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Clinical Case

Mixed-type renal nephroblastoma in a three-year-old female dog: Case report

Nefroblastoma renal de tipo mixto en un canino hembra de tres años de edad: Reporte de caso

Nefroblastoma renal tipo misto em uma cadela de três anos de idade: Relato de caso

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Abstract

Anamnesis: Renal nephroblastoma is a rare neoplasm in dogs. This case corresponds to a 3-year-old female Golden Retriever who was treated for bilateral abdominal distention and weight loss. **Clinical and laboratory findings:** There were no alterations in the hemogram or blood biochemistry (AST, AP, BUN, and creatinine). Radiographic findings revealed an enlarged left kidney with a cystic center. **Treatment approach:** A median laparotomy was performed; the intestines and spleen were displaced to expose the left kidney, which was then dissected from the abdominal roof, the ureter, renal artery, and vein were ligated and sectioned, and the affected kidney was excised. Macroscopically, it presented a mass of 15 × 10 × 8 cm with a central cavitation of 4 × 5 cm. A Grade II Mixed-type nephroblastoma (SIOP and NWTSG) was diagnosed by histopathology. Immunohistochemistry was performed to confirm the neoplasm and identify proliferating cell portions using cytokeratin AE1-AE3, Pax-8, and WT-1. **Conclusion:** Given the rare presentation of this neoplasm, it is crucial to describe prognostic indicators in dogs with nephroblastoma. In this case, the use of these markers was useful in confirming the diagnosis.

Keywords: *canine; immunohistochemistry; kidney; nephrectomy; nephroblastoma; radiographic findings.*

Resumen

Anamnesis: El nefroblastoma renal es una neoplasia rara en los caninos. Este caso corresponde a un canino hembra, Golden Retriever de 3 años de edad, atendida por distención abdominal bilateral y pérdida de peso. **Hallazgos clínicos y de laboratorio:** El hemograma y la bioquímica sanguíneas no mostraron alteraciones (AST, FA, BUN y creatinina). El hallazgo radiográfico fue un aumento de tamaño del riñón izquierdo, con centro quístico. **Aproximación**

terapéutica: se realizó una laparotomía media, desplazando el bazo y los intestinos para exponer el riñón izquierdo. Posteriormente, este se disecó del techo abdominal, y se ligaron y seccionaron el uréter, la arteria y la vena renales, para luego proceder a la excisión del riñón afectado. Macroscópicamente, este presentó una masa de 15 × 10 × 8 cm con una cavitación central de 4 × 5 cm. En la histopatología, se diagnosticó un nefroblastoma de tipo mixto, grado II (SIOP y NWTSG). Se realizó inmunohistoquímica para confirmar la neoplasia y caracterizar las porciones celulares en proliferación usando citoqueratina AE1-AE3, Pax-8 y WT-1. **Conclusiones:** Dada la rara presentación del nefroblastoma, es muy importante describir indicadores pronósticos en perros. En este caso, el uso de estos marcadores fue útil para confirmar el diagnóstico.

Palabras clave: *canino; hallazgo radiográfico; inmunohistoquímica; nefrectomía; nefroblastoma; riñón.*

Resumo

Anamnese: O nefroblastoma renal é uma neoplasia rara em cães. Este caso corresponde a uma cadela Golden Retriever de 3 anos de idade, tratada devido a distensão abdominal bilateral e perda de peso. **Achados clínicos e laboratoriais:** Não houve alterações no hemograma ou na bioquímica sanguínea (AST, FA, BUN e creatinina). Os achados radiográficos mostraram um rim esquerdo aumentado com centro cístico. **Abordagem e tratamento:** foi realizada laparotomia mediana, com deslocamento dos intestinos e do baço para expor o rim esquerdo, Em seguida este foi dissecado do teto abdominal, e o ureter, a artéria e a veia renais foram ligados e seccionados, permitindo a excisão do rim afetado. Macroscopicamente, apresentava uma massa de 15 × 10 × 8 cm com cavitação central de 4 × 5 cm. A histopatologia diagnosticou um nefroblastoma de tipo misto, grau II (SIOP e NWTSG). A imunohistoquímica foi realizada para confirmar a neoplasia e identificar porções celulares proliferativas usando citoqueratina AE1-AE3, Pax-8 e WT-1. **Conclusão:** Dada a rara apresentação desta neoplasia é muito importante descrever indicadores prognósticos em cães com nefroblastoma. Neste caso, a utilização desses marcadores foi útil para confirmar o diagnóstico.

