“ONCE UPON A TIME”

Metastatic Prostatic Transitional Cell Carcinoma in the Canine Patient

Rachel C. Myers (Praver)

Mississippi State University, College of Veterinary Medicine – Class of 2019

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Advised by: Wes Baumgartner, DVM, PhD, ACVP Diplomat – Assistant Professor

Department of Pathobiology and Population Medicine

Introduction

Transitional cell carcinoma (TCC) is the most common cancer of the urinary tract in dogs and is thought to account for 1.5-2% of all canine cancers (Mutsaers, 2003). Tumors resulting from TCC are often localized within the bladder, though can develop anywhere along the urinary tract of male and female dogs. Spontaneous development of prostatic TCC is often recognized, with few environmental and genetic predisposing factors documented. This specific cancer has a high propensity for slow growing regional and distant tumor metastases, and therefore, when a patient presents with clinical signs, they are typically in the late-stages of this disease (Borjesson, 1999). Thus, prognosis at the time of diagnosis is often poor to grave. While TCC remains a challenging (and often frustrating) cancer in many facets, let us explore an exemplary case that demonstrates the progression of this disease, yet where treatment and management options yielded a surprising conclusion.

Patient History

On December 14, 2017, a 12-year-old male neutered red and white American Pitbull Terrier named "Henry Mills" presented to MSU-CVM Diagnostic Laboratory Services for necropsy after being humanely euthanized. Henry was a well-known patient throughout the veterinary hospital as he first presented at MSU-CVM Emergency Service nearly 2 years ago on the night of March 2nd, 2016. Henry had for a four-day history of lethargy, inappetence, and intermittent vomiting. The owner also stated that earlier that same afternoon, he noticed Henry Mills straining to urinate for over 40 minutes before any urine was produced. He was admitted to the MSU-CVM Intensive Care Unit that night, and on physical exam, Henry's rectal temperature was 105.8°F, his heart rate was 140 beats per minute, and he had a panting respiratory rate. His abdomen was tucked, tense, and painful on palpation. Henry was estimated to be mildly

dehydrated at 3-5 percent. Thoracic and cardiac auscultation revealed no abnormalities. Digital rectal exam revealed an enlarged and painful prostate. The remainder of his physical exam was within normal limits.

Diagnostics were then pursued, including a FAST SCAN ultrasound examination, which revealed an enlarged prostate and abnormal architecture of the left kidney, but no free fluid. Bloodwork, including complete blood count (CBC) and serum chemistry were also performed, and results were unremarkable. Urinalysis via free-catch method revealed moderate hematuria, moderate leukocyturia, and marked proteinuria. Lastly, abdominal radiographs were performed, which showed an enlarged prostate that was compressing the colon. It was recommended that Henry stay overnight for observation, pain management, nausea control, and correction of dehydration. An abdominal ultrasound was scheduled for the following day, which revealed an enlarged and cavitated prostate, mildly enlarged medial iliac lymph nodes, and mild mineralization in both kidneys. While undergoing the abdominal ultrasound, fine needle aspirates of the prostate and the enlarged lymph nodes were acquired. The resulting cytology revealed a definitive diagnosis of Transitional Cell Carcinoma (TCC) originating from the prostate, and inflammation of the surrounding lymph nodes. Following the diagnosis, thoracic radiographs were performed to evaluate the presence of tumor metastasis, and no abnormalities were seen at that time. After discussing treatment options with the owners, Henry Mills began a therapeutic regiment of Piroxicam and Omeprazole. He was discharged from the MSU-CVM Emergency Service the following day and was additionally sent home with Trimethoprim-sulfa (TMS) antibiotic for his urinary infection, Gabapentin for pain management, and Maropitant (Cerenia®) for vomiting and nausea control. For nearly two years since his diagnosis, Henry's cancer was well-managed, and sequelae from this disease (including recurring urinary tract

infections) were successfully treated. Henry finally succumbed to his cancer in December of 2017, when he presented for humane euthanasia.

Presentation and Post-Mortem Findings

On necropsy examination, the patient's prostate was bilaterally enlarged, irregular, and firm on digital manipulation. Cross sections of the prostate revealed parenchyma that was effaced and expanded significantly by a tan to white mass that was multifocally mottled with red and purple foci. The periphery of the mass was partially calcified, whereas the center was necrotic, with irregular cavities filled with cloudy, dark yellow urine, and subsequently, making the prostatic urethra unidentifiable. The mass continued into the trigone of the bladder, partially obscuring and compressing the ureteral openings. The bladder wall was diffusely thickened and filled with cloudy urine mixed with pinpoint, dark brown friable flecks, assumed to be minute blood clots. Both kidneys have multifocal, irregular, sunken foci along the subcapsular surfaces.

