Canine Urethral Transitional Cell Carcinoma

A Case Report

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Abstract:

The following case report describes the presentation and diagnostic evaluation of a 6-year-old spayed female mixed-breed dog, with a 1.5-month history of dysuria, that was referred to the Small Animal Oncology Service at Cornell University's College of Veterinary Medicine. The chief complaint of recurrent or persistent stranguria, pollakiuria, and hematuria in the dog, is consistently associated with a relatively defined list of differential diagnoses. Among these differentials is lower urinary tract neoplasia, with transitional cell carcinoma (TCC) being the most common type. Therapeutic modalities for urinary transitional cell carcinoma include surgery, radiation therapy, and chemotherapy. Regardless of the treatment modality, the majority of dogs are not cured of transitional cell carcinoma, and survival time is usually limited.

Case History and Signalment

A 6-year-old spayed female mixed-breed dog was referred to the Companion Animal Hospital at Cornell University's College of Veterinary medicine in June, 2003. The dog had originally presented to its referring veterinarian 1.5 months previously with chief complaints of stranguria, pollakiuria, and hematuria. At that time, the referring veterinarian treated the dog empirically for a presumptive urinary tract infection with different antibiotics (Baytril, Clavamox), with no resolution of clinical signs. Caudal abdominal ultrasound examination was performed, and an ill-defined area of mineralization was identified near the neck of the bladder. No other abnormalities were noted. Because of the possibility of the mineralization being associated with a tumor, the dog was then referred to the Oncology Service at Cornell for further evaluation.

Upon physical examination, the dog was found to be in good body condition and adequately hydrated. She was bright, alert, and responsive, with all vital general health parameters within normal limits. Thoracic auscultation and abdominal palpation were both unremarkable. Visual inspection of the vulva

and vestibule was also unremarkable. Digital rectal examination revealed a markedly thickened pelvic urethra. Physical examination otherwise revealed no abnormalities.

Ancillary Procedures

Blood was submitted for complete blood count and serum biochemistry profile. All results were unremarkable. Urinalysis from a voided sample revealed an orange, opaque liquid, with urine specific gravity of 1.050, 100mg/dL protein, marked hematuria (4+ hemoprotein), 5-20/hpf white blood cells, 5-20/hpf red blood cells, and few bacteria. No abnormal cells were identified on sediment analysis.

Complete abdominal ultrasound examination revealed a moderate-sized (1.5 x 0.6cm) lesion at the urinary bladder neck that distended the proximal urethra. The lesion had multifocal areas of mineralization and did not change position with gravity. The lesion extended caudally into the pelvic canal, where it could no longer be imaged via ultrasound because of the surrounding bone. No other substantial abnormalities were detected. Abdominal radiographs were obtained, but the lesion identified on ultrasound was not seen; the films were interpreted as normal. Thoracic radiographs were taken as well, and they also were within normal limits.

A contrast cystourethrogram was attempted to better visualize the abnormalities associated with the bladder and urethra. The patient was placed under general anesthesia. Several attempts at urinary catheterization were made, but the catheter could only be advanced [retrograde] approximately 1cm into the distal urethra before reaching a mechanical obstruction. Flushing saline through the catheter did not relieve the obstruction, and the contrast study therefore could not be performed. Even without the contrast study, inability to pass the urinary catheter confirmed lower urinary tract signs due to pathology involving the urethra.

The saline sample that had been flushed into the urethra was collected and evaluated cytologically. Cytologic evaluation of the urethral fluid was quite cellular and contained many clusters and individual epithelial cells, presumably of transitional epithelial origin. The cells displayed numerous cytologic criteria of malignancy, including multiple large nuclei and marked anisokaryosis and anisocytosis. There was also some cellular debris, indicating necrosis, and mixed inflammatory cells, indicating some concurrent inflammation. Many of the macrophages were cytophagic. There was additionally evidence of chronic hemorrhage. A diagnosis of urethral carcinoma was made, with transitional cell carcinoma (TCC) being the most likely.

