History

An 11-year-old 13.2-kg castrated male Poodle was referred to the North Carolina State University Veterinary Hospital because of acute paraplegia and a 5-week history of lethargy and severe signs of pain refractory to treatment with gabapentin (7.5 mg/kg, PO, q 8 to 12 h) and methocarbamol (19 mg/kg, PO, q 8 to 12 h).

Clinical and Gross Findings

On physical examination, the dog was laterally recumbent and paraplegic, with the ability to bear weight on thoracic limbs only with physical assistance. The dog seemed mildly anxious but showed signs of normal mentation, and findings on cranial nerve examinations were clinically normal. There were moderate signs of pain elicited upon paravertebral palpation at the level of the thoracolumbar and lumbar vertebrae, and the dog had a high rectal temperature (40.3 °C). Postural reactions, withdrawal reflexes, and nociception were absent in both hind limbs, and cutaneous trunci reflexes were absent caudal to T12, which progressed to T4 on the day after the initial presentation. Patellar reflexes and thoracic limb reflexes were clinically normal. Localization of severe myelopathy was to T3 through L3 with presumptive spinal shock.

A serum biochemical profile and a CBC performed by the referring veterinarian about 1 month before the presentation were unremarkable except for moderately high alkaline phosphatase activity (446 U/L; reference range, 23 to 212 U/L) and moderately high BUN concentration (53 mg/dL; reference range, 7 to 27 mg/dL). Thoracic and abdominal radiography revealed an aggressive osseous lesion with a compression fracture of the T2 vertebral body and suspected bony lysis of T9 and T10 along the spinous processes. Additionally, a moderate generalized bronchointerstitial pattern (suspected age-related change) and moderate prostatomegaly were observed. Magnetic resonance imaging of the thoracolumbar vertebrae (T3 through S3) revealed cortical destruction of T6 and T9 vertebral bodies with hyperintense material extending into the ventral spinal canal resulting in severe compression to the spinal cord, in addition to compression fractures of T2 and T9. Occasional intervertebral disk degeneration along with spondylosis deformans at L4 to L5, L5 to L6, and L6 to S1 were noted. Given the clinical signs of paraplegia without nociception and evidence of cortical destruction in multiple vertebral bodies with associated compression fractures, the patient’s prognosis was considered poor to extremely poor, and euthanasia was elected.

Gross postmortem examination revealed severe effacement of the medullary cavity of the T6 vertebral body by a pale pink to tan, gelatinous material (Figure 1). Compression fractures of the vertebral bodies of T2 and T9 were present with craniocaudal collapse and associated mild to moderate hemorrhage. The ventral aspect of the vertebral bodies of T2, T6, and T9 had firm to hard proliferations that
bulged up to 5 mm into the thoracic cavity. Within the medullary cavity of the T5 vertebral body was a focal area of increased firmness and opacity, consistent with sclerosis. Smooth osseous bony bridging proliferations (spondylolysis deformans) between the ventral aspect of the vertebral bodies of L4 to L5 and L6 to S1 were present. Intervertebral disks between C3 through C7 and occasional lumbar intervertebral disks appeared dry, friable, and pale yellow with slight protrusion into the spinal canal (consistent with intervertebral disk degeneration). Spinal cord lesions were not appreciated grossly. On the right eighth rib at the level of the costochondral junction was a firm to hard, 2.5 X 1.5 X 1-cm, irregular, pale tan proliferation. Both stifle (femorotibial) joints had multiple osteophytes along the femoral trochlear ridges with multifocal cartilage erosions along the articular surfaces (consistent with degenerative joint disease).

The prostate was mildly enlarged (3.2 X 3 X 2.6 cm) with multifocal pale tan to white pinpoint foci and multiple cavitations filled with a thick, yellow, pasty material. Multifocally scattered throughout the hepatic parenchyma were slightly raised, smooth, pale red to tan nodules up to 2.5 cm in diameter, which appeared similar to the adjacent hepatic parenchyma on the cut surface. The gallbladder was moderately enlarged with dark green-black debris, and gelatinous material adhered to approximately 30% of the gallbladder mucosal surface (early mucocle formation). The lungs were diffusely red, wet, and heavy with foamy fluid exuded on cut surface (edema and congestion). Minimal to mild mitral valve endocardiosis was evident. No other notable postmortem findings were observed.

Formulate differential diagnoses, then continue reading.

