A Case Report: An Unusual Presentation and Behavior of Transitional Cell Carcinoma in the Dog

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Introduction

Although urinary bladder cancer only makes up about 2% of all canine tumors, transitional cell carcinoma (TCC) is reported to affect 20,000 dogs every year.[1] There have been many factors associated with the etiology of TCC. Topical insecticides for flea and tick control, environmental insecticides, and cyclophosphamide administration have all been linked to an increased risk of development of bladder cancer. Females, certain breeds (e.g. Scottish Terriers), older and obese animals are all considered to be predisposed to the development of TCC.

The most common presenting signs are hematuria, stranguria, and pollakiuria. Lameness, lethargy, and weight loss can also be observed in these animals, but these signs are less common.[2] Histopathology is needed for the diagnosis of transitional cell carcinoma. Often cytology or urine sediment is evaluated first; however, abnormal epithelial cells can occur in conditions other than TCC. Tissue may be collected by cystoscopy, cystotomy, or traumatic catheterization for histopathologic evaluation.[3] Practitioners have refrained from fine needle aspiration due to the risk of seeding the tumor. In a recent study, however, only 4.4% of dogs with TCC who underwent fine needle aspiration had evidence of TCC in the abdominal wall. Many clinicians are beginning to use this method as it is an efficient diagnostic method with high yield.[4]

History and Presentation

An -11-year-old inact male Staffordshire Bull Terrier presented to the primary care veterinarian on April 5th, 2016, for coughing and lethargy. Thoracic radiographs showed infiltrates in the lungs, and the CBC and serum chemistry were within normal limits. He was prescribed 500 mg of cephalexin twice daily for suspect pneumonia. A few days later, he became weak and was shivering. The patient improved with 100 mg of Vetprofen. On the 11th, however, he became

inappetent. Prednisone (10 mg) was administered twice daily and 250 mg of Levaquin once daily, which was discontinued by the owner before presenting to MSU-CVM on April 17th, 2016.

On presentation, the patient was quiet, but alert and responsive. The heart rate was elevated (156 beats/minute), but the temperature (100.3 F) and respiratory rate (28 breaths/minute) were normal. Mucus membranes were tacky, but they were pink with a capillary refill time of less than 2 seconds. The patient had a pot-belly appearance, and lung sounds were harsh bilaterally. A rectal examination was performed, but the prostate could not be palpated. No other abnormalities were present on physical exam. The night of presentation, the patient was administered supportive care, including Plasmalyte, pantoprazole, Cerenia, and methadone.

Diagnostic Approach

Blood was drawn for routine evaluation of bloodwork. A complete blood count showed a moderate neutrophilia (19,998 /ul; reference interval = 3500-14200), and a mild lymphopenia (202 /ul; reference interval = 1200-6500). The serum chemistry revealed a mild elevation in ALP (480 U/L; reference interval = 11-140).

The next day, 4/18/16, a three view thoracic radiographic study was performed. There was a large (13.6 x 19.9 x 14.1 cm), sharply marginated mass of soft tissue opacity in the right caudal lung lobe. The mass crossed over midline, which resulted in a left mediastinal shift and border effacement of the right aspect of the diaphragm. A small amount of pleural effusion was present, evidenced by a pleural fissure between the right cranial and middle lung lobes. There was a diffuse bronchial pattern with thickening of the walls of the larger airways, and an unstructured, patchy interstitial pattern. The existence of one large, focal mass in the lungs suggested a primary lung tumor, with consideration given to adenocarcinoma, bronchoalveolar carcinoma,

and histiocytic sarcoma. The bronchial pattern could have been due to metastatic neoplasia, hemorrhage or edema. Differentials for the pleural effusion included neoplastic effusion, exudate, modified transudate, chyle and hemorrhage.

The same day, a two view abdominal radiographic study was performed. The left kidney was 4 times the length of the second lumbar vertebrae, and the right kidney could not be visualized. There were triangular, sharply marginated, mineral opacity structures varying in size within the lumen of the bladder. In the area of the prostate, there was an irregularly shaped, soft tissue opacity mass with mineralization within it, and spondylosis deformans was present at L7-S1. Differentials for the enlarged left kidney included hydronephrosis, hypertrophy due to contralateral disease, and neoplasia. The mineral opacity structures within the lumen of the bladder were considered likely to be cystoliths; either struvite or calcium oxalate dihydrate stones due to their radiodensity. Differentials for the prostatomegaly with irregular shape included neoplasia, consideration given to prostatic adenocarcinoma or transitional cell carcinoma, chronic prostatitis, or a prostatic cyst. The mineralization within this mass was thought to be either metastatic calcification or urethrolithiasis.

To further characterize the pulmonary lesions, thoracic ultrasound was performed. The mass in the right caudal lung lobe was heterogenous and hypoechoic with multiple hyperechoic foci ranging from 1mm to 1.4 cm in diameter. Throughout the rest of the thorax, there were multiple small, round, sharply marginated, hypoechoic nodules. The large mass, again, was considered to likely be primary pulmonary neoplasia. The primary differential for the smaller nodules was metastatic neoplasia, but granulomatous disease was also considered. Fine needle aspirates of the lung mass were performed using 22-gauge, 1.5 inch needles. The aspirates were submitted for cytologic evaluation.

