A Transitional Lie

A Case of Canine Urinary Tract Leiomyosarcoma

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Introduction:

Neoplasia of the urinary tract composes less than one-half of a percent of all primary neoplasia in the canine. Approximately eighty percent of these are epithelial in origin, typically transitional epithelial cells, and are malignant. Only twelve percent are represented by mesenchymal tumors such as leiomyomas and leiomyosarcomas (Silveira, et al, 2014). Because transitional cell carcinomas represent the vast majority of cases, familiarity with their presentation and pathophysiology is vital. However, it is likewise important to avoid making assumptions when examining a case, as several disease processes may present similarly.

Transitional cell carcinomas are the most common of all these urinary tract neoplasms and can arise from transitional cell epithelium in the bladder, urethra, ureter or renal pelvis. Transitional cell carcinomas generally exhibit an aggressive behavior and ordinarily involve space occupying lesions of the trigone of the bladder (Knapp, 2013). These transitional cell tumors have a relatively high metastatic rate, traveling through the lymphatics then typically to the lungs, with thirty to forty percent of animals having pulmonary metastasis at diagnosis (Chun, 2006). Leiomyosarcomas are less common in the bladder than transitional cell carcinomas, are typically locally aggressive, but less likely to metastasize as compared to transitional cell carcinomas. Leiomyosarcomas arise from any smooth muscle tissue throughout the body and when they metastasize, they tend to spread via the bloodstream. Leiomyomas and leiomyosarcomas represent less than one-half of a percent of canine bladder neoplasms (Heng, et al, 2006). Both transitional cell carcinomas and leiomyosarcomas may extend to obstruct the ureters, urethra or urethral sphincter, causing life threatening complications. The report below

will outline a case emphasizing the similarity of these disease processes and the importance of diagnosis and intervention.

History and Presentation:

In June of 2017, Gracie, an approximately eight-year-old female spayed German Shepherd, and her housemate were being watched while their owners were away. The pet sitter noticed that Gracie needed to go outside frequently and that her urine was dark red tinged and mentioned this to the owners. When the owners returned and the urine remained red colored, they took her to her primary veterinarian. On June 15th, Gracie's regular veterinarian performed a urinalysis which showed a pH of 8. 3, was positive for protein, contained a large amount of red blood cells, and had a specific gravity of 1.038. She was placed on enrofloxacin and returned on June 23rd for reexamination. Her urine was still dark and her bladder was solid feeling upon palpation. No calculi were observed on abdominal radiographs, and abdominal ultrasound revealed an approximately 3.4cm mass in the trigone of the bladder. Due to the size and location of the mass Gracie was prescribed piroxicam for symptomatic treatment of a presumptive transitional cell carcinoma. Gracie seemed more comfortable and was urinating less frequently, but soon developed inappetence and diarrhea. The piroxicam was discontinued and she was prescribed grapiprant, afterwhich her gastrointestinal upset resolved.

Gracie had periodic flare ups of "bloody urine," but lived overall comfortably for approximately nine months. At this time, she began to seem uncomfortable, getting up to urinate frequently in the night, not eating, and not acting like herself. Due to quality of life concerns, Gracie's owners elected humane euthanasia along with necropsy.

Gracie presented to the MSU-CVM lab services department on March 8, 2018. Necropsy on March 9th revealed considerately marked post-mortem autolysis. The abdominal cavity contained approximately 20-30 mLs of hemorrhage, and approximately 10-20 mLs of dark red to brown cloudy fluid. The right kidney had two round, raised, dark red-purple smooth, soft nodules on the surface approximately 3 x 3 cm and 1x1cm in addition to one extracapsular cyst at the cranial pole of the kidney that was roughly the size of a tennis ball, firm, and filled with a dark red-brown cloudy fluid. The left kidney had multifocal cysts at the corticomedullary junction that were approximately 0.5 x 0.5 cm. The bladder contained a single large, approximately 6 x 6 cm, dark red-purple, ovoid mass arising from the trigone that was irregularly marginated and took up roughly 90% of the bladder. There was approximately 1-3 mLs of red-tinged cloudy fluid in the bladder. There was a small, approximately 1 cm x 0.5 cm, ovoid to cylindrical dislodged portion of the mass obstructing the proximal urethra. There was severe cartilage loss of the right coxofemoral joint, consistent with degenerative joint disease. Samples were submitted for histopathology.

