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Pathology in Practice

Catherine J. Benson, DVM, Amber T. Stiller, DVM, Erin E. Corbin, DVM, Adrienne Schucker, DVM, and Davis M. Seelig, DVM, PhD

Departments of Veterinary Clinical Sciences (Benson, Stiller, Corbin, Seelig) and Veterinary Population Medicine (Schucker), College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108.

History

A 3.75-year-old 20-kg (44-lb) neutered male Standard Poodle was evaluated because of lethargy, decreased appetite of 2 weeks' duration, and 1 episode of vomiting. The dog was noted to have lost 5 kg (11 lb) during the preceding 6 months.

Clinical Findings

On physical examination, the dog's mucous membranes were hyperemic, with a prolonged capillary refill time of 3 seconds. The dog was hyperthermic (40.0°C [104°F]) and had a body condition score of 2 of 9. The dog had a grade 3 of 6 left basilar systolic heart murmur, and signs of pain were elicited on palpation of the thoracolumbar vertebral column and the abdomen ventral to that region.

A CBC revealed marked leukocytosis (WBC count, 127.10×10^3 WBCs/ μ L; reference interval, 3.88×10^3 WBCs/ μ L to 14.57×10^3 WBCs/ μ L) characterized by neutrophilia (114.39×10^3 neutrophils/ μ L; reference interval, 2.1×10^3 neutrophils/ μ L to 11.2×10^3 neutrophils/ μ L), lymphocytosis (6.36×10^3 lymphocytes/L; reference interval, 0.78×10^3 lymphocytes/ μ L to 3.36×10^3 lymphocytes/ μ L), and monocytosis (6.36×10^3 monocytes/ μ L; reference interval, 0 monocytes/ μ L to 1.2×10^3 monocytes/ μ L), and an absence of band neutrophils. The abnormal hematologic findings included mild microcytic nonregenerative anemia and moderate thrombocytopenia. Microscopic examination of a peripheral blood smear revealed mildly low RBC density, markedly high WBC density (predominantly neutrophils, some with mild toxic change), and moderately to markedly low platelet density. There was mild anisocytosis and mild polychromasia with low numbers of codocytes, occasional reactive lymphocytes, and macroplatelets. Serum biochemical abnormalities included hypoalbuminemia, hyperglobulinemia, high alkaline phosphatase activity, and hypercholesterolemia. In a urine sample (collected via cystocentesis), specific gravity was 1.026 and proteinuria (2+ [dipstick test]) was detected; urine sediment contained some WBCs.

Address correspondence to Dr. Benson (amourdvm@gmail.com).

Dr. Benson's present address is IDEXX Laboratories, Unit 20, 38–46 South St, Rydalmere, NSW 2116, Australia.

Dr. Stiller's present address is VCA SouthPaws Veterinary Specialists and Emergency Center, 8500 Arlington Blvd, Fairfax, VA 22031.

Abdominal ultrasonography revealed a 5-cm-diameter mass arising from the cranioventral aspect of the left kidney and minimal pyelectasia. The mass appeared solid with mixed echogenicity and was well vascularized. Radiographic views of the thorax and vertebral column were considered normal. Ultrasound-guided fine-needle aspirate samples of the left kidney were obtained and stained with modified Wright-Giemsa stain (Figure 1). The samples were highly cellular and consisted of moderate numbers of clusters of epithelial cells, numerous inflammatory cells, and moderate numbers of RBCs. Epithelial cells were polygonal to slightly elongate, with a moderate amount of vacuolated basophilic cytoplasm and a single round nucleus that had finely stippled chromatin and a single nucleolus. Mild to moderate anisocytosis and anisokaryosis were noted, and mitotic figures were rare. Within the background were numerous neutrophils and fewer cytophagic macrophages, with small amounts of cellular debris.

Additional Gross and Clinicopathologic Findings

Left unilateral nephrectomy was performed following the cytologic evaluation of the renal aspirate samples. The left kidney was partially effaced by a $4.0 \times 4.2 \times 2.5$ -cm round, red to tan, slightly firm, bulging mass. On section, the mass was well demarcated and extended from the renal capsule through the cortex and compressed the medulla and renal pelvis (Figure 2). No other abnormalities were apparent during surgery.

Five weeks following nephrectomy, a CBC was repeated. The dog's leukocytosis (11.39×10^3 leukocytes/ μL) and neutrophilia (7.4×10^3 neutrophils/ μL) had resolved. Mild eosinophilia was present (1.59×10^3 eosinophils/ μL).

Histopathologic Findings

Examination of H&E-stained sections (Figure 3) from the extirpated kidney revealed a highly cellular, unencapsulated, well-demarcated, and compressive neoplasm extending from the renal capsule to the renal calyx. The mass consisted of dense lobules, tubules, acini, and rare papillary projections of epithelial cells on a fine fibrovascular stroma with occasional dense bands of fibrocollagenous connective tissue. Neoplastic tubules and acini were defined by a single cell layer or multiple cell layers. The neoplastic cells were cuboidal and contained moderate to large amounts of highly vacuolated lightly eosinophilic cytoplasm. Neoplastic nuclei were round to oval and had finely stippled chromatin and 1 to 4 nucleoli. Moderate to marked anisocytosis and anisokaryosis were evident, with frequent binucleation and occasional multinucleation of cells; the mitotic index varied from 0 to 6 mitotic figures/hpf. Multifocal areas of coagulative necrosis, hemorrhage, and low numbers of mixed inflammatory cells were present within the mass. Within rare medium-caliber blood vessels adjacent to the mass, small clusters of neoplastic epithelial cells (intravascular invasion) were observed.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis and case summary: renal adenocarcinoma (solid and tubular, clear cell type) with intravascular invasion and paraneoplastic leukocytosis in a dog.

