Fenway Strikes Out

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Introduction

Transitional cell carcinoma, also known as invasive urothelial carcinoma, is the most common urinary tract cancer in dogs and accounts for 2% of all canine cancers[1,2]. Canine transitional cell carcinoma is usually highly invasive, metastatic and often locally advanced at the time of diagnosis. Metastasis to regional lymph nodes, lungs, abdominal organs, and bones is typically present in approximately 20% of dogs at the time of diagnosis with over 50% in dogs at time of death[1,3]. TCC most frequently arises from the trigone of the urinary bladder, with variability in urethra and prostatic involvement[4]. Mainstay treatment for TCC includes cyclooxygenase inhibitors in conjunction with cytotoxic chemotherapy and less commonly surgical excision and radiation therapy[3]. Better control of the primary neoplasm and better management of urethral obstruction have resulted in longer survival times[6]. However, with increased survival times, distant metastases are more frequent[6]. Although TCC is usually not curable in dogs, approximately 75% of dogs respond favorably to treatment and can enjoy several months to a year or more of good quality of life[1].

History and Presentation

Fenway, an approximately 10-year-old male neutered Labrador Retriever, presented to Mississippi State University-Animal Health Center Internal Medicine Service on November 29th, 2018 for oral pain upon opening his mouth and dysuria for a 3-week duration. Fenway's oral pain had progressed to spinal pain and difficulty rising prior to presentation. He was initially started on Amoxicillin for a suspected urinary tract infection. Two weeks prior to presentation at MSU, Fenway presented to his referring veterinarian for these clinical signs and was prescribed carprofen and gabapentin with the addition of tramadol and diazepam when the

signs progressed. At the rDVM, abdominal radiographs were performed which revealed a mass effect in the mid-abdomen, a suspected enlarged prostate, and enlarged medial iliac lymph nodes. Bloodwork and a urinalysis showed an elevated ALP enzyme and a normal urine specific gravity, indicating he was adequately concentrating his urine.

On initial presentation to MSU-CVM, Fenway was bright, alert, and responsive. He weighed 42.2 kgs and had a body condition score of 8 out of 9. He had a temperature of 102.7°F, a heart rate of 112 beats per minute, and a respiratory rate greater than 60 breaths per minute. There were no murmurs, arrhythmias, crackles or wheezes on auscultation. His mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. Upon palpation and manipulation of the right side of his mouth, Fenway appeared extremely painful. He also had evidence of severe dental disease. On palpation of his thoracolumbar spine, there was mild pain elicited. On rectal palpation, Fenway was painful, and the left lobe of the prostate was subjectively enlarged when compared to the right. The right submandibular lymph node and popliteal lymph nodes were also mildly enlarged. A neurologic exam revealed mildly decreased conscious proprioception deficits in the right hind limb. The rest of his physical exam was unremarkable.

Diagnostic Approach

Thoracic radiographs were performed the same day as his presentation. The images revealed a moderate, diffuse, bronchial pulmonary pattern with mineralization of the walls of the larger bronchi. Within the right caudal lung lobe, there was a round, ill-defined, soft tissue opaque nodule that measures 16mm in diameter. In the caudal subsegment of the left cranial lung lobe, there was a variably shaped, smoothly marginated, soft tissue opaque nodule that

measured 8 mm in diameter. There was smoothly marginated spondilytic new bone formation with bridging on the ventral margin of T5-6 consistent with spondylosis deformans. Osteoarthritis of the right glenohumeral joint was also seen. On November 30th, 2018, Fenway's overall health status was assessed. A serum chemistry revealed a moderately increased ALP enzyme, mildly decreased BUN, and mildly decreased magnesium. A urinalysis revealed a urine specific gravity of 1.016 with no other significant abnormalities and a urine culture showed no growth of bacteria.

An abdominal ultrasound was performed and revealed an enlarged spleen with rounded margins containing numerous, round, smoothly marginated, hyperechoic nodules. The left renal pelvis was dilated with anechoic fluid, measuring 0.5 cm. The left and right ureters were dilated throughout their entire length from the kidney to the urinary bladder. The urinary bladder neck was thickened, measuring up to 0.99 cm, with hyperechoic, heterogenous, irregularly marginated parenchyma. The parenchyma was confluent with abnormal prostatic parenchyma. The prostate and urinary bladder neck also contained patches of increased echogenicity with distal acoustic shadowing consistent with mineralization. The prostate was also enlarged measuring 2.95 x 3.51 x 2.86 cm with a 0.42 cm, round, smoothly marginated, anechoic structure within the parenchyma suggestive of a prostatic cyst. However, the medial iliac lymph nodes were of appropriate size.