Pathophysiology:

According to studies 73-97% of tumors in the urinary bladder are epithelial in origin, and of these, 77-97% are malignant (Sapierzynski, et al, 2007). Based upon these statistics, and the apparent trigonal origin of the bladder mass, Gracie's tumor originally diagnosed as a transitional cell carcinoma by the referring veterinarian, and was suspected to be a transitional cell carcinoma at gross necropsy. However, histopathologic review found elongate cells with moderate eosinophilic cytoplasm and ovoid to cigar shaped nuclei; consistent with mesenchymal

rather than epithelial cells, leading to a diagnosis of a leiomyosarcoma. Connective tissues, such as smooth muscle, are composed of mesenchymal cells. The root leiomyo- refers to involuntary smooth muscles that are found throughout the body; such as blood vessels, skin, gastrointestinal and genitourinary tract. Sarcoma refers to any malignant tumor arising from mesenchymal cells; including, fat, muscle, nerves, tendons, blood and lymph vessels. A major difference between the behavior of mesenchymal originating sarcomas and epithelial originating carcinomas, is how they spread. If this had been a transitional cell carcinoma, it would have been expected to invade the local lymph nodes and metastasize via lymphatics. However, sarcomas spread via the bloodstream, and as such, can be found almost anywhere there are blood vessels (Thway, 2009). In Gracie's case, there was a significant amount of postmortem autolysis hindering interpretation, and the degree of spread was unable to be determined.

The signs of urinary tract neoplasms are often similar as they are dependent on the location of the tumor rather than the tumor type itself. Most often, signs are non-specific and include lethargy, weight loss, nausea, vomiting, inappetence and pain. As the tumor grows, signs may include urinary incontinence, dysuria, hematuria, pollakiuria, or a palpable caudal abdominal mass (Heng, et al, 2006; Ribeiro, et al, 2016; Brown, 2018). The location or growth of the mass may cause an obstructive condition either of the ureter(s) or urethra that can progress to hydronephrosis. This may cause signs of abdominal pain, or animals may have palpable, enlarged kidneys. Signs of uremia may also be seen in animals with bilateral ureteral obstruction and hydronephrosis or with urethral obstruction as a result of post renal azotemia (Mackin, 2016). Ascending urinary tract infections may occur due to urine stasis and can progress to renal damage and sepsis (Brown, 2018).

In Gracie's case, the histopathology revealed that the kidneys contained multiple large cystic spaces lined by thick fibrous connective tissue walls and filled with neutrophil containing fluid. The adjacent renal parenchyma were fibrotic and infiltrated by lymphocytes and plasma cells. The fluid was cultured and revealed growth of *Streptococcus*, *Enterococcus,* and *Escherichia coli*. This infection was likely due to urine stasis and an ascending urinary tract infection. The bladder contained an expansive mass composed of cells arranged in streams and interlocking bundles in a fibrovascular stroma. The cells were elongate with moderate eosinophilic cytoplasm and ovoid to cigar shaped nuclei indicative of a leiomyosarcoma. The mass was transmural, affecting the trigone area of the bladder where the ureters attach.

Diagnostics:

Hematuria, dysuria, stranguria, and pollakiuria are the most common signs, though animals with obstructive conditions may show uremia, abdominal pain, or have palpable, enlarged kidneys (Heng, et al, 2006; Ribiero, et al; Brown, 2018). Because these clinical signs are not specific to the individual tumor type, they are best used to guide further diagnostics.

Various imaging modalities may be utilized to aid in diagnosis. Radiographs may show a nonspecific mass or mass effect in the bladder or caudal abdomen, the diagnostic value of which may be enhanced by utilizing contrast. Radiographs may also be utilized to investigate the thorax for metastasis. Ultrasonography can aid in localization of any abdominal masses and may be used to guide sampling and assess vascularity. Computed tomography is useful to determine exact location and extent of the tumor(s) and is, therefore, typically used for the purpose of surgical planning or metastatic staging.

As aforementioned, many tumors found in or near the urinary tract behave similarly. As such, a sample must be obtained for definitive antemortem diagnosis. Samples may be obtained via urinary catheterization, cystoscopy or surgery. Cystocentesis and ultrasound guided biopsies are discouraged as they may cause tumor seeding (Chun, 2006). Urine cytology is often unrewarding due to lack of exfoliation, especially in the case of sarcomas, or due to inflammation confounding results (Malek, 2011). Considering such, surgical biopsy or resection and histopathology is the gold standard for antemortem diagnosis.

Postmortem diagnosis is made via histopathologic examination of tumor tissues revealing cells indicative of a leiomyosarcoma. These are typically characterized by elongated spindle cells with cigar shaped nuclei and moderate eosinophilic cytoplasm arranged in interlocking bundles, as seen in this case (Heng, et al, 2006).

Treatment and Management:

Treatment options for bladder neoplasms vary from symptomatic care incorporating tumor reduction medications, such as piroxicam or galiprant, to surgical excision with or without radiation or chemotherapeutics, such as cisplatin or mitoxantrone. Due to the invasiveness of leiomyosarcomas and their location and extent, surgical intervention can be difficult, and symptomatic therapy is often pursued. In Gracie's case, the transmural location of the tumor at the trigone of the bladder significantly reduced the likelihood of successful surgical resection.

Piroxicam is a non-steroidal anti-inflammatory drug that is primarily used to adjunct treatment of transitional cell carcinomas. This adjunctive benefit is believed to be due to the action on the immune system in the form of a reduction in prostaglandin synthesis and

superoxide formation, and may, therefore, also aid in treating other neoplasms. Because it is an NSAID, limiting side effects often include gastrointestinal upset, ulceration and bleeding, renal papillary necrosis, or peritonitis (Plumb, D.C., 2018).

