Pathology in Practice

In cooperation with

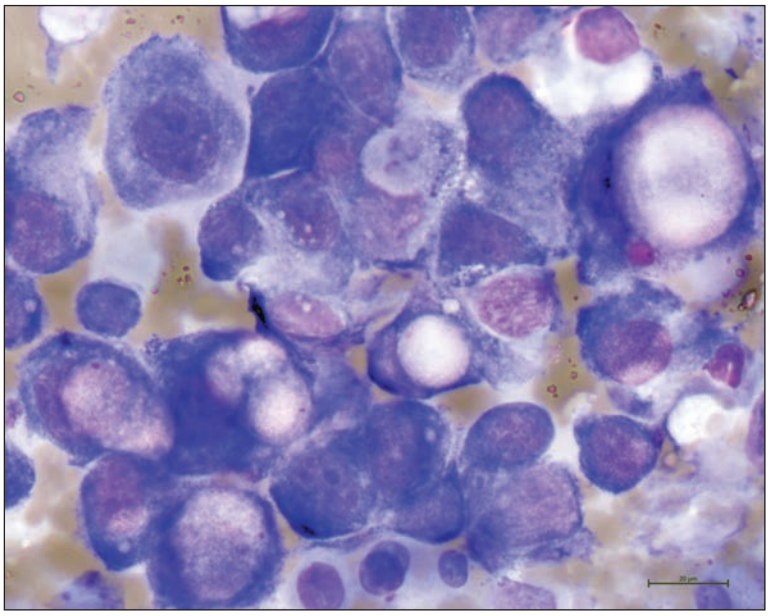

Figure 1—Photomicrograph of a smear preparation from a splenic aspirate specimen collected from a dog that was evaluated because of urinary tract obstruction. Multiple splenic nodules were identified on abdominal ultrasonography. Notice the cluster of epithelial cells, many of which contain large colorless to pink intracytoplasmic vacuoles. Wright-Giemsa stain; bar = 20 µm.

History

A 12-year-old 15.5-kg (34.1-lb) spayed female English Springer Spaniel was referred for evaluation of a urinary tract obstruction. The dog was initially evaluated by a referring veterinarian because of signs of constipation. On physical examination, the referring veterinarian palpated a severely distended, turgid urinary bladder. Abdominal radiography and ultrasonography revealed an enlarged urinary bladder with no evidence of cystoliths. At that time, a handheld blood analyzer[a] revealed high concentrations of BUN, creatinine, and potassium. Because the urinary bladder could not be expressed and a catheterization attempt failed, the dog was referred.

Clinical and Clinicopathologic Findings

At the referral evaluation, physical examination findings included a low body condition score (2 on a scale from 1 to 9), dehydration (8% to 10%), and tachycardia (180 beats/min). Abdominal palpation revealed marked caudal abdominal distension and a markedly turgid urinary bladder; palpation of the bladder elicited signs of pain. A CBC revealed neutrophilia. Serum biochemical analysis revealed high SUN concentration, high creatinine concentration, hyperglycemia, and hyperkalemia. Urinary catheterization was performed, and urinalysis revealed a urine specific gravity of 1.035. The urine sample contained a large amount of blood (> 500 RBCs/hpf; reference range, 0 to 5 RBCs/hpf), 5 to 10 WBCs/hpf (reference range, 0 to 5 WBCs/hpf), and 5 to 10 epithelial cells/hpf (reference range, 0 to 5 epithelial cells/hpf) as well as 3+ protein on dipstick analysis (scale of 0 to 4+). All other dipstick analysis results were negative. Rare fine granular casts were observed. Epithelial cells observed during urine sediment examination were uniform in appearance.

Thoracic radiography revealed bronchial mineralization with a diffuse bronchial pattern, a spinous process cyst of the eighth thoracic vertebra, multiple chronic rib fractures, moderate degenerative changes of the elbow joint and vertebral column, probable pleural thickening, and vascular mineralization. Abdominal ultrasonography revealed pronounced medial iliac lymphadenopathy; caudal abdominal peritonitis with scant peritoneal effusion; a large, striated, avascular structure within the urinary bladder (probable hematoma); multiple splenic nodules; and a single hyperechoic nodule in the left side of the liver. The urinary bladder wall was thickened, but there was no ultrasonographic evidence of a urinary mass. Fine-needle aspirate specimens were collected from the splenic nodules (**Figure 1**) and medial iliac lymph nodes.

Formulate differential diagnoses from the history, clinical findings, and Figure 1—then turn the page →

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Cytologic Findings

The fine-needle aspiration specimens collected from the dog's splenic nodules and medial iliac lymph nodes at the time of the initial referral evaluation were stained with Wright-Giemsa stain. The splenic nodules were of high cellularity; there were many large clusters of and individualized round to polygonal cells with a large, round to oval to irregular nucleus; single to multiple, round to irregular, prominent, dark blue nucleoli; open chromatin; and a moderate amount of deeply basophilic cytoplasm (Figure 1). The cells had moderate to marked anisocytosis and anisokaryosis with frequent bi- and multinucleation. Frequently, the cells contained large eosinophilic, vacuole-like inclusions within their cytoplasm. Rare mitotic figures were present. Rare small lymphocytes were scattered in the background in proportion to the degree of hemodilution, but a robust lymphoid population was not observed. The lymph node specimens were of high cellularity; the cell population was similar to that in the splenic nodules, but no lymphoid tissue was evident. Follow-up with biopsy of any affected lymph nodes and histologic evaluation of a biopsy specimen was recommended. Owing to the extensive lesions and declining condition of the dog, the owners elected euthanasia by means of IV injection with pentobarbital sodium with phenytoin and consented to a complete postmortem evaluation.