Canine Urinary Transitional Cell Carcinoma

TCC is the most common form of urinary tract cancer in the dog, comprising about 1.5-2% of all canine cancers.[13] These are malignant tumors arising from a transitional type of stratified epithelium. TCC most commonly occurs in the urinary bladder, specifically the trigone, although it can be found anywhere along the lower urinary tract, from the kidneys down to the urethra. TCC may also be present at single or multiple simultaneous sites within the bladder. Urethral TCC is rare, being $1/100^{th}$ as common as bladder TCC. Other primary lower urinary tract cancers include squamous cell carcinoma, adenocarcinoma, hemangiosarcoma, myxosarcoma, rhabdomyosarcoma, leiomyosarcoma, and lymphoma. The majority of this discussion, however, will focus on TCC of the urinary bladder, as this is the most common location, and therefore the location we have the most information about.

Signalment

TCC is typically a disease of older dogs, with the average age of affected dogs being ten years. Canine breeds reportedly at risk include Beagles, Scottish Terriers, Shetland Sheepdogs, Airedale Terriers, and Collies. The cause of this breed-associated risk is not known, but in all likelihood it represents genetic predisposition to bladder cancer, such as differences in the biochemical pathways that activate and

detoxify carcinogens.[13] Female dogs are reportedly affected with bladder tumors more frequently than males, which is the opposite of the situation in humans. Behavioral differences between male and female dogs have been suggested as possible factors in the development of canine LUT tumors in general, specifically TCC. Male dogs are believed to urinate more frequently, thereby decreasing contact time between the bladder epithelium and urinary carcinogens. The female dog may only urinate one or two times per day, thus storage and hence contact time with urinary carcinogens is presumably increased. Additionally, the urinary tract of the female is shorter and has fewer anatomic constraints compared with the male (e.g. prostate and penis), which may allow extensive tumor progression with minimal change in clinical signs associated with urination.[16] In human beings, the frequency of bladder tumors is greater in the male, but this is believed to reflect increased exposure of male factory workers to industrial carcinogens.[14] Neutered dogs of both sexes have been reportedly at increased risk for TCC compared to sexually intact dogs of the same sex, but this association is not explained at this time.[13] The etiology of canine TCC is most likely multifactorial, and identified risk factors include exposure to topical insecticides for flea and tick control, exposure to marshes that have been sprayed for mosquito control, obesity, and possibly cyclophosphamide administration.

History and Clinical Signs

Common presenting clinical signs of tumors of the LUT include hematuria, pollakiuria, stranguria, dysuria, vulvar discharge, and incontinence. Due to the common location of TCC in the trigonal region of the bladder, patients may also present with urinary tract obstruction. Less common clinical signs of lameness (due to bone metastasis), lethargy, and weight loss, may be evident. None of these signs are pathognomonic, and the most common signs are typical for any lower urinary tract disease. Differential diagnoses also include lower UTI, urolithiasis, vaginitis/vulvitis, prostatic disease, and granulomatous urethritis. TCCs initially are often misdiagnosed as UTIs or other LUT disorder. Additionally, often times patients with TCC present with concurrent UTIs, making diagnosis even more challenging.

Physical examination may reveal a caudal abdominal mass, urethral thickening, and/or prostatomegaly. Urethral extension of tumors may be more commonly palpable via rectal examination. In some patients, physical examination may be unremarkable.

Bloodwork

Hematology and serum biochemistry findings are usually normal or nonspecific. Post-renal azotemia may be seen in patients with advanced disease.

Urinalysis

Urinalysis will often reveal hematuria, pyuria, and/or proteinuria—findings that are also compatible with inflammatory disease of the lower urinary tract (cystitis, urethritis). Occasionally, neoplastic cells can be seen on urine sediment analysis, but only about 30% of patients have identifiable neoplastic cells. Additionally, it may be difficult to distinguish these cells from benign reactive transitional epithelial cells, particularly when there is concurrent pyuria.