The right kidney is smaller, measuring 7cm in length, whereas the left measured 8.5cm. Additionally, the right kidney has marked dilation of the renal pelvis with loss of medullary tissue and a rim of tan, sunken, soft, irregular foci towards the periphery. The left kidney appeared likewise, but lesions were not as severe. The right ureter measures 0.8cm wide, compared to 0.5cm of the left. The liver has a diffuse lobular pattern with multifocal, irregular to round, dark purple foci scattered throughout all lobes, measuring 0.5-1cm wide. Few small raised, tan masses measuring 1-2cm wide are also in multiple liver lobes. Both adrenal glands were mildly enlarged and were diffusely mottled in appearance with tan, brown, and red coloration and a complete lack of corticomedullary distinction. The head of the spleen had a raised, dark red nodule, measuring roughly 3cm wide. Five to six smaller nodules with similar appearance are observed throughout the spleen, and on cut surface, were tan with firm centers.

The lungs are poorly collapsed, dark/bright red, and purple and mottled. There are widely disseminated, palpable or raised, firm, tan nodules throughout tall lung lobes, measuring from 0.3cm to 5cm wide. Several of the larger nodules have cystic centers filled with turbid, mucus. The heart is mildly enlarged with all chambers appearing dilated. Both atrioventricular valves are thickened, with round, pinpoint 1mm smooth, tan nodules.

Histologic Findings

Histologic examination of lung tissue revealed an infiltrative, un-encapsulated, densely cellular, poorly demarcated epithelial neoplasm that infiltrates arteries and lymphatics around airways. Cells formed cords and nests in abundant scirrhous stroma. They are large and pleomorphic with distinct cell borders and abundant amphophilic cytoplasm, large ovoid nuclei, and large central nucleoli. Cell variation is moderate with many mitoses present. Arteries and airways are largely filled by the neoplasm and stromal response, leading to effacement and deformation of the tissues. A nodule is present, with cells that form papillary structures lined by simple cuboidal epithelium, with abundant caseous necrosis throughout. The alveoli are filled with pink fluid and large foamy brown macrophages, and few red cells. Based on these findings, a diagnosis of prostatic transitional cell carcinoma with systemic metastasis was confirmed.

Pathophysiology

Let us now discuss why the present lesions are to be expected in a patient with end-stage prostatic TCC. In a healthy patient, the male canine prostate the only accessory sex gland of dogs, and appears as a bilobed structure encapsulated by a fibromuscular layer. Each lobe is composed of lobular trabeculae and tubuloalveolar glands, in which glandular secretions are deposited into the urethra (Smith, 2008). The prostate grossly encircles the proximal urethra, and lies cranially to the bladder, dorsally to the rectum affixed via a fibrous band of tissue, and

ventrally to the pubic symphysis. Each lobe has a corresponding ductus deferens that enters the craniolateral aspect of the prostate and courses caudoventrally before entering the urethra (Smith, 2008). Histologically, the normal prostate is an exocrine gland with a tubular, alveolar structure with a glandular component surrounded by smooth muscle and connective tissue stroma. The prostatic acini within the lumen are composed to columnar epithelial cells (LeRoy, 2009).

Canine TCC in general often erupts as a spontaneous round cell tumor, though several factors have been associated with increased risk. Positive correlation with exposure to topical insecticides, such as those for fleas, ticks, and mosquitos, as well as cyclophosphamide administration, obesity, being of female sex, and the Scottish Terrier and West Highland White Terrier breeds have shown a genetic predisposition to this neoplasia (Mutsaers, 2003).

Prostatic TCC has been shown to follow similar trends and affect similarly predisposed groups, except or sex predilection only applies to male canines, and marginally favors castrated males. Several ideas as to the specific etiologic and pathologic development of prostatic TCC include increased estrogen concentrations that up-regulate expression of androgen receptors on prostatic cells, as well as prolonged interaction between neoplastic cells and bladder tissues (Bryan, 2007). These findings are consistent with the population of castrated male dogs developing prostatic TCC more frequently, as intact male dogs tend to exhibit frequent urinary marking and therefore, have less contact with cancerous cells (Bryan, 2007).

Prostatic TCC is further defined by its aggressive nature and high affinity to metastasize. Most commonly, metastasis is noted in the regional lymph nodes (and more specifically, the sub-lumbar and iliac lymph nodes), the lungs, and bone (Cornell, 2000). Metastasis to the liver, kidney, spleen, and brain are infrequently reported. The presence of cancerous tissue within the urinary bladder is often severe due to local invasion of the urinary tract, with tumors frequently

localized to the trigone of the bladder. These neoplastic cells spread without inhibition into the prostatic lymphatics, perineural space, and pelvic musculature. (Paclikova, 2006).

Clinical Signs

The neoplastic properties of prostatic TCC lead to the presence of clinical signs only once the disease process is significantly advanced and metastasis has occurred. In a retrospective analysis by Cornell, *et. al.*, 80% of canine patients diagnosed with canine prostate carcinoma showed evidence of metastasis, and shockingly, also found that the median interval from the time of diagnosis of TCC presentation for necropsy, was 0 days (Cornell, 2000). A typical patient with prostatic TCC presents as a geriatric male canine with clinical signs of hematuria, stranguria, pollakiuria, and other forms of dysuria. TCC patients may also present with symptoms including lameness, depression, and sudden, rapid weight loss (Mutsaers, 2003). On physical examination, the prostate will feel irregular in shape and size, may be firm or lobulated, and elicits a pain response on digital manipulation. Additional signs of tenesmus, changes in urination and defecation, and preputial or urethral discharge are common (Smith, 2008).

