September 4, 2020, Allye was prepped for surgery to identify the source of the hydronephrosis and hydroureter. A ventral midline approach was made into the abdomen. Upon entrance into the abdomen, there was a significant amount brown abdominal fluid (as previously noted in the abdominal ultrasound) which was removed by suction. There were numerous adhesions noted throughout the jejunum, and it was noted that the jejunum was tightly adhered to the urinary bladder. The left kidney was enlarged, and fluid filled. Fibrous adhesions were present from kidney to body wall, jejunum, and omentum. Adhesions were broken down until the ureter was able to be clearly identified and isolated. A cystotomy was performed on the ventral aspect of the bladder and both ureteral openings appeared normal. A guidewire was passed retrograde into the right ureter but was unable to be fed through the left ureter. Further dissection revealed that the left ureter had previously been transected, and there were two free ends of the ureter approximately 1cm apart from each other. The bladder was closed and leak tested with sterile saline flush. The left kidney was then dissected to free it from any other adhesions. The renal artery and vein were ligated and sharply transected leaving one encircling ligature with the kidney and two with the body. The kidney was aspirated for culture, revealing similar brown purulent fluid that was initially seen in the abdominal cavity. The left kidney was submitted in its entirety for histopathology. The abdomen was copiously lavaged with sterile saline. Gloves and instruments were changed. A Jackson-Pratt (JP) drain was placed in the abdominal cavity exiting the right body wall. It was secured with a purse string and finger trap. The linea alba, subcutaneous tissue, and skin were closed. The incision was covered with a non-adhesive bandage.

Diagnosis

Definitive diagnosis of TCC requires histopathology of affected tissues. It arguably can also be achieved by a combination of a BRAF urine test and cytology, but in Allye's case histopathology was used. The findings from Allye's kidney showed that the tumor was diffusely and aggressively infiltrating the majority of the renal pelvis. Most of the renal cortex and medulla were gone, with only some renal tubules remaining. There were few if any functioning glomeruli in the kidney resulting in a largely non-functional kidney. Over time, the tumor and subsequent hydronephrosis caused compression, pressure necrosis, renal congestion, and tubular degeneration to occur[11]. The TCC was revealed to be the cause of the obstruction, leading to the hydronephrosis, hydroureter, and subsequent chronic kidney disease. Areas of necrosis from the rapid and compressive growth of these tumors are associated with a poor prognosis[5]. The right kidney also showed some pathology on ultrasound, which was likely why she displayed early signs of decreased renal function on her chemistry panel, because when there is 75% loss of functioning nephrons, animals begin to show signs of azotemia[12].

The formation of these tumors commonly is linked to a mutation of the BRAF genes (B-isoform of rapidly accelerated fibrosarcoma) in humans, which leads to abnormal proliferation and differentiation of cells[7]. This information, has extended into veterinary medicine, and has been demonstrated that the BRAF mutation is found in 65-85% of dogs with TCC[7]. As a result of this research most patients suspicious for TCC have a genetic test performed for a BRAF mutation. This is now a recommended screening test and shows a higher sensitivity (73%) in terrier breeds as compared to non-terrier breeds[7]. The BRAF urine test can assess for the BRAF mutations in the epithelial cells that can be found in urine[8]. At this time, Allye was not screened for a BRAF mutation.

Treatment and Management

In Allye's case, the main presenting issue was the hydronephrosis and hydroureter of the left kidney which was initially masked by more nonspecific clinical signs. It was not until after surgery and histopathology that a diagnosis of TCC was made. The mainstay of treatment of TCC, is medical therapy in dogs[2]. Even though Allye's tumor was removed with no signs of metastasis, a chemotherapy regimen was still recommended due to the potential seeding in the abdomen. Chemotherapy was declined, and instead Allye continues to be monitored for signs of metastasis. TCC is not considered curable, but there are many drugs that have success in prolonging life and reducing cancer pathology[2]. The recommended chemotherapy regimen is a combination of mitoxantrone (chemotherapeutic agent) and piroxicam [nonsteroidal anti-inflammatory drug (NSAID)] which has a reported median survival time of 9-12 months[13]. Other chemotherapy agents including doxorubicin, carboplatin, cisplatin, vinblastine, and chlorambucil have had success as well, but mitoxantrone has demonstrated superior efficacy[7]. Piroxicam is used in the treatment of TCC because it is a non-selective cyclooxygenase (COX) inhibitor and up to 100% of TCC have been positive for COX-2 expression[2]. A study of 76 dogs with diagnosed TCC exclusively received piroxicam as medical therapy showed a median survival time of 244 days, with 59.2% maintaining a stable disease state with a less than 50% change in tumor volume and no new lesions identified[2].