Imaging Studies

Survey abdominal radiographs rarely reveal evidence of bladder tumors, although urinary distention secondary to outflow obstruction may be identified. They are useful to help exclude prostatic disease or urolithiasis, as well as to screen for bony metastasis. Contrast cystograms are better for visualizing the primary tumor, often revealing marked mucosal irregularity, localized thickening, an intraluminal mass, and occasionally ulceration of the bladder wall. Excretory urography is also an alternate cystographic method to help determine the location and extent of obstructive urinary tract disease if a urinary catheter cannot be passed. The frequency of urethral neoplasia is probably underestimated using contrast urethrograms because they are more difficult to perform and interpret.

Ultrasonography may be a valuable tool in detection of bladder tumors. Bladder tumors may appear as singular or multiple polypoid lesions, a single large mass, or a thickening of the bladder wall with loss of luminal space. On the microscopic level, TCCs are described as having a dense, fibrous stroma. Such scirrhous change could account for the increased echogenicity at the urethral epithelial surface.[5] Inflammation of the urethral mucosa may contribute a hyperechoic appearance. Hypoechogenicity of the thick urethral wall surrounding the hyperechoic epithelium found in several subjects may be explained by edema or hemorrhage, which commonly occur in TCC. Infiltrating bladder tumors have been reported to be less echogenic than the normal bladder wall, so the hypoechoic urethral wall may be due to the presence of neoplastic cells alone.[5] Although blood clots may have the same echogenicity as do bladder tumors, an index of suspicion for the presence of blood clots should exist based on history or physical examination findings. Blood clots are also generally mobile, which helps distinguish them from neoplastic lesions. Cystitis secondary to a primary UTI will cause either no mucosal lesions or a mild, generalized thickening in chronic cases. Polypoid cystitis may appear as several small masses protruding into the lumen from a thickened bladder wall. These lesions are often pedunculated, whereas bladder neoplasms are usually sessile. While not pathognomonic for neoplasia, the findings of a well-defined, smooth or irregular hyperechoic line at the epithelial margin, accompanied by uniform or asymmetric, hypoechoic thickening of the deeper muscular layers, should raise the possibility of TCC.[5] Visualization of abnormalities of the urethra with ultrasonography may be difficult. Scanning the canine distal male urethra is difficult and time consuming, and the distal female urethra is often inaccessible to ultrasonography because of the pubis. As urethral neoplasms are twice as likely to occur in female dogs, this limitation may be significant. Thus, the extent of urethral involvement may be best assessed with contrast urethrography and careful rectal palpation.[5] Abdominal ultrasound is also useful for screening for intra-abdominal metastasis to locations such as the medial iliac lymph nodes.

Other Diagnostics

Transurethral cystoscopy is the principal method used to diagnose TCC in humans, allowing for direct visualization and biopsy. This has been used minimally in the investigation of bladder disease in veterinary patients.

The bladder tumor-associated antigen urine dipstick test (Bard BTA) is a non-invasive diagnostic test, initially developed and tested in human TCC patients. This test is a qualitative, rapid, latex agglutination test utilizing antibodies to a bladder tumor-associated glycoprotein complex that is detectable in the urine of patients with TCC. A similar veterinary test has been developed, and the test has proven sensitive for the detection of canine TCC. It may serve as a useful adjunct to diagnosis, especially when cytology or biopsy is questionable or impractical. However, significant hematuria, pyuria, proteinuria, and glucosuria preclude confident diagnosis of disease (false positives may be seen with moderate to severe urinary tract infections) and differentiation between chronic inflammatory or reactive conditions and neoplasia.[2]

Radiographs of the thorax should be obtained if a lower urinary tract tumor is suspected because pulmonary metastasis at the time of diagnosis has been reported. Pulmonary metastasis secondary to TCC may appear on radiographs as a diffuse pattern, lacy interstitial opacity, nodular interstitial opacity, or consolidated lung lobe.[19]

Biopsy and Histopathologic Characteristics

Definitive diagnosis of urinary tract tumors requires histopathologic examination of tissues obtained via surgery, cystoscopy, or catheter biopsy. Fine needle aspiration of bladder tumors has a reported success rate of greater than 90%; cytology can be useful as well, although histopathology is preferred for

definitive diagnosis. Traumatic catheterization techniques are recommended instead of a trans-abdominal approach due to decreased risk of tumor seeding.