Palavras-chave: *achado radiográfico; canino, imuno-histoquímica; nefrectomia; nefroblastoma; rim.*

Introduction

Nephroblastoma is a rare neoplasm resulting from poor differentiation of the metanephrogenic blastema (Baskin and De Paoli 1977); in humans, it is known as Wilms tumor (Kaste et al., 2008); These tumors are the most common renal neoplasms in pigs and chickens and are usually recognized as incidental findings at slaughter. They are the second most common primary renal tumor in dogs and occur less frequently in cattle (Zachary, 2022).

Under normal conditions, the differentiation of the metanephrogenic blastema is induced to form an epithelial component, which develops into nephrons, and a stromal component, which constitutes the connective tissue of the kidney (Brown and malik 2001). Nephroblastoma is considered an embryonal cancer of the developing kidney (Pode-Shakked and Dekel, 2011). It is speculated that these neoplasms result from malignant transformation during normal nephrogenesis or from the neoplastic transformation of embryonic tissue remnants that persist postnatally.

At necropsy, nephroblastomas can be solitary or multiple masses that often reach considerable size, obscuring recognizable renal tissue. Because nephroblastomas arise from primitive pluripotent tissue, their histologic features vary but are morphologically similar to the developmental stages of embryonic kidneys. Typically, three components can be identified in various ratios: (1) undifferentiated loose myxomatous mesenchymal tissue, (2) primitive tubules and structures that resemble primitive glomeruli, and (3) scattered nests of cells resembling the metanephric blastema (Zachary, 2022).

The average age of presentation in dogs in a study involving five nephroblastomas was 5.2 years (Bryan et al., 2006); other reports describe this neoplasm in young animals

under six months of age (Baskin and De Paoli, 1977; Montinaro et al., 2013). In humans, it is the most common pediatric renal neoplasia in North America (Kaste et al., 2008). Some cases of extrarenal nephroblastoma have been reported in the spinal cord of dogs (Brewer et al., 2011). Nephroblastoma has also been described in other animal species, such as a renal nephroblastoma in a Buffalo calf (*Bubalus bubalis*) (Rama Devi et al., 2011), in a mare (*Equus caballus*) (Jardine and Nesbit, 1996), in an African hedgehog (*Atelerix albiventris*) (Ueda et al., 2019), and a nasopharyngeal nephroblastoma in a Boer goat (*Capra aegagrus hircus*) (Athey et al., 2020).

The most important clinical signs of canine renal neoplasms include hematuria, lethargy, loss of appetite, a palpable abdominal mass, and polyuria/polydipsia (Bryan et al., 2006). Since it is a rare neoplasm in veterinary medicine, there are no well-established prognostic indicators, and some reports have mentioned that several factors may influence the prognosis (Chen et al., 2018). Histological classification is based on human criteria, using the NWTSG (National Wilms Tumor Study Group) and SIOP (Société Internationale d'Oncologie Pédiatrique) systems (Kaste et al., 2008). The prognosis is variable; recent studies using the NWTSG classification have described some cases with metastases and malignant behavior (Chen et al., 2018); while others reported a good prognosis after surgery, especially in low-grade tumors (Hergt et al., 2019; Richardson 2020; Seaman et al., 2003) In dogs with renal neoplasms, surgery is the only treatment that improves survival (Bryan et al., 2006).

Case presentation

Anamnesis

A 3-year-old Golden Retriever, weighing 30 kg, was presented for consultation due to severe bilateral abdominal distention with progressive weight loss.

Clinical findings

During the clinical examination, an abdominal mass was palpated. The mass had a firm consistency and was adhered to the abdominal roof.

Diagnostic aids used

There were no alterations in the hemogram or blood biochemistry, specifically aspartate aminotransferase (AST), alkaline phosphatase (AP), blood urea nitrogen (BUN), and creatinine. Radiographic findings revealed enlargement of the left kidney, which exhibited greater radiopacity compared to the normal parenchyma, while its central portion had a radiolucent cystic appearance measuring approximately 3 × 4 cm (Figure 1). An abdominal ultrasound study was performed (Mindray BC56 ultrasound machine) using a 5MHz micro-convex transducer. The kidney showed an abnormal architecture with a heterogenous echo-texture and a 4 cm diameter cavity in the caudal portion of the renal parenchyma.

