Renal Nephroblastoma in the Canine Patient

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Introduction

Primary renal tumors account for approximately 2% of all canine cancers.[11] Tissues of origin include the renal epithelium, renal mesenchyme or embryonal tissue of mixed origin.[1] Roughly 10% of primary renal tumors originate from embryonal pluripotential blastema, which include Wilms' tumor, nephroblastoma, and embryonal nephroma.[11] The majority of diagnosed renal tumors occur in older dogs; however, nephroblastoma is unique in that it is seen in juveniles. The mean age for diagnosis of nephroblastoma is 5.2 years, but they have been diagnosed in dogs as young as 1 year and as old as 12 years.[1] Nephroblastomas are usually malignant but can be benign.[8] They are most commonly unilateral and have a lower metastatic rate than other primary renal tumors. Nephrectomy is the treatment of choice for unilateral renal tumors that have not metastasized, and it may be curative for some cases of nephroblastoma.[11]

History and Presentation

Clinical signs of nephroblastoma are often non-specific and minimal until the tumor reaches an advanced stage.[2] Typically, the chief complaint by owners includes one or more of the following: hematuria, lethargy, inappetence, abdominal mass, weight loss, vomiting, polyuria/polydipsia, abdominal pain or discomfort, or behavior changes.[1, 3, 5, 8] In some cases acute collapse and anemia can be included in the presenting complaint.[2] Bone metastasis or hypertrophic osteopathy is uncommon but has been reported in one dog at the University of Tennessee College of Veterinary Medicine Teaching Hospital.[8] Extensive metastasis to the liver and lung occur in more than 50% of the canine cases.[4]

Ectopic nephroblastomas of the spinal cord in dogs have been reported, but they typically occur independent from primary renal nephroblastomas.[10] Nephroblastomas reported in the

spinal cord are believed to have originated from renal progenitors that are trapped in the intradural and extramedullary space during development.[10] These tumors are primarily seen at the 10th thoracic vertebrae to the 2nd lumbar vertebrae but are not limited to these locations. They can manifest in intradural, extramedullary or intramedullary locations.[3] These tumors have been identified in mixed-breed dogs, and no longer is one breed overrepresented; however, ectopic nephroblastomas of the spinal cord were once thought to be most prevalent in German Shepherd Dogs.

Pathophysiology

The 5th most common pediatric malignancy in humans is nephroblastoma, or Wilms' tumor.[8] Although the exact pathophysiology is not completely understood in the canine patient, it is suggested that canine nephroblastomas share a similar pathogenesis and histogenesis to the Wilms' tumor in humans.[4] They originate from primitive nephrogenic blastema, one of the two embryologic structures that give rise to the kidney, and from foci of renal dysplasia during development. [4] Nephroblastoma has been reported in tissues other than the kidney, such as the spine and bone marrow. It is suggested that this tumor originates from the pluripotential mesenchyme of the metanephron due to the presence of tissues that are usually not associated with the kidney.[4] These tissues include skeletal muscle and cartilage.[4] The tumor will mimic various stages of nephrogenesis, which indicates abnormal differentiation of the metanephric blastema.[7]

Differential Diagnoses

With non-specific clinical signs and physical examination findings that are consistent with an abdominal mass (with or without pain upon palpation), consideration should be given to

splenic mass, hepatic mass, renal mass, mass in the bladder, hydronephrosis, abdominal trauma or coagulopathy with peritoneal or retroperitoneal bleeding.[2] Once the location of the mass is determined to be in the region of the kidney via radiographs and ultrasonographic evaluation, renal carcinoma, renal sarcoma, and hemangiosarcoma are considered; however, these tumors typically occur in older dogs.

Diagnostic Approach/Considerations

A thorough physical examination should be performed after obtaining a complete history. Diagnostic approach should then include a complete blood count, serum chemistry profile and urinalysis. The complete blood count may reveal anemia secondary to hematuria, neutrophilia as a response to stress or infection, and thrombocytopenia due to blood loss or a paraneoplastic syndrome.[1] The serum chemistry profile abnormality most commonly reported is azotemia and possibly hypoproteinemia, but abnormalities are often non-specific.[9] Urinalysis results often include evidence of hematuria and proteinuria.[9]

Abdominal radiographs should be performed to verify evidence of the suspect abdominal mass, and loss of serosal detail could also indicate ascites. Three-view thoracic radiographs are also performed at this time to rule out pulmonary and intra-thoracic lymph node metastasis. Pulmonary metastases are most commonly reported, but other sites reported include lymph nodes, liver, bone, serosal surfaces, ipsilateral adrenal gland, contralateral kidney, brain, heart and skin.[1,3,9] Depending on whether or not disseminated intravascular coagulation is suspected, prothrombin time and partial thromboplastin time should be measured.[2] Abdominal ultrasound will aid in determining the origin of the mass and confirm the presence of fluid in the abdomen, if suspected from abdominal radiographs.