Cellular and Molecular Features

In a study performed by Clemo et al.[13], 79% of canine TCCs were aneuploid. Basic fibroblast growth factor (bFGF) is a proangiogenic peptide that has been found in high concentrations in the urine of people with urologic and nonurologic cancer. The concentration of bFGF in the urine of dogs with TCC was found to be significantly higher than that of normal dogs or dogs with bacterial cystitis.[13]

Treatment

Therapeutic modalities for TCC of the bladder primarily have included excisional surgery, urinary bypass surgery, radiotherapy, and chemotherapy.

Surgery

Surgery is the preferred treatment method for all tumors located at the apex of the bladder (in the absence of concurrent gross metastatic disease), but such tumors represent the minority of TCC's in dogs. There is limited efficacy for tumors located at the bladder trigone, and with urethral or ureteral involvement. In animals, 80% of the bladder can be safely resected without affecting long-term bladder capacity, but most surgical treatment is limited to debulking procedures. When thinking about surgery, the entire mucosal surface should be examined; TCC is usually red and friable. In a series of 102 dogs with TCC, complete resection of the primary tumor (with histopathologically tumor-free margins) was only accomplished in two dogs[13]. Additional disadvantages of surgical treatment include a high rate of local recurrence, as well as transplantation of TCC tumor cells along the laparotomy incision line. This should attempt to be avoided by isolating the site from the rest of the abdomen via laparotomy pads,

using new instruments for closure, and thoroughly flushing the bladder surgery site with saline after closure.

The surgical urinary diversion techniques described in dogs are ureterocolonic anastomosis and trigonal-colonic anastomosis, but these are used with little frequency. Both techniques unfortunately can result in hyperchloremic metabolic acidosis, hyperammonemia, and peculiar-smelling watery feces that most owners find objectionable.[17] Incontinence typically occurs if the trigone is removed. Resection of focal lesions of the urethra is possible with a transpubic surgical approach and urethral resection and anastomosis. Prepubic urethrostomy with resection of neoplastic tissues may be preformed if the distal urethra is involved alone. Urethral tumors that involve the entire length of the urethra or the bladder trigone are generally inoperable.

Placement of a permanent cystostomy catheter to relieve urine outflow obstruction is a possible acceptable alternative for owners of dogs with TCC and secondary urine outflow obstruction. Many dogs with this disease are clinically normal with the exception of signs associated with urinary obstruction. This surgical procedure relieves the stranguria associated with urine outflow obstruction without directly treating the tumor, and it may also be an option to consider allowing drainage of the bladder while awaiting a response to another treatment modality. Although median survival time with this alone is short, it is thought to be similar to that of dogs receiving other treatment for nonresectable tumors involving the bladder and urethra.

Radiation Therapy

Radiation therapy has been used infrequently in canine bladder TCC, as partial damage to abdominal viscera precludes its used. Radiation therapy has been associated with high morbidity, poor tumor control, and high complication rates. Acute complications may include cystitis, stranguria, and urge

incontinence, while late effects may include bladder fibrosis, hydronephrosis/hydroureter, and permanent incontinence. Because canine TCC often involves the entire bladder, urethra, and ureters, the extent of bladder irradiation required in dogs is much greater than the recommended maximum used in humans.

In contrast, radiation therapy for TCC confined to the urethra may be tolerable. Patients with other tumors in the pelvic and perianal regions (e.g. anal sac adenocarcinoma) have been treated with radiation therapy. Irradiation of the urethra is unavoidable, but there are minimal, if any, clinically observable adverse reactions. There is little information regarding the efficacy of radiation therapy for urethral TCC at this time.

Chemotherapy

Chemotherapy is used for local disease not amenable to surgical resection. It is recommended for metastatic disease as well. In veterinary patients, chemotherapy is now more commonly used as the sole treatment for bladder tumors because of the high rate of recurrence following partial cystectomy and poor results with total cystectomy and urinary diversion surgeries. Unfortunately, though, TCC is considered to have a poor response to chemotherapy.