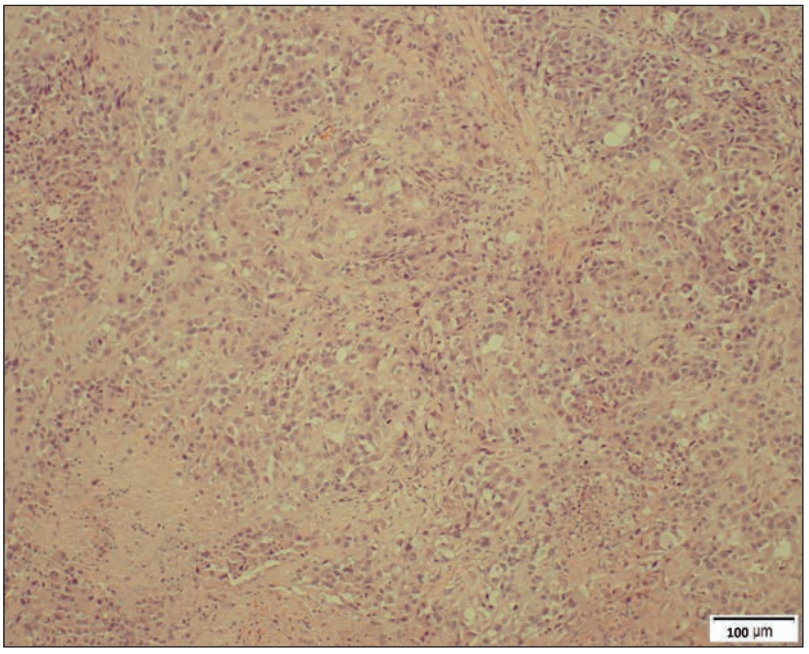

Figure 2—Photomicrograph of a section of urethra obtained from the dog in Figure 1 after euthanasia. The neoplastic mass contains trabeculae and islands of atypical urothelial cells, supported by a coarse, fibrovascular stroma. H&E stain; bar = 100 µm.

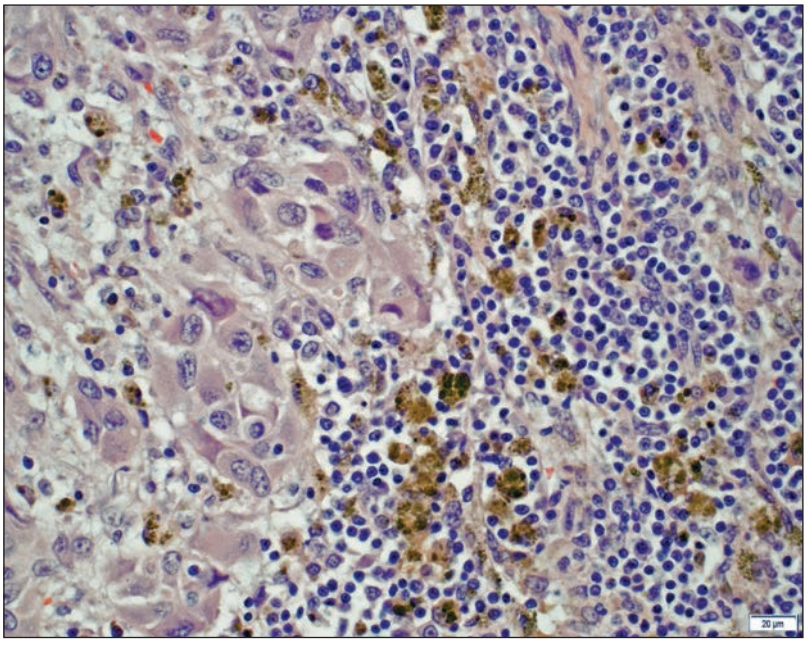

Figure 3—Photomicrograph of a section of medial iliac lymph node obtained from the dog in Figure 1. Normal lymph tissue (right) is infiltrated by atypical epithelial cells. Numerous extra- and intracellular aggregates of yellow-brown material consistent with hemosiderin and hemosiderin-laden macrophages are also present. H&E stain; bar = 20 µm.