Diagnostic Approach and Consideration

A significant factor in detecting early signs of TCC include routine rectal palpation in all canine patients, along with complete prostatic examination in castrated and intact male dogs alike. Those suspected of TCC should minimally receive a transrectal prostate exam, a complete blood count (CBC), chemistry panel, and urinalysis. Bloodwork often reveals a non-regenerative anemia and leukocytosis, along with azotemia. Urinalysis mirrors clinical signs, showing pyuria, hematuria, and bacteriuria most frequently. Cancerous cells indicative of TCC can be visualized in urine sediment stained with Wright's solution. (Axlak, 2012).

Complete cancer staging includes physical examination, radiography of the thorax and abdomen, and imaging of the bladder with either contrast cystography, ultrasonography, or computed tomography (Mutsaers, 2003). If a tumor is localized by one of these imaging modalities, great care to obtain tissue samples must be observed, as this carcinoma has a high affinity for tumor seeding. Other diagnostics can be utilized, such as a urine bladder tumor antigen screening test (Bard BTA test), which has shown some promising results, including an overall sensitivity of 90%, and a specificity of 78% in a study in conducted by Borjesson, Christopher, and Ling in 1999. Additional genetic testing of specific biomarkers is available, but is seldom warranted, and not a cost-effective option. A definitive diagnosis of TCC comes from histopathologic examination of tissues obtained via cystotomy, cystoscopy, or catheter biopsy.

Treatment Options

Treatment of TCC can include multiple modalities, with non-steroidal anti-inflammatory drugs combined with chemotherapy being the most effective standard of care. Simultaneous use of piroxicam and mitoxantrone was shown to have a response rate of 35% in canine patients, and a median survival time of 291 days in this population, according to a study performed by Walters, Martin, Price, and Sula in 2017.

Piroxicam is almost always instituted in TCC treatment, as this medication inhibits COX-2 expression. The presence of COX-2 at tumor locations is thought to result from local inflammatory processes, yet interestingly, has not been found in healthy bladder epithelial tissues (Robat, 2013). Therefore, Piroxicam is attributed to increase apoptosis rates, slow angiogenesis, and possibly suppress regulatory T-cells via COX-2 inhibition (Robat, 2013). Long-term therapy is generally well-tolerated, but reports of gastrointestinal issues and nephrotoxicosis has been reported. Additional gastroprotectants such as omeprazole or famotidine are commonly used to

counter these expected side effects, as seen in the case of Henry Mills. Piroxicam as a stand-alone therapy has been researched, with a median survival time estimated to be less than 6-months (Allstadt, 2014), or averaging approximately 10-12 months (291 days) (Walters, 2017). This is what makes Henry's case so extraordinary – with Piroxicam therapy and supportive management alone, he survived for 33.5 months (1,016 days).

Other drugs and drug combinations have been studied, including deracoxib, carboplatin, carboplatin/gemcitabine, cisplatin/firocoxib, vinblastine and metronomic chlorambucil, yet these therapies have not comparable with the results of piroxicam and mitoxantrone administration (Walters, 2017). Palliative options such as permanent cystostomy tube placement, radiation therapy, urethral stent placement, and laser or surgical debulking are often unrewarding and therefore, seldom performed (Allstadt, 2014).

Management of TCC

Care must also be taken in management of secondary issues arising from this cancer. Common sequelae to prostatic and bladder carcinomas include bacterial urinary tract infections (UTIs), urethral obstruction, and renal damage secondary to the cancer and recurring urinary tract complications. UTIs are considered complicated to treat because the tumor growth leads to mechanical blockage, and therefore, urine retention (Allstadt, 2014). Culture and sensitivity of urine should be performed so as appropriate antibiotic therapy can be prescribed, and development of antibiotic resistance is highly recognized. Acquiring urine for sampling via cystocentesis is controversial; while it leads to more accurate culture and sensitivity results, TCC have a high propensity of seeding cancerous cells along needle tracts. As the tumor continues to grow, urethral obstruction is also noted with advanced TCC. Remember that metastasis to local tissue is common, and the urethra can be subsequently ingrained with cancerous cells via

increased exposure to urine containing cancerous transitional and epithelial cells (Allstadt, 2014). Subsequent renal damage to the kidneys and ureters is common due to hydronephrosis and urinary blockage due to tumor expansion. The ureters often lose their contractility and pulsating mechanism, causing enlargement, and further backflow of urine into the kidneys. Additional kidney damage may result from long term Piroxicam usage, and therefore, reoccurring urinalysis and bloodwork to assess renal function is vital (Smith, 2008).

Conclusion

Canine transitional cell carcinoma is the most common form of urinary cancer in dogs, and while many therapeutic modalities have been tried, due to the characteristics of TCC and late diagnosis, many challenges in this disease process continue to plague veterinarians and owners alike. A need is present for additional investigation into the pathophysiology and molecular understanding of this cancer, as well as continued efforts to be made in development of safer diagnostic procedures, early screening options, and additional treatment protocols.

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