The cytology revealed a mixed population of inflammatory cells including neutrophils, macrophages and small lymphocytes. Hemosiderophages were present indicating there had been chronic hemorrhage. A significant number of cells displaying anisocytosis and anisokaryosis were present in clusters. The nuclei within these cells were round to oval, centrally to eccentrically located, and had a stippled to lacy chromatin pattern. There were rare multinucleated cells and mitotic figures. The atypia present within these cells suggested neoplastic epithelium. Diagnostic imaging and cytology suggested a neoplastic process that had aggressively metastasized. Due to the grave prognosis associated with metastatic neoplasia, the owners elected humane euthanasia and necropsy.

Necropsy

The necropsy revealed abnormal lung, lymph nodes, adrenal gland, kidney, prostate, and vertebra. The right caudal lung lobe was firm with a red to purple mottled appearance. Fibrin was present on the parietal surface of that lung lobe. Along the medial surface of the right caudal lung lobe, there were several dark red bulging foci with tan margins, consistent with infarction. The lung lobe felt nodular, which was found to be due to fibrous tissue surrounding the airways and vessels. The bronchi were markedly irregular and enlarged. The tracheobronchial lymph nodes were 5 times normal size, and were fibrous on cut section. One of the adrenal glands had a lobe twice the normal size due to the presence of a mass. The left kidney was about 3 times its normal size and exhibited hydronephrosis. The proximal 3 cm of the ureter of this kidney was entangled with dense fibrous tissue, which constricted the lumen significantly. At the level of the bladder, this ureter is normal. Within the lumen of the bladder were approximately a dozen dull green stones that were smooth and ranging from 5-15 mm wide. The prostate was irregular with a spongy consistency. It was 8x8x5 cm with multiple cysts measuring 5-30 mm in width, which

were filled with clear to light yellow fluid. The remaining prostate was hyperplastic. At the pelvic urethra, another stone (10-15 mm wide) was present. The right kidney was normal. A bony proliferation of about 2x2x2 cm deviated ventrally in the lumbosacral area. On cut surface, tan, soft, friable material was present. The mass was a dorsal and ventral expulsion of the disc between L7 and S1, which went dorsally 4 mm, and ventrally 1 mm. The ventral expulsion was surrounded by trabecular bone and a pseudophysis that allowed minimal movement.

Histopathology

Several samples were evaluated histopathologically. The urothelium of the left kidney and ureter was replaced by a poorly demarcated neoplasm of one cell type. The kidney had a very wide pelvis with an almost non-existent medulla and thin cortex. There was abundant fibrous tissue, hemorrhage, and necrosis with a complete loss of renal parenchyma due to the obstruction of the ureter leading to hydronephrosis. The cells were large and anaplastic with well defined borders. The cytoplasm was fine and amphophilic with large round to ovoid nuclei that had large nucleoli. There was marked anisocytosis and anisokaryosis, as well as 1-4 mitotic figures per high-powered-field.

The adrenal gland revealed two neoplasms that compressed the cortex and expanded the medulla. One of the neoplasms arose from the medulla, and the other was similar to that described in the kidney. The right caudal lung lobe was also infiltrated by a similar neoplastic process. The neoplastic cells expanded the stroma around the bronchi and large vessels that were in the grossly affected lobe. There were many hemorrhagic areas with infarcted alveoli. The neoplastic cells stem from and were largely around the lymphatics, arteries and veins, but extend to some extent into the alveoli. The tracheobronchial lymph node was affected by the same neo-

plastic process described in the kidney, lung, and adrenal gland. The prostate was found to be expanded by the irregular cysts observed grossly, and had hyperplastic epithelium; no neoplastic cells were appreciated, so this was likely due to benign prostatic hyperplasia.

Ancillary diagnostics

To characterize the neoplastic processes, special staining was used. The neoplastic cells within the kidney were strongly positive for pancytokeratin and vimentin. Pancytokeratin is a cytoplasmic marker that is used to screen for carcinomas, and vimentin is another cytoplasmic marker that can identifies mesenchymal cells, so it is useful in identifying sarcomas. The neoplastic cells within the adrenal gland were chromagranin positive, a marker that can identify neuroendocrine tumors, such as pheochromocytomas.[5]

Because the initial staining revealed both carcinoma and sarcoma characteristics, immunohistochemistry was submitted to Purdue University. The neoplastic cells in the lung and urothelium tested positive for GATA-3, a marker used to characterize mammary, urothelial, renal, and germ cell tumors, mesotheliomas, and paragangliomas in human medicine.[6] The superficial layers of the neoplastic urothelium were positive for Uroplakin II, a specific marker for urothelial carcinoma.[5]

The presence of GATA-3 in the pulmonary masses, and the presence of Uroplakin II in the urothelium led to the diagnosis of primary renal transitional cell carcinoma with adrenal, pulmonary, and lymph node metastasis. The presence of chromogranin in the adrenal confirms the diagnosis of a pheochromocytoma.