Cisplatin is the chemotherapeutic agent we have the most information about with regard to veterinary patients, as this agent is commonly used to treat TCC in humans. Cisplatin, when used as a single agent in dogs, has been shown to have remission rates of 12-20% and median survival times around 130 days. Isolated responses have additionally been seen with other agents such as doxorubicin, actinomycin D, and mitoxantrone. No efficacy has been documented with carboplatin.

Intravesicular chemotherapy using thiotepa has been reported with poor results, likely because of the invasive nature of the tumor at diagnosis and the inability of the chemotherapy to reach infiltrated bladder muscularis. However, even a small reduction in tumor size could result in improved micturition, especially in dogs with urethral obstruction.

Nonsteroidal Anti-Inflammatory Drug (NSAID) Therapy

Cyclooxygenase-1 (Cox-1) has shown to be constitutively expressed in many normal tissues, including the epithelium of the urinary bladder in healthy dogs. Cox-2 is not expressed in normal bladder epithelium, but is found to be expressed in epithelial malignancies, including canine transitional cell carcinoma. Cox-2 expression has been detected by immunohistochemistry in 21 of 21 cases of canine TCC.[6] This suggests that this isoform may be involved in tumor cell growth. Inhibition of Cox-2 is a likely mechanism of the antineoplastic effects of nonsteroidal anti-inflammatory drugs.

Piroxicam, a potent non-selective cyclooxygenase inhibitor, has antitumor activity against TCC, with response rates around 15-20% when used as a single agent. In one study evaluating 34 dogs with TCC that were treated with single-agent piroxicam, complete and partial response rates of 6% and 20%, respectively, were observed. Median survival time was 181 days.[10] The 6% with complete remission (complete resolution of all clinical and radiographic evidence of TCC) lived 2.1-3.3 years, and were tumor free on postmortem examination. Fifty-three percent of dogs in the same study had stable disease (less than 50% change in tumor volume). Even in the absence of clinical remission, most dogs treated with piroxicam show signs of improved comfort due to the drug's anti-inflammatory and analgesic effects. The piroxicam therapy tends to be generally well tolerated, with minimal gastrointestinal and renal toxicity seen when used alone. It is not thought to work like other chemotherapeutic agents; it is not directly cytotoxic at concentrations achieved therapeutically. Instead, its anti-tumor effects result from inhibiting the production of certain prostaglandins that have pro-neoplastic effects.

A study conducted to determine whether cisplatin combined with piroxicam would induce remission more frequently than cisplatin alone showed that the combination did induce remission more frequently (71% remission rate, 246 days median survival), but was also associated with frequent and dose-limiting renal toxicity.[8]

Prognosis

Prognostic factors in dogs with TCC include the histologic grade, clinical stage, nodal status (TNM staging), presence of metastatic disease, and location and extent of the tumor. Metastatic rates have been reported to be as high as 50% at the time of diagnosis. Common metastatic sites include the sublumbar lymph nodes, pelvic and lumbar vertebrae, and lungs. Using data from the series of 102 dogs studied with TCC (Perdue University VTH), two factors associated with the development of metastasis between diagnosis and death were vascular invasion and urethral involvement of the tumor.[13] TCC of both the bladder and urethra has a worse prognosis than does TCC of the bladder or urethra alone. The majority of canine TCCs are associated with a poor prognosis because of the advanced stage at diagnosis and proximity of the tumor to the trigone, ureters, and neurovascular supply of the urethra and bladder, which significantly complicates management of these tumors. Most cases recur or metastasize within 6-12 months. When the primary tumor is not controlled, death by urinary tract obstruction occurs in many dogs with TCC prior to the development of lethal metastasis. When the primary tumor can be controlled, metastatic disease occurs more frequently.[13]

Although much progress has been made in the treatment of TCC, most affected dogs still die of this disease, as current treatment options have their limitations. Unfortunately, diagnosis and treatment of this disease still remains a challenge.

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