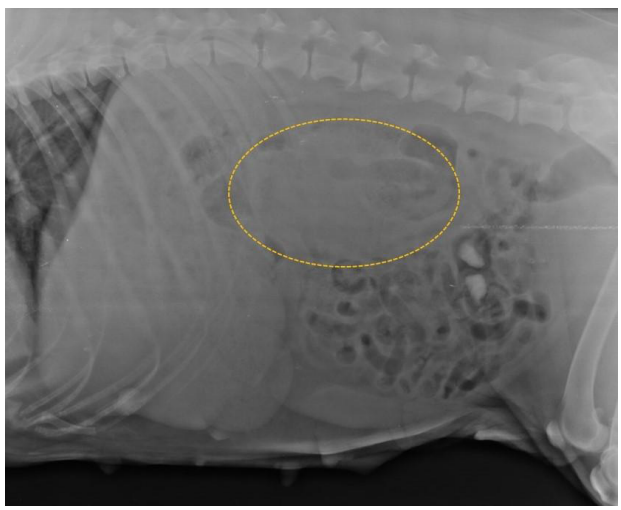

Figure 1. Left lateral X-ray showing the marked size increase of the left kidney (orange arrows) with displacement of intestines and stomach.

Treatment approach

The affected kidney was excised via median laparotomy. The intestines and spleen were displaced to expose the left kidney, which was then dissected from the abdominal roof. The ureter, renal artery, and vein were ligated and sectioned before removing the kidney.

Macroscopic examination of the left kidney revealed a mass measuring 15 × 10 × 8 cm. On longitudinal sectioning, it presented a central cavitation of 4 × 5 cm with yellow serous fluid. The mass had a hard consistency and was whitish with a few reddish foci smaller than 1 cm (Figure 2).

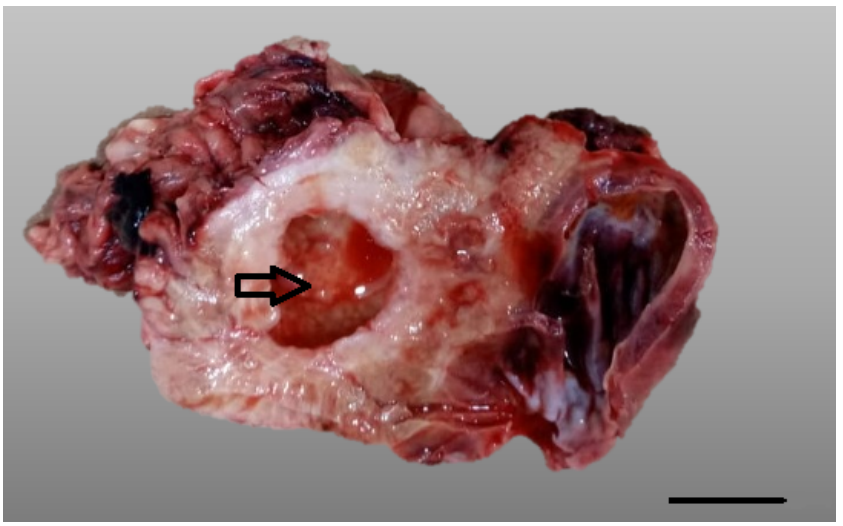

Figure 2. Section of the left kidney in which a 3 × 4 cm cavitation is evidenced (black arrow), and deformation is observed with respect to normal parenchyma. Bar 3 cm.

Histopathology.

Histopathology revealed a mixed neoplastic proliferation, with an epithelial component characterized by multiple structures with glomerulus-like morphology. Some of these structures had a small diameter, while others were dilated within Bowman's space (Figure 3). Additionally, several tortuous tubules of small diameter with flattened epithelium were observed. Tissue portions of mesenchymal origin, composed of spindle cell tracts resembling connective tissue, were identified. In some nodular areas, small groups of round cells measuring approximately 10-12 µm in diameter and exhibiting intense basophilic nuclei were observed, corresponding to undifferentiated blastema cells (Figure 4).