Advanced imaging was recommended following initial radiographs and ultrasound. A positive contrast CT-scan of his head and abdomen allowed further characterization of the right temporomandibular joint, suspected pulmonary metastasis, and the extent of the thickened urinary bladder neck that intimately connects to the enlarged prostate. The CT identified a heterogenous soft tissue and fluid attenuating structure at the level of the right zygomatic bone

with extension into the right temporomandibular joint. Differentials at that time were possible abscess formation or neoplasia. Incidentally, a pituitary macroadenoma was identified measuring 1 cm in diameter. Abdominal CT confirmed the findings of the previously identified bilateral hydroureter, most likely due to obstruction at the level of the trigone, and probable prostatic and urinary bladder neoplasia.

Ultrasound guided fine needle aspirates were taken of the spleen and prostate, and cells were submitted for cytologic review. The slides of the spleen revealed no atypical cell populations, leading to a diagnosis of reactive lymphoid hyperplasia and splenic hematopoiesis. Slides of the prostate revealed rare epithelial cells in a small cluster that were cuboidal in shape, with moderate amounts of basophilic cytoplasm and round nucleoli. The chromatin was coarse, and the cells had 1-3 prominent nucleoli that varied in size and shape. Because the sample was of low cellularity, a definitive diagnosis could not be made based on the sample but was highly suspicious of carcinoma. Cytology and culture samples were also taken of Fenway's right temporomandibular joint lesion. A urinary catheter was then placed to remove urine from his bladder and a tissue sample was obtained and submitted for histopathology.

With a presumptive diagnosis of TCC Fenway was initiated a nonsteroidal anti-inflammatory medication, piroxicam, a urethral relaxer, prazosin, and clindamycin, pending the culture and sensitivity results of his TMJ lesion.

Pathophysiology

Transitional Cell Carcinoma (TCC) is a malignant tumor of epithelial cell origin with most considered as a high grade, papillary, infiltrative tumor. Canine urinary TCC most commonly arises at the trigone of the bladder. It also involves the urethra in more than half of

affected dogs and the prostate in 1/3rd of affected male dogs[8]. All dogs are susceptible to developing TCC, however predisposed breeds are Scottish Terriers, West Highland Terriers, Wire Hair Fox Terriers, Shetland Sheepdogs, and Beagles, [6]. Other risk factors for TCC include female sex, obesity, and exposure to old generation flea control products and lawn chemicals[1]. The most common clinical signs associated with canine TCC closely mimic those of a urinary tract infection which include stranguria, hematuria, and pollakiuria[1,2,4]. Other possible signs include tenesmus, lethargy, lameness, and weight loss[1,4]. Antibiotic therapy may cause a reduction or temporary resolution of symptoms, therefore the duration of associated clinical signs can range from weeks to month prior to diagnosis[1,4,5,7].

Non-invasive diagnostics that are valuable in obtaining a diagnosis of TCC include urine cytology, bladder tumor antigen test, and testing for the presence of a BRAF mutation by PCR assay. Relying solely on cytology of a voided urine sample is not recommended because reactive hyperplastic transitional cells can have a pleomorphic appearance indistinguishable from that of malignant cells[5]. A commercially available bladder tumor antigen test is a sensitive test that can support a diagnosis of TCC; however, false positive results are obtained in the presence of proteinuria, glucosuria, pyuria, or hematuria. This test is more commonly used to screen at risk breeds. Now available is a PCR assay that detects mutation of the BRAF gene (cBRAF V595E) in voided urine samples[7]. This genetic alteration has been identified in approximately 80% of dogs with bladder or prostate cancer and has a sensitivity of 85% and specificity of 100%[7]. Therefore, a positive BRAF mutation test can be considered diagnostic for TCC in dogs. A definitive diagnosis of lower urinary tract TCC usually requires histopathological assessment of the affected tissue and is considered the gold standard[4,5]. Tumor grade, degree of invasiveness, and margin analysis (if surgically removed) can be

established by histopathology. A definitive diagnosis is vital in determining appropriate treatment recommendations and prognostic information. Tissue samples from the bladder can be obtained by cystotomy, cystoscopy, or traumatic catheterization[1,4].

In dogs with diagnosed with or suspected to have TCC, a thorough evaluation of systemic health should be performed. A physical examination (including rectal exam), bloodwork, urinalysis, urine culture, thoracic and abdominal imaging, and additional lower urinary tract imaging should be included. A rectal examination will often reveal urethral thickening, enlarged prostate, distended bladder, or sublumbar lymphadenopathy[1]. Urine can be obtained by voiding or catheterization. Cystocentesis should be avoided in dogs with suspected TCC, due to the risk of tumor seeding within the abdomen or body wall[1,4]. Dogs with TCC are predisposed to developing secondary urinary tract infections, therefore a urine culture is also recommended. The cancer can be staged by thoracic and abdominal radiographs and ultrasound[8]. These can be useful for evaluating the evidence of local and metastatic disease. A recent study showed a correlation between the presence of mineralization within the prostate of a neutered dog is highly suspicious of carcinoma[9]. Additional imaging, such as CT, should be considered if lameness is appreciated, to evaluate possible bone metastasis[4,6]. A recent study suggests that a total body CT could be beneficial in detecting skeletal metastases as well as identifying clinically “silent” sites of skeletal metastases[6]. Ultrasound and cystography are important imaging modalities used to evaluate the urinary tract in order to determine tumor location, extent, feasibility of surgery, prognostic information, and monitor response to implemented treatment.