Surgical resection is a challenging intervention strategy due to the predilection sites of tumor growth and the high likelihood of metastasis or recurrance[13]. The trigone of the bladder is a difficult area to perform surgery on, and hard to ensure that good margins are achieved. In Allye's case, the TCC was in a less common location and was localized to the renal pelvis of her left kidney. This allowed for the surgeon to get clean margins via a nephrectomy which greatly improved her prognosis. Recent studies have shown that radiation therapy may prove beneficial

in cases of TCC in the bladder and urethra[1]. Low-dose intraoperative radiation therapy shows promise with less severity of side effects as high-dose radiation including cystitis, urinary incontinence, colitis, colonic perforation, and colonic/ureteral stricture[1,9]. In addition, the urogenital system is challenging to reach with radiation therapy due to the mobility of the bladder[9]. Monitoring for metastasis is important regardless of treatment strategy due to the considerable metastatic rate ranging from 21-51% in most TCC[9]. Most likely areas for metastasis include the spleen, liver, lungs, and bone[10].

Discussion

Hydronephrosis is a sequela of urethral obstruction due to several etiologies including calculi, neoplasia, stricture, infection, etc[11]. Outflow obstruction leads to increased pressure and subsequent dilation of the renal pelvis and formation of a diverticula within the renal parenchyma[11]. The pronged pressure on the kidney, ultimately results in compression atrophy and ischemia of the renal tissue[11]. In Allye's case, her hydronephrosis was caused by a TCC which was preventing outflow of urine, leading to the increased pressure and ultimate necrosis of the left kidney.

Looking at cancer in broad sense, there are numerous biological capabilities acquired during the development of human tumors, which can be extrapolated into veterinary medicine[4,8]. There are essentially six hallmarks of cancer which promote tumor growth and metastasis. These include (1) sustaining proliferative signaling, (2) evasion of growth suppressors, (3) resisting cell death, (4) enabling of replicative mortality, (5) induction of angiogenesis, and (6) activation of invasion and metastasis[4,8]. Sustaining proliferative signaling entails the cancer cell's ability to maintain chronic proliferation against the body's natural defenses[4,8]. Normally the body produces cytokines, which regulate communications and interactions between cells based on adaptations

from different environmental signals[4,8]. If there is a dysfunction of this normal mechanism, oncogenes can be produced which are mutated versions of cells that allow for self-sufficiency of the cell, deviating from the environmental signals it recieves[8]. Evading growth suppressors involves eluding the effects of signals produced by tumor suppressor genes, which essentially are there to prevent tumor formation[8]. It has been demonstrated that 50% of companion animal tumors, have loss of function of tumor suppressor genes[8]. Typically, all cells undergo a programmed cell death (apoptosis), cancer cells, however, can evade these mechanisms in a number of ways[8]. Immortality is another feature of cancer that derives from improved telomere integrity, which allows *infinite* replication by cancer cells[8]. Lastly, cancer has the ability to activate mechanisms for invasion and metastasis[4,8]. This involves the initial local invasion followed by intravasation into nearby blood and lymphatic vessels eventually allowing for the growth of tumors in distant tissues[4,8]. These 6 hallmarks of cancer provide the basis of tumor formation for all types of cancer, including TCC.

When looking at causes of cancer, sustained inflammation often plays a significant role. In Allye's case, it was noted in her history that she had a "traumatic spay". Exact details on what this entailed were not provided, but this could have contributed to an inflammatory process, that may have evoked tumor production in the kidney. In relation to inflammation, cancer is often described as "wounds that never heal", as defined by Dvorak in 1986[8]. This is attributed to the fact that tumors are frequently infiltrated by inflammatory cells produced by the innate and adaptive immune system, consisting of granulocytes, histiocytes, and macrophages[8]. It has been shown that inflammation contributes to tumor growth and survival which may have been the case in the development of Allye's TCC following her traumatic OHE[8]. It is also important to note

that inflammatory cells themselves release reactive oxygen species, which are known to be mutagenic often promoting tumor growth further[8].

Allye's case emphasizes the importance of early detection of TCC due to the long term affects that it can cause, like a non-functioning kidney. There are many complications that can arise with TCC including urinary tract obstruction (as seen in this case), distant metastasis, secondary hydronephrosis, and even concurrent urinary tract infections[10,13]. Looking to the future, there may hold promise in new therapies targeted towards TCC. The canine TCC is very similar to human TCC, and there have already been studies showing some efficacy of antitumor oncolytic measles virus in *in-vitro* studies[6].

Case Outcome

Over one year out from surgery, Allye is currently doing well and has no signs of abdominal metastasis or recurrence. She continues to be monitored for metastasis every 3 months via routine abdominal ultrasound. It is important when using ultrasound that the same person performs the ultrasound so there will be less user variability in detecting minor changes[2]. It is also important the patient positioning and degree of bladder distension is consistently maintained at each ultrasound screening[2]. Since Allye is currently functioning on one kidney, it is critical that we continue to monitor her renal values closely including blood urea nitrogen (BUN), creatinine, and avoid administration of any nephrotoxic drugs. Allye is no longer experiencing abdominal pain, inappetence, lethargy, or lower urinary tract signs, which is a major component of management for most TCC patients. Should metastasis arise, medical management would be her best option to help slow the progression of disease. Allye's presentation of this disease process highlights the spectrum of Transitional Cell Carcinomas and the important clinical keys to unlocking the correct diagnosis.

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