Histopathologic, Immunohistochemical, and Microbiological Findings

Histologic examination of the prostate revealed a poorly demarcated, infiltrative neoplasm consisting of variably sized, multifocal to coalescing islands of epithelial cells arranged in haphazard layers with frequent individualization and formation of small cohesive clusters supported by a moderate amount of fibrovascular stroma (Figure 2). Frequently within the center of these neoplastic epithelial islands, there was abundant lytic necrosis with occasional mineralization and cholesterol clefts. The neoplastic epithelial cells had a moderate amount of cosinophilic cytoplasm, occasionally with a single large discrete colorless vacuole that displaced the nucleus to the periphery (signet-ring appearance). The nuclei were round to ovoid with stippled to vesiculated chromatin and occasionally one small nucleolus. Anisocytosis and anisokaryosis were moderate with frequent binucleation and occasional multinucleation; 19 mitotic figures were present in 10 hpfs (2.37 mm²). Neoplastic cells were seen within the lymphatics. Moderate numbers of lymphocytes and plasma cells often were multifocally infiltrating the neoplasm. Immunohistochemical staining with uroplakin III (urothelial marker) was applied, and 20% to 40% of the neoplastic cells exhibited strong membranous and occasional cytoplasmic immunoreactivity.

The thoracic vertebral bodies (T2, T6, and T9) were effaced and replaced by similarly described neoplastic cells as observed in the prostate with associated extensive osteolysis of the medulla and dorsal cortex and neoplastic infiltration into the overlying dorsal longitudinal ligament (Figure 2). Immunohistochemical staining for uroplakin III was applied to a vertebral section, and 70% of neoplastic cells exhibited strong membranous and cytoplasmic immunoreactivity for uroplakin III (urothelial marker). Examination of representative sections from the entire length of the spinal cord revealed moderate to severe segmental myelomalacia with Wallerian-like (axonal) degeneration in the T9 segment and minimal to mild Wallerian-like degeneration in the T5 and T6 segments. Histologic examination of the grossly described proliferation along the costochondral junction of the right eighth rib revealed similar neoplastic infiltration, osteolysis, and periosteal reaction. Within the liver were few small aggregates of neoplastic epithelial cells forming irregular tubules supported by a moderate amount of loose fibrous stroma. Given the slightly different arrangement of these neoplastic cells, immunohistochemical staining with uroplakin III was also performed on sections of liver and revealed positive membranous or cytoplasmic immunoreactivity in about 20% to 30% of the neoplastic cells.

Bacterial culture of a swab from the prostate yielded *Escherichia coli* (1+), *Enterococcus faecium* (1+), and *Klebsiella pneumoniae* (1+). Given the low yield and mixed growth of bacteria in the absence of histologic lesions of bacterial infection in the prostate, these findings were considered to represent postmortem bacterial contamination.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: prostatic urothelial carcinoma with metastases in the thoracic vertebrae, rib, and liver.

Case summary: metastatic urothelial carcinoma in a dog.

Comments

Given the clinical and gross findings in this case, differential diagnoses included multiple myeloma and other round cell tumors as well as primary neoplasms with a propensity for skeletal metastasis, such as those originating from the thyroid gland, lung, mammary gland, bladder, and prostate.1 Multiple myeloma appears as lytic foci that consist of soft,
fleshy, or gelatinous, dark red to gray/pink masses that may be associated with pathological fractures, which paralleled the gross presentation in the case reported herein. Prostatomegaly increased the index of suspicion for prostatic carcinoma and urothelial carcinoma, both of which frequently metastasize to bone. Histopathology and immunohistochemical findings were crucial for definitive diagnosis.

Microscopic examination of the prostate revealed a neoplastic population that exhibited immunoreactivity to uroplakin III with similar neoplastic populations in the thoracic vertebrae, rib, and liver, consistent with metastatic urothelial carcinoma. Urothelial carcinoma is a malignant neoplasm derived from urothelium, which overlies the luminal surface of the entire urinary tract extending from the renal pelvis through the ureter and urinary bladder to the prostatic urethra and distal urethra. Two percent of all malignant canine neoplasms originate from the urinary bladder and urethra, with urothelial carcinoma being the most common tumor by a wide margin. Urothelial carcinoma in dogs is predominantly (> 95%) diagnosed as high grade (loss of cellular polarity; disorganized growth; marked cellular atypia; marked nuclear pleomorphism; clumped chromatin; prominent nucleoli; numerous mitotic figures; and invasive behavior. These tumors typically have a high metastatic potential. Predisposing factors for urothelial carcinoma include female sex, castration, obesity, exposure to pesticides, age (average, 9 to 11 years), and breed (Scottish Terriers, West Highland White Terriers, Wire Haired Fox Terriers, Shetland Sheepdogs, and Beagles). Urothelial carcinoma carries a grave prognosis with less than 20% of dogs treated with a combination of chemotherapeutics.