Definitive diagnosis is made on histopathology via needle-core biopsy, nephrectomy, or at post-mortem examination. Histologic diagnosis relies on the triphasic appearance of the mass with the presence of epithelial, mesenchymal, and blastemal components characteristic of nephroblastoma.[5] WT1 is a protein that is aberrantly expressed in nephroblastomas.[5] Biopsy specimens can be stained with an immunohistochemical stain for WT1 to confirm the diagnosis of nephroblastoma.[5]

Treatment and Management

Nephrectomy is considered the treatment of choice for unilateral renal nephroblastoma.[9] Prior to anesthesia, the patient should be stabilized as much as possible and the function of the contralateral kidney should be assessed. Patient stabilization varies case by case and may include the correction of dehydration with crystalloid fluid therapy, analgesics to control pain, blood transfusion if there has been significant blood loss, and anti-emetics. The tumor is usually contained within the renal capsule, but invasion of the caudal vena cava, adrenal gland, musculature in the lumbar region and renal vein is sometimes present.[9] Although there is no evidence of the efficacy of chemotherapy against nephroblastoma in dogs, it is a part of the standard protocol for nephroblastoma in humans along with nephrectomy and radiation therapy. [9]

The primary chemotherapeutic protocol in humans includes vincristine and actinomycin D, but in several dogs, doxorubicin was used instead of actinomycin D.[8] This protocol was preferred due to the greater efficacy and familiarity in veterinary oncology of doxorubicin than actinomycin D in the treatment of lymphoma in canine patients.[8] The degree of tissue differentiation of renal nephroblastoma in humans (into blastemal, epithelia, or stromal tissue)

may directly correlate to the response to therapy and prognosis. In other words, if the tumor is more differentiated, the prognosis and response to therapy is better.[3]

Case Outcome/Prognosis

The prognosis for renal neoplasia in general is poor; however, for nephroblastoma, the prognosis may be slightly better than for carcinomas and sarcomas.[9] At the time of death, 75% of dogs with nephroblastomas had metastases present.[11] The National Wilms' Tumor Study Group (NWTSG) has created a staging system for renal tumors based on favorable or aggressive histopathology.

Table 1. Humans' Wilms' tumor (nephroblastoma) grading[a]

Stage I	Tumor confined to the kidney, completely removed without rupture; vessels of the renal sinus are not involved; no tumor evidence at or beyond the margins of resection
Stage II	Tumor extends beyond the kidney but is completely excised without tumor evidence at or beyond the margins of resection
Stage III	Tumor not completely excised with extension confined to the abdomen
Stage IV	Hematogenous metastasis or metastasis to distant lymph nodes outside the abdominopelvic region
Stage V	Bilateral kidney involvement at the time of diagnosis
Histopathological classification	Favorable: no evidence of anaplasia Unfavorable: evidence of anaplasia or sarcomatous component

[a] From National Wilms' Tumor Study Group (NWTSG) Staging System for Renal Tumors[1]

In dogs with Stage I renal nephroblastoma and unfavorable histopathology, it is possible to have a greater than 2 year survival with nephrectomy, doxorubicin and vincristine.[8] Stage I nephroblastoma with favorable histopathology does not warrant chemotherapy.[8] In one case report, a puppy with Stage II disease and favorable histopathology remained disease-free for 19 months with nephrectomy alone.[6] In a study that included eighty-two dogs with primary renal neoplasia, the mean survival time of those with nephroblastoma was 6 months.[1] These dogs

underwent a nephrectomy, and those that were treated with chemotherapy did not live a measurably longer time than those not treated with chemotherapy.[1] Adjuvant chemotherapy may play a role in the management of these tumors, but currently there is not enough evidence to support the benefit of chemotherapy.[1]

Summary

Renal nephroblastomas are rare tumors in dogs. They are unique in that they are usually diagnosed in younger dogs, but they have been reported in dogs as old as twelve.[1] They are commonly unilateral and malignant. The metastatic rate of nephroblastoma is less than that of other primary renal tumors. The most common locations of metastasis are the liver and lungs.[1,4] The clinical signs are often vague until the tumor has progressed to an advanced stage. Nephrectomy is the treatment of choice and can be followed by chemotherapy depending on the level of metastasis; however, there is no concrete evidence demonstrating that chemotherapy improves outcome.[1] The prognosis is poor for primary renal neoplasia in general but may be slightly better for nephroblastoma. Prognosis is subject to the stage of the disease and the level of metastatic disease.

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