Historically, canine transitional cell carcinoma of the bladder has been treated with surgical excision, chemotherapy, cyclooxygenase inhibitors, and radiation therapy. Surgical

intervention has a limited role in the treatment of TCC due to the typical trigone location, urethral and prostatic involvement, and potential for malignant transformation ("field effect") of the urothelium[1,4]. Because of the poor outcomes associated with a partial cystectomy, it is generally not recommended. Occasionally, surgical intervention can be a palliative treatment aimed at maintenance or restoring the urinary tract patency. Using a minimally invasive technique and fluoroscopic guidance, urethral stents have been used to maintain urinary flow in the face of urinary obstruction[1,4]. Multimodal medical therapy is the mainstay treatment of canine TCC that consists of a combination of nonsteroidal anti-inflammatory agents and chemotherapeutics[4]. Piroxicam, a nonselective cyclooxygenase inhibitor, showed disease stabilization in 53%, partial responses in 12%, and complete responses in 6%. Piroxicam, when used as a single agent has a reported progression free interval of 4.3 months and an overall median survival time of 5.9 months[3]. Although usually tolerated well, care must be taken to monitor for and detect gastrointestinal ulceration. If melena, vomiting, or anorexia occur, it is recommended to switch to a selective COX-2 inhibitor, such as deracoxib and meloxicam, which have shown similar results and less associated side effects[1,5]. The most commonly used intravenous chemotherapy agents include mitoxantrone and vinblastine and are generally well tolerated. Cisplatin and carboplatin appear to be the most active agents but are more likely to cause adverse side effects. Piroxicam combined with mitoxantrone is commonly used and has a reported response rate of 35%, median PFI of 194 days, and an MST of 291 days in dogs with TCC[3,4]. In a phase II clinical trial, carboplatin combined with piroxicam induced remission in 38% of dogs, although toxicity was relatively common[8]. Another study demonstrated the use of carboplatin or mitoxantrone in conjunction with piroxicam; in this study, carboplatin in combination with piroxicam induced partial remission in 13% and static disease in 54%,

indicating that there was not a substantial difference in outcome in comparison to mitoxantrone in combination with piroxicam[3,7]. Although medical therapy is not curative, remission or stable disease can be accomplished with several different drugs and are generally well tolerated[1].

Treatment and Management

Cytology of the right temporomandibular joint revealed low numbers of mesenchymal cells scattered throughout the slides with mild anisokaryosis and anisocytosis. Because of the minimal cells present on the sample, a diagnosis of probably sarcoma was made with recommendations of histopathology of the lesion. Fenway received an injection of pamidronate to help alleviate the bone pain he was experiencing. A palliative procedure of a right condylectomy was performed on December 4th, 2018, removing the caudal portion of his right mandible and zygomatic process. An esophageal feeding tube was placed at this time. Immediately following surgery, the excised mass was submitted for histopathology.

Fenway recovered uneventfully from anesthesia and surgery in ICU. His comfort level improved drastically following the procedure, however it was discovered that his bladder was distended with a large volume of urine. A urinary catheter could not be passed, although Fenway was still able to consciously void urine at this time. Two days post operatively, a urethrocystogram was performed to further evaluate the extent of the urinary obstruction as well as obtain measurements for a urethral stent if indicated. The cystourethrogram revealed an approximately 21 x 7.0 mm filling defect at the neck of the urinary bladder that was causing almost complete attenuation of the lumen of the proximal urethra. The filling defect was also identified along the ventral aspect of the proximal urethra at the same site and spanning along the dorsal aspect of the trigone and approximately 61 mm along the proximal urethra. These

findings verified Fenway was a candidate for urethral stent placement at this time. Upon deliberation, it was elected that chemotherapy prior to urinary stent placement would be pursued.

Case Outcome

On December 7th, 2018, a complete blood count revealed adequate cell lines for Fenway to receive chemotherapy. He received a dose of carboplatin in his right accessory cephalic vein without complications. He was discharged from MSU-Animal Health Center on December 8th, 2018 with the instructions to come back in 7 days to have a complete blood count performed, his incision site rechecked, and have his feeding tube potentially removed if indicated. It was also recommended to come back in three weeks, December 29th, 2018, for a CBC, renal panel, and his next dose of carboplatin chemotherapy.