Figure 2—Photomicrographs of sections of prostate (A), liver (B), and T6 vertebral body (C and D) from the dog described in Figure 1. A—The prostatic parenchyma is replaced by multifocal to coalescing islands of neoplastic epithelial cells arranged in multiple haphazard layers with frequent individualization and formation of small cohesive clusters supported by a moderate amount of fibrovascular stroma. H&E stain; bar = 100 µm. Inset—Neoplastic cells exhibit strong immunolabeling for uroplakin III. Anti-uroplakin III immunohistochemical staining; bar = 20 µm. B—Small aggregates of neoplastic epithelial cells in the liver form irregular tubules. H&E stain; bar = 50 µm. Inset—Neoplastic cells exhibit immunolabeling for uroplakin III. Anti-uroplakin III immunohistochemical staining; bar = 20 µm. C—There is extensive osteolysis of the medulla and dorsal cortex of T6 with neoplastic infiltration into the overlying dorsal longitudinal ligament. H&E stain; bar = 500 µm. D—The neoplastic cells in T6 seen here are similar to those in the prostate. H&E stain; bar = 20 µm. Inset—Neoplastic cells exhibit strong immunolabeling for uroplakin III. Anti-uroplakin III immunohistochemical staining; bar = 20 µm.
and cyclooxygenase (COX) inhibitors surviving for 1 year or more.\textsuperscript{5}

Canine urothelial carcinomas are most commonly present in the trigone region of the urinary bladder, and 30\% of bladder urothelial carcinoma will have concurrent involvement of the prostate.\textsuperscript{1} In the present case, the dog was determined to have primary urothelial carcinoma of the prostate likely arising from the prostatic urethra because no alterations were observed in the urinary bladder grossly nor microscopically. Urothelial carcinoma is thought to be the most common prostatic tumor in castrated dogs; however, the distinction between prostatic carcinoma and urothelial carcinoma can be difficult and has not been historically pursued.\textsuperscript{6} Distinguishing between these 2 neoplasms of the prostate requires the use of immunohistochemistry for specific urothelial or prostatic markers. Tumors of urothelial origin are expected to demonstrate immunoreactivity to uroplakin III with as little as 5\% immunoreactivity considered a positive result.\textsuperscript{1} Other immunohistochemical markers for urothelial tumors include cytokeratin 7, cytokeratin 20, and arginine esterase, but uroplakin III is the marker of choice for canine urothelial neoplasms.\textsuperscript{7,8} Uroplakin III is a transmembrane protein that is present in a specialized plasma membrane (asymmetrical unit membrane) of superficial (umbrella) cells of the urothelium and helps stabilize the urothelium during bladder enlargement.\textsuperscript{7} Uroplakin III immunoreactivity has been demonstrated to be highly specific (95\%) and moderately sensitive (57\%) for detecting primary and metastatic urothelial carcinoma in humans and is used to discriminate primary urothelial carcinomas from other primary carcinomas of the urogenital tract.\textsuperscript{9} Furthermore, uroplakin III detected 91\% of canine urothelial carcinomas and did not react with normal nonurothelial tissues, 285 nonurothelial tumors (prostatic carcinoma not included), and 4 nonepithelial bladder tumors.\textsuperscript{7} Additionally, uroplakin III immunoreactivity is restricted to the prostatic urethra in normal prostates of dogs.\textsuperscript{10} However, one report\textsuperscript{11} demonstrated 17 out of 20 canine prostate tumors expressed uroplakin III. In the present case, uroplakin III immunoreactivity of at least 20\% of the neoplastic cells within the prostate, liver, and vertebrae supports a diagnosis of urothelial carcinoma.\textsuperscript{1} Furthermore, neoplastic cell infiltration into lymphatics, high mitotic activity, moderate nuclear atypia, and frequent binucleated and occasional multinucleated cells are consistent with a high-grade urothelial carcinoma in this case.\textsuperscript{12,13} A recently developed noninvasive method for detection of canine urothelial carcinoma utilizes droplet digital PCR technology to detect highly recurrent DNA copy number aberrations characteristic of canine urothelial carcinoma in tissue and urine samples; this is an additional diagnostic tool particularly valuable in clinical settings.\textsuperscript{13}