Comments

In the case described in the present report, the final diagnosis of renal carcinoma with secondary paraneoplastic leukocytosis was made on the basis of the cytologic findings for the evaluated fine-needle aspirates, pre- and postoperative CBC data, ultrasonographic findings, and results of histologic evaluation. Although a confident cytologic diagnosis of primary renal carcinoma can be difficult, particularly because of the cytomorphologic overlap with renal nephroblastoma, round cell neoplasia, or metastatic neuroendocrine neoplasia, the consistent finding of cohesive clusters of neoplastic cells was convincing. Owing to this diagnostic difficulty, histologic evaluation of the extirpated kidney was recommended; histopathologic findings confirmed the original cytologic interpretation in this case.

Primary renal tumors are rare in dogs, with a reported incidence of 0.3% to 1.7%.¹ A study² of 464 canine primary renal tumors revealed that the vast majority (91%) are malignant and that most (76%) are epithelial. Histologically, canine renal adenocarcinomas can be classified as papillary, tubular, and solid types, although there does not appear to be prognostic value associated with this classification scheme.³ Median reported survival time for dogs with renal carcinomas is 16 months (range, 0 to 59 months); surgery and chemotherapy are recommended because they have been shown to prolong survival time.⁴ Following the nephrectomy, the dog of the present report had complete resolution of clinical signs and gained 1.2 kg (2.64 lb) during a 6-week period following surgery. The dog received chemotherapy approximately 6 weeks following surgery, which included piroxicam (0.25 mg/kg [0.114 mg/lb], PO, q 24 h) and toceranib (2.5 mg/kg [1.14 mg/lb], PO, q 48 h). Follow-up with the owner and referring veterinarian revealed that the dog received toceranib for a couple of weeks and received piroxicam until it was euthanized approximately 6 months after nephrectomy owing to recurrence of signs of pain and the clinical concern for possible recurrence of carcinoma.

Paraneoplastic leukocytosis or a leukemoid response (defined as 50×10^3 WBCs/ μ L) is most often characterized by marked neutrophilia with a left shift and monocytosis,^{5,6} although there are rare reports of eosinophilic leukocytosis.⁷ In the absence of strict criteria, the diagnosis of paraneoplastic leukocytosis, in both veterinary and human medicine, can be a diagnostic dilemma necessitating the exclusion of inflammation, infection, myeloproliferative disease, treatment-related causes, and leukocyte adhesion disorders. For the dog of this report, infectious, inflammatory, and treatment-related processes were excluded on the basis of the radiographic and ultrasonographic findings and the absence of supporting clinical evidence. In addition, there was no history of exogenous corticosteroid or growth factor administration, excluding these treatments as causes for the leukemoid response. The strongest support for a paraneoplastic origin of the leukemoid response was complete resolution of the dog's leukocytosis and neutrophilia at 5 weeks following nephrectomy. Mild eosinophilia was present at that time. Although concentrations of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor were not measured, the paraneoplastic leukemoid response is thought to be a consequence of the elaboration of granulocyte colony-stimulating factor or granulocyte-

macrophage colony-stimulating factor by tumor cells; central necrosis and inflammation of rapidly growing tumors may also contribute.⁶

Renal carcinomas with paraneoplastic leukocytosis in dogs, albeit uncommon, have been described,^{4,5,8} and findings for the dog of the present report were similar. In addition to renal carcinomas, Patterino et al⁵ have reported various tumor types including renal and pulmonary carcinomas, sarcomas, reproductive tumors, and round cell tumors in association with possible paraneoplastic leukocytosis. In the study by Bryan et al⁴ on primary renal neoplasia in 82 dogs, the most common hematologic abnormalities were neutrophilia (22/63), anemia (21/64), and thrombocytopenia (6/68). In addition to leukocytosis, there are other paraneoplastic syndromes reported for dogs with renal carcinomas, including hypertrophic osteopathy,^{8,9} hypoglycemia,¹⁰ and polycythemia,¹¹ although these were not observed in the dog of the present report. The cause of the dog's resolved thrombocytopenia remains uncertain, although we favor disseminated intravascular coagulation or a paraneoplastic process as the leading differential diagnosis.

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Figure 1. Photomicrographs of fine-needle aspirate samples from the left kidney of a 3.75-year-old neutered male Standard Poodle that had a history of lethargy, decreased appetite of 2 weeks' duration, 1 episode of vomiting, and weight loss (during the preceding 6 months). A—Clusters of neoplastic renal epithelial cells, numerous inflammatory cells, and moderate numbers of RBCs are evident. Modified Wright-Giemsa stain; bar = 100 µm. B—Higher-magnification image of a cluster of neoplastic renal epithelial cells that have mild to moderate anisocytosis and anisokaryosis; notice the prominent nondegenerate neutrophils. Modified Wright-Giemsa stain; bar = 20 µm.

Figure 2.
Photograph of the cut surfaces of the left kidney that was removed from the dog in Figure 1.
A well-demarcated mass extends from the renal capsule through the cortex and compresses the medulla and renal pelvis.

Figure 3.

Photomicrographs of sections from the left kidney that was removed from the dog in Figure 1. A—Section in which tubular and papillary projections are evident. H&E stain; bar = 200 µm. B—Another section in which more solid portions of tissue have occasional tubules and acini formations of epithelial cells. H&E stain; bar = 100 µm. C—Higher-magnification image of neoplastic renal epithelial cells that have highly vacuolated lightly eosinophilic cytoplasm and occasionally marked criteria of malignancy. H&E stain; bar = 20 µm. D—Section containing a medium-caliber blood vessel in which small foci of neoplastic cells (intravascular invasion) are present. H&E stain; bar = 50 µm.