Grapiprant is a prostaglandin E2 EP4 receptor antagonist that provides anti-inflammatory and analgesic effects without as many side effects. As opposed to blocking the synthesis of numerous prostaglandins, including those associated with renal and gastrointestinal health, grapiprant blocks the receptor for a single particular prostaglandin associated with pain and inflammation. It's primary, and only currently labelled, use is to control pain and inflammation associated with osteoarthritis; however, studies are ongoing to test for the efficacy of grapiprant to control pain and inflammation associated with other conditions. Studies in human medicine have been investigating the role and overexpression of the EP4 receptor in breast cancer as well as other neoplasms and metastases. These studies have show that EP4 antagonists may be a viable therapeutic to reduce tumor angiogenesis and lymphangiogenesis (Majumder et al, 2018; Majumder et al, 2014).

Case Outcome:

The mean survival time of transitional cell carcinoma ranges from 109-300 days depending on the level of treatment (Knapp, 2013). Because of the rarity and aggressiveness of leiomyosarcomas, scant data is available to determine a mean survival time. In this case, symptomatic treatment was pursued and Gracie lived for approximately 270 days prior to humane euthanasia.

Gracie's case is a relevant reminder of the continual balance practitioners must maintain between the knowledge that common things occur commonly, and the knowledge that zebras occasionally wander among horses. Although tumors of the urinary tract are rare, and transitional cell carcinomas occur most commonly of these, other tumors can and will likely be seen. It is, therefore, important to recall these rare tumors as differentials when presented with signs of hematuria, stranguria, pollakiuria, or abdominal pain. In this case, the treatment options were similar for both tumor types and; therefore, Gracie could be treated without a definitive diagnosis. However; this will not always be the case and presumptive diagnoses may lead to inappropriate treatment and poor clinical outcomes.

References

1. Brown, S. “Neoplasia of the Urinary System in Small Animals.” *Merck Manual.* 2018.

2. Chun, R. “Canine Bladder Tumors Beyond Peroxicam.” North American Veterinary Conference. 2006.

3. Gan Heng, H. et al. “Smooth Muscle Neoplasia of the Urinary Bladder Wall in Three Dogs.” *Veterinary Radiology and Ultrasound.* 47:1:83-86. 2006

4. Huynh, E. Clifford, B.“Imaging Essentials: Small Animal Abdominal Ultrasonography The Urinary Tract: Urinary Bladder & Urethra.” *Today's Veterinary Practice*, vol. 6, no. 5, 2016.

5. Knapp. D.W. “Canine Bladder Cancer.” *Purdue University.* 2013.

6. Luiza Silveira, T. et al. “Leiomyosarcoma of the Urinary Bladder in a Young Dog - Case Report.” *World small Animal Veterinary Association World Congress Proceedings.* 2014.

7. L’Eplattenier, H. “Urinary Incontinence.” *Proceedings of the European Veterinary Conference Voorjaarsdagen*, 27 Apr. 2011. IVIS.

8. Mackin, A. “Urinary Neoplasia.” Small Animal Medicine and Surgery I. 2016.

9. Malek, S. et al. “Metastatic Transitional Cell Carcinoma in Proximal Humerus of a Dog.” *The Canadian Veterinary Journal.* 52:9:1013-1017. 2011

10. Majumder, M. et al “Prostaglandin E2 receptor EP4 as the common target on cancer cells and macrophages to abolish angiogenesis, lymphangiogenesis, metastasis, and stem-like

cell functions." *The Official Journal of the Japanese Cancer Association.* 105(9): 1142-1151. 2014

11. Majumder, M. et al. "EP4 as a therapeutic target for aggressive human breast cancer." *International Journal of Molecular Sciences.* 19(4): 1019. 2018.

12. Nacahisa, A. Okumura, T. "Pharmacology of grapiprant, a novel EP4 antagonist: receptor binding efficacy in a rodent postoperative pain model, and a dose estimator for controlling pain in dogs." *Journal of Veterinary Pharmacology and Therapeutics,* 40:285-292. 2016.

13. Plumb, D.C. "Piroxicam." Plumb's Veterinary Drug Handbook 9th Edition. 2018.

14. Ribeiro, J. et al. "Giant Leiomyosarcoma of the Urinary Bladder." *Journal of Clinical and Diagnostic Research.* 10(5): PD15-PD16. 2006

15. Sapierzynski, R. et al. "Tumors of the Urogenital System in Dogs and Cats. Retrospective Review of 138 Cases." *Polish Journal of Veterinary Sciences.* 2007.

16. Shankar, V. "Soft tissue: Smooth Muscle: Leiomyosarcoma." PathologyOutlines.com. 2018.

17. Tway, K. "Pathology of Soft Tissue Sarcomas." *Clinical Oncology.* 21: 695-705. 2009.

18. Veterinary Information Network. "Grapiprant." VIN Veterinary Drug Handbook. 2017