Clinical findings typically associated with canine urothelial carcinoma include hematuria, pollakiuria, cystitis, and dysuria, which were not noted in this case. Approximately 10\% of cases of canine urothelial carcinoma present for clinical signs unrelated to the urinary system including lameness due to bone metastases or dyspnea from pulmonary metastases.\textsuperscript{1} The dog in the current report was presented for acute paraplegia with absent nociception due to a spinal cord injury secondary to pathologic vertebral body fracture from osteolysis associated with metastasis of urothelial carcinoma from the prostate. At the time of diagnosis of urothelial carcinoma, 20\% of dogs have radiographic evidence of metastases to the pulmonary parenchyma, 15\% to the lymph nodes, and 6\% to the lumbar or pelvic bones.\textsuperscript{1} Prevalence of metastases in dogs diagnosed with urothelial carcinoma at necropsy is 50\% to 90\%.\textsuperscript{1} Skeletal metastasis is frequently documented in dogs with urothelial carcinoma, with reports ranging from 9.5\% to 14\% on necropsy with histopathology confirmation.\textsuperscript{3} The processes involved in skeletal metastasis are not well elucidated, but it is hypothesized that neoplastic cells escape the primary site, travel through the vasculature to the wide-channeled sinusoids of bone marrow, and invade the marrow stroma to form solid metastases.\textsuperscript{14} The neoplastic cells stimulate osteoclasts and/or osteoblasts and form osteolytic or sclerotic lesions, respectively.\textsuperscript{14} In human studies of urothelial carcinoma, the pelvis and vertebrae are the most common sites of skeletal metastasis, and a report\textsuperscript{3} of canine urothelial carcinomas demonstrated metastasis to the lumbar vertebral bodies in all cases of skeletal metastasis of urothelial carcinoma, suggesting this is also a common site for metastases in dogs. Interestingly, in the present case, skeletal metastasis occurred multicentrically to the thoracic vertebrae and rib.

In domestic cats, the incidence of urinary bladder neoplasia is lower than it is in dogs. This difference is postulated to be due to lower quantities of tryptophan metabolites in feline urine, species-specific differences in ectoparasite preventative formulations, and underdiagnosis in geriatric cats with comorbidities.\textsuperscript{1,15,16} Similar to dogs, urothelial carcinoma is the most common malignant neoplasm in the feline urinary bladder.\textsuperscript{1} History of lower urinary tract disease may be a predisposing factor in the development of urothelial carcinoma in cats.\textsuperscript{17} Clinical signs include classic lower urinary tract signs such as hematuria, stranguria, dysuria, and pollakiuria as well as more nonspecific signs of anorexia, lethargy, and vomiting.\textsuperscript{17} The trigone is the most common location for urothelial carcinoma in both cats and dogs.\textsuperscript{17,18} Microscopically, feline urothelial carcinomas are most frequently characterized as high grade with invasive behavior, comparable to urothelial carcinoma in dogs and humans.\textsuperscript{16} Accordingly, urothelial carcinoma in cats has a similar metastatic potential to dogs with 20\% of cats showing evidence of pulmonary metastases at the time of diagnosis.\textsuperscript{1} Analogous to dogs, medical management with chemotherapeutic agents and COX inhibitors is a common treatment...
strategy for urothelial carcinoma in cats.\textsuperscript{17} Additionally, treatment with partial cystectomy is more frequently pursued because it is reported to have an improved prognosis in cats.\textsuperscript{17} Overall, the prognosis is guarded with median survival times of 46 days for untreated cats, 176 days for cats treated with medical management, and 294 days for cats treated with partial cystectomy.\textsuperscript{17}

Prostatic material from the multiple cavitations filled with a thick, yellow, pasty exudate from the dog reported herein was cultured for suspected prostatitis at necropsy. Bacterial culture yielded low numbers of Escherichia coli, Enterococcus faecium, and Klebsiella pneumoniae colonies. Urinary tract infections occur when the healthy defense of the urinary bladder is altered, and urothelial carcinoma can cause the failure of host barriers, including disruption of urothelial mucosal defenses and systemic immunosuppression. In one report,\textsuperscript{19} 55\% percent of dogs with urothelial carcinoma had positive results for urine bacterial culture, which increased to 75\% with urethral involvement. Escherichia coli was the most common isolate in dogs with urothelial carcinoma.\textsuperscript{19} In this case, given the low yield of mixed bacteria and the absence of histologic lesions of neutrophilic inflammation, postmortem contamination of the culture is considered most likely.

Metastatic urothelial carcinoma should be considered as a differential diagnosis for dogs with multifocal osteolytic lesions in the vertebral bodies and may be associated with spinal cord compression, pathologic fractures, and paralysis. As for the dog in the present report, given the relatively high percentage of neoplastic cells exhibiting immunoreactivity for uroplakin III, a diagnosis of urothelial carcinoma was favored in this case. Immunohistochemical staining for prostate-specific antigen and prostate-specific membrane antigen could also be performed to further evaluate the neoplasm for prostatic origin.\textsuperscript{1} However, the distinction between urothelial carcinoma and prostatic carcinoma using solely immunohistochemistry is challenging. Healthy urethral luminal epithelium has been reported to show variable prostate-specific membrane antigen immunoreactivity and strong prostate-specific antigen immunoreactivity; therefore, the efficacy of these markers in distinguishing between urethral and prostatic origin remains uncertain.\textsuperscript{20} Further research is needed to establish an immunohistochemical panel to help differentiate the origin of these tumors.

References