Pathophysiology

Transitional cell carcinoma, or urothelial carcinoma, is a malignant tumor that forms from transitional epithelium.[7] Transitional epithelium lines the excretory passages from the kidney, the ureter, the bladder, and the proximal urethra.[8] Carcinogenesis may occur in any of these, however, the bladder is the most common, especially in the trigone.[9] Common metastatic sites include the regional lymph nodes, lungs, and bone.[10] Hypertrophic osteopathy (HO) has also been reported as a paraneoplastic syndrome associated with TCC. The normal metastatic pulmonary patterns are nodular interstitial, cavitating pulmonary lesions, unstructured interstitial patterns, multiple nodules, or normal pulmonary opacity.

Commonly, these animals present with stranguria, hematuria, and pollakiuria, as if they have a urinary tract infection. Because many transitional cell carcinomas cause partial obstructions, a secondary urinary tract infection is likely due to urine retention. Many patients will have a history of improvement with antibiotics.[9]

The case reported herein is unique in that the patient presented with respiratory signs, had an atypical pulmonary metastatic pattern, and had a primary renal tumor. What is proposed to have happened in this case, is a primary renal transitional cell carcinoma obstructed urine outflow leading to hydronephrosis. Eventually, this neoplasm metastasized to the adrenal gland, colliding with a pheochromocytoma. The neoplasm metastasized hematogenously to the lungs inducing a scirrhous response and subsequent infarction of the right caudal lung lobe. It is unclear as to why the one lung lobe would have been so severely affected, but this is a unique presentation of metastasis.

Treatment and Management

To determine an appropriate treatment or management strategy for a patient with transitional cell carcinoma, staging of the disease must be performed. A complete blood count (CBC), serum chemistry, urinalysis (+/- urine culture), and thoracic, abdominal and urinary tract imaging are important tools when determining the stage and treatment plan for the disease.[3] The World Health Organization Clinical staging system (TNM) for bladder cancer is typically used in cases of transitional cell carcinoma. Because the tumor invaded neighboring structures, like the ureter, this case would be a T_3. There was distant lymph node involvement, and distant metastasis, so this case would be an N_2 and M_1. Mean survival time associated with T_3 tumors is 118 days, and distant metastasis (M_1) is associated with a 105 day mean survival time. At the time of necropsy, the reported metastatic rate for transitional cell carcinoma has been reported to exceed 50%.[9]

In cases without detectable metastatic disease, there are several management options. Surgery, radiation, and medical management are available, however, medical management has become the mainstay due to its non-invasive nature and appeal to owners. Medical management usually includes a combination of chemotherapy and cyclooxygenase (COX) inhibitors. Although this is not usually curative, studies of different combinations have resulted in favorable remission rates, and stable disease.

Chemotherapies like carboplatin, cisplatin, doxorubicin, mitoxantrone, and vinblastine have been use in trials as single treatments and in combination with cyclooxygenase inhibitors like piroxicam, deracoxib, and firocoxib to determine success rates. Cisplatin used in combination with piroxicam in one study resulted in a very favorable mean survival time of 329 days; however, this combination resulted in high complication rates like renal, gastrointestinal, and

bone marrow toxicity. The most commonly used intravenous chemotherapy drugs have been mitoxantrone and vinblastine, which result in less adverse effects. These have given remission rates as high as 35% and stable disease in 50-55%. Piroxicam alone has even resulted in occasional full remission, while deracoxib and firocoxib have resulted in partial remission and stable disease.[3]

Case Outcome and Conclusion

Although many animals with transitional cell carcinoma may have a favorable survival time post-diagnosis, the case reported herein was much too advanced to have pursued surgery, radiation or medical management. Due to the grave prognosis associated with the probable aggressive metastatic disease, the owners elected humane euthanasia and necropsy. The presentation, primary site of the neoplasia, and metastatic pattern of this case of transitional cell carcinoma was unusual. The patient was 11 years old, and presented with chronic respiratory disease; this led to a running diagnosis of primary pulmonary neoplasia. The primary tumor, however, was of renal origin, specifically the renal pelvis, which is also unique. Only 0.3–1.7% of all canine neoplasms are reported to be primary renal tumors.[11] In one study, only 9 out of 82 dogs with primary renal neoplasia were diagnosed with transitional cell carcinoma. [12] The most common metastatic sites reported are regional lymph nodes, lungs, and bone.[10] Typically, the radiographic appearance of the lung metastasis is nodular interstitial, cavitating lesions, unstructured interstitial, multiple nodules, or a normal pulmonary opacity.[9] This case presented as one, focal, large mass taking up most of the right caudal lung lobe. The metastasis invaded around the bronchi and vessels in the lungs causing infarction and fibrosis. Metastasis to the adrenal gland is not uncommon, however, the finding of a collision tumor is unique. Transitional cell carcinoma is

often predictable in it's presentation and metastasis, however, as evidenced by the case reported herein, unusual behavior of this neoplasia can occur.

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