Gross and Histopathologic Findings

Postmortem examination revealed a markedly thickened (0.3 to 0.6 cm) and irregular urethra, 3 markedly enlarged medial iliac lymph nodes (ranging from 3.0 × 3.0 × 2.0 cm to 4.0 × 4.0 × 3.0 cm), and scattered tan to dark red, unencapsulated, well-demarcated, 0.5- to 1-cm nodules throughout the spleen. Histologic examination of postmortem tissue samples collected from the urethra (**Figure 2**) and medial iliac lymph nodes (**Figure 3**) revealed an unencapsulated, infiltrative, moderately cellular neoplasm composed of atypical pseudostratified urothelial cells. The neoplastic cells were arranged in solid trabeculae and islands supported by coarse stroma. The urothelial cells had well-defined cell borders with moderate amounts of granular to foamy basophilic cytoplasm surrounding an oval to round nucleus. Nuclei contained finely stippled chromatin and 1 to 2 prominent nucleoli. Moderate anisocytosis and anisokaryosis were noted, with occasional karyomegalic cells and 12 mitotic figures/10 hpfs.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis and case summary: transitional cell carcinoma (TCC) with metastasis to medial iliac lymph nodes and spleen in a dog.

Comments

Transitional cell carcinoma is the most common of all lower urinary tract tumors in dogs and accounts for up to 90% of all canine urinary bladder tu-

mors and 1.5% to 2% of cancers in dogs overall.[1,2] These tumors are most commonly located in the trigone of the urinary bladder with or without secondary urethral involvement. On the other hand, primary neoplasia of the urethra is rare. In dogs, there is a predilection for TCC in older females (mean age, 10.4 years), and predisposed breeds include the Scottish Terrier, Shetland Sheepdog, and Beagle.[1,3] Metastasis to the regional lymph nodes or more distant sites occurs in only 33% of cases of urethral TCC, with regional lymph nodes being the most common sites.[4] Other common sites of metastasis include the liver and lungs.[5]

In dogs, hematuria and stranguria are the most common clinical signs reported in association with TCC. These are nonspecific findings, and other urinary tract disorders must be excluded. Lameness caused by bone metastasis or hypertrophic osteopathy is less commonly reported.[2] Urinary tract signs can be apparent for months and may even temporarily resolve with administration of antimicrobials. Physical examination may reveal urethral or bladder thickening, iliac lymph node enlargement, or a mass in the urinary bladder.

Histopathologic findings are required for definitive diagnosis, and TCC does have some distinct cytologic features. In addition to markedly pleomorphic transitional epithelial cells, TCCs often have characteristic colorless to eosinophilic cytoplasmic inclusions.[6] These inclusions have been described for TCCs in humans, and in human medicine they are known as Melamed-Wolinska bodies. Their clinical importance is unknown, but they are found within degenerating urothelial cells. Typically, they are seen as single to multiple, round to oval, red or green-blue cytoplasmic inclusions of various sizes. Their contents remain unknown, with some researchers suggesting they contain mucopolysaccharides and others suggesting that they are lysosomes enlarged owing to cellular degeneration. In human medicine, it is reported that Melamed-Wolinska bodies outside the urinary tract should raise suspicion of metastatic TCC.[7]

The case described in this report was particularly unusual because of the involvement of the spleen. Differential diagnoses for splenic nodules, in general, include fibrohistiocytic nodules, lymphoid hyperplasia, extramedullary hematopoiesis, and primary or metastatic neoplasia. The most common neoplasms to involve or metastasize to the spleen in dogs include lymphoma, mast cell tumor, histiocytic sarcoma, and hemangiosarcoma. Although carcinomas have been reported to metastasize to the spleen as well, it is an uncommon phenomenon; in a 2003 study[8] of 50 dogs with TCC, only 4% had splenic involvement.

In dogs, TCC is often refractory to treatment, and long-term survival rates are poor; however, several treatments have been identified that lead to remission or static disease for several months with excellent quality of life. Surgical intervention can be considered for tumor debulking, especially if the TCC is in a nontrigonal location, or for reestablishment of urine flow in oliguric or anuric patients. Ureteral stents can be placed in an attempt to increase the probability of short-term survival. Radiation therapy has also been used on a limited basis in the treatment of dogs with TCC. In 1 report, 1 of 7 dogs treated with radiation intraoperatively was alive after 1 year. In another report[5] of 13 dogs with TCC, 9 were still alive after 1 year, and 3 were still alive after 2 years; however, complications such as urinary incontinence detracted from quality of life.

Systemic medical treatment is the backbone of TCC treatment. Medical treatment typically involves the use of chemotherapy, cyclooxygenase inhibitors, and combinations of these drugs. By taking initial measurements of the tumors and changing treatment protocols as the disease progresses, tumor growth can be controlled in approximately 75% of dogs. Their quality of life is frequently very good, and median survival times have been reported to be as much as a year or longer.[5]

Despite the treatments currently available, most dogs with TCC still ultimately die as a result of the disease. World Health Organization TNM staging guidelines, wherein cancer stage is classified on the basis of size of the original tumor (T), involvement of regional lymph nodes (N), and metastasis to distant sites (M), can be helpful in predicting survival time of affected dogs. Factors associated with a more advanced stage of TCC and decreased survival time include younger age, prostatic involvement, and larger size and greater invasiveness of the primary tumor.[5] Although the case described in the present report involved an older dog with no evidence of a large primary tumor, euthanasia was elected given the poor prognosis associated with distant metastasis.

a. i-STAT, Abbott Laboratories, Abbott Park, Ill.

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