Fenway became inappetent on December 9th, 2018 and taken to his primary veterinarian on December 10th, 2018 where thoracic radiographs were performed, that raised suspicion for pneumonia. He was prescribed an appetite stimulant along with antibiotic therapy. Due to continued inappetence, his owner began feeding him through his esophageal feeding tube. On December 12th, 2018, Fenway vomited the contents of the previous day's food and began to have extremely watery, black diarrhea. His respiratory rate and effort had increased however, but he was still able to urinate small amounts at a time prior to re-presentation to MSU-CVM on December 13th, 2018.

Upon presentation, Fenway was quiet, alert, and responsive. He walked into the exam room but laid down in lateral recumbency and became unwilling to rise. An initial triage exam was performed at that time. He was tachycardic with all other parameters within normal limits.

His systolic blood pressure with within normal limits and no free fluid was observed of abdominal fast scan. His pulse ox was 96%. Blood was obtained and submitted for a CBC and serum chemistry. Complete blood count revealed moderate anemia, moderate thrombocytopenia, mild lymphopenia, and mild neutrophilia. Serum chemistry revealed a mildly elevated BUN, mildly elevated ALP, mild hypoproteinemia, mild hypoalbuminemia, mild hyperphosphatemia, mild hypocholesteremia, and a mildly elevated CK. A PT and PTT were within normal limits. After blood collection, Fenway began to have increased respiratory rate and effort. Pulse ox was repeated and was 88% but increased to 95% with supplemental oxygen. Fenway was placed in the oxygen cage and closely monitored for changes in his respiratory status. Thoracic radiographs were then performed to evaluate his lungs. While undergoing imaging, Fenway went into cardiac arrest and chest compressions were immediately started. During this time, Fenway's family was notified, and they elected to discontinue resuscitative efforts.

On gross exam, there is a 9 cm incision that is opposed on the right side of the face below his eye extending caudally. The liver is pale with a diffuse lobular pattern. The spleen was mottled dark red and had multifocal, disseminated, raised nodules, with the largest measuring 4.5 x 2 x 0.5 cm. Within the lumen of the entire gastrointestinal tract, there was an abundant amount of thin, opaque, red fluid (frank blood) in the more proximal portions which transitioned to dark red to black in the large intestine. Within the lumen of the stomach fundus, there were approximately 8-10 multifocal, disseminated, variably sized, erosions of the mucosal surface with some erosions being surrounded by a prominent rim (granulation tissue). The kidneys were symmetrically enlarged with dilation of the renal pelvis and reddening of the corticomedullary junction bilaterally. The ureters were dilated bilaterally. The bladder

epithelium at the level of the trigone and urethra is roughened and ulcerated. The prostate was symmetrically enlarged measuring 4.5 x 3.5 x 2 cm and homogenously tan on cut surface. Multifocal areas of the lung lobes were mottled tan to dark red and associated with variably sized firm nodules. The right atrium and ventricle were severely dilated. The pituitary was mildly enlarged measuring 1 cm x 1 cm x 6 mm.

Histopathology of the bladder, prostate, and urethra confirmed the diagnosis of transitional cell carcinoma. A tissue sample of the prostate revealed an infiltrative, unencapsulated, poorly demarcated mass that expanded the lamina propria and submucosa. The neoplastic mass originated from the transitional epithelium and completely effaced the normal tissue architecture. Cells formed variably sized trabeculae and nests within a dense fibrous stroma. The neoplastic cells were polygonal, with variably distinct borders and had a large, ovoid, central nucleus with marginated chromatin and one to two prominent nucleoli. Frequently, the neoplastic cells contained large, clear, cytoplasmic vacuoles and a moderate amount of eosinophilic cytoplasm. There was mild anisocytosis and moderate anisokaryosis. There was a moderate mitotic rate with 6 mitotic figures per high power field. There were large areas within the neoplastic mass that was consistent with necrosis. Expanding from the epithelium down to the muscularis of the urethra and trigone of the bladder, histopathology revealed the same neoplastic process as observed in the prostate. Neoplastic nests of cells were also identified throughout the lungs and expanding the myocardium of primarily the papillary muscles of the left ventricle. The surface of the epithelium of the stomach is sloughed off with a matt of homogenous pink material overlying the surface, indicating the presence of acute and chronic, severe gastric ulceration.

The macroscopic and microscopic findings are consistent with the aggressive nature of TCC and the potential adverse side effects of systemic medical therapy. The metastatic lung carcinoma combined with the severe gastrointestinal hemorrhage, likely caused the significant respiratory distress Fenway underwent which ultimately lead to his demise.

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