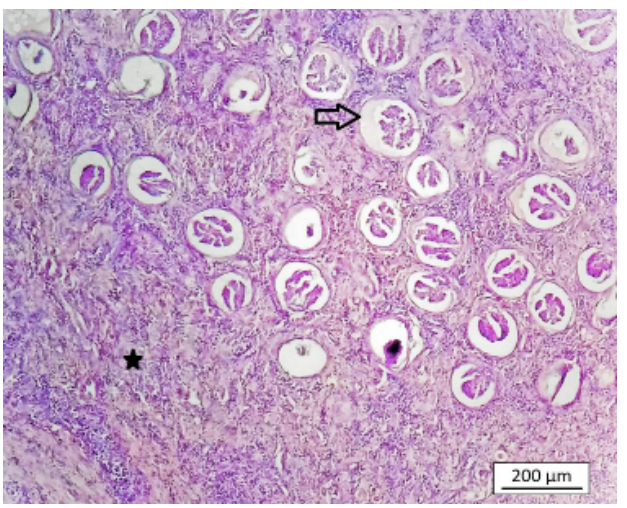

Figure 3. Histopathology H&E. In this neoplasm portion is evident the normal kidney morphology; the glomeruli proliferate (black arrow), separated by connective tissue similar to the portion identified with the asterisk; there are few tubules in this portion. 40x magnification.

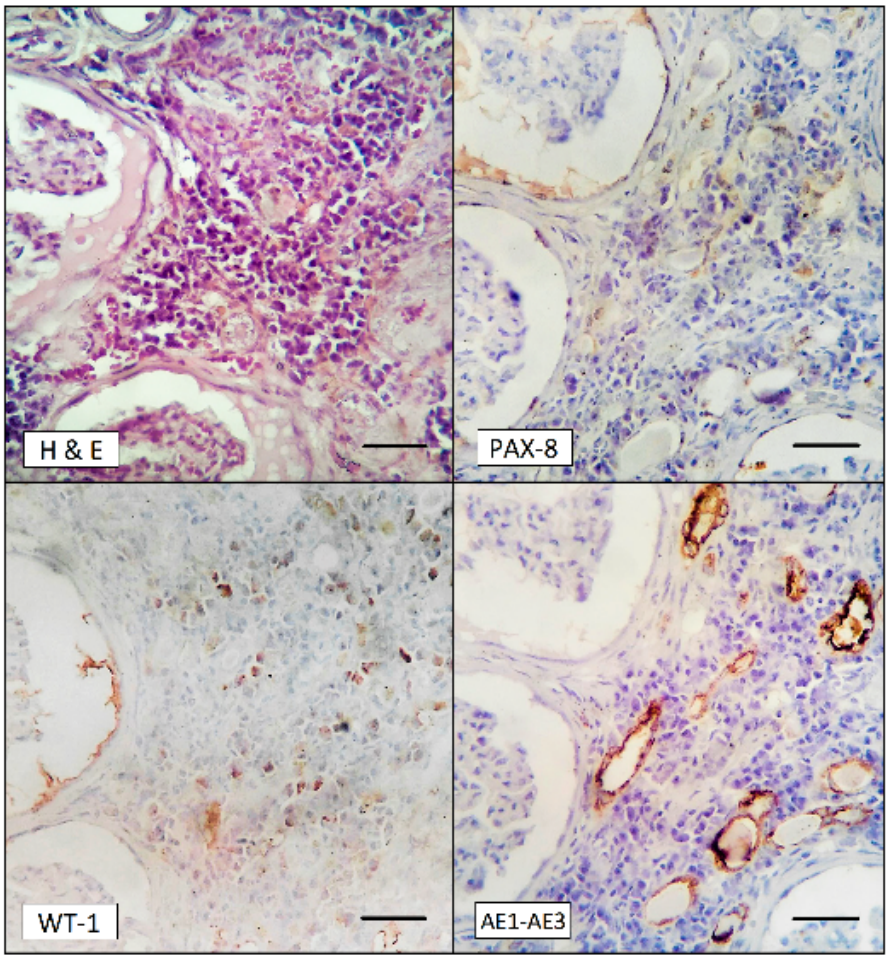

Figure 4. Immunohistochemistry H&E: In this magnification, in the interstitium, the basophilic round-shape blastema cells of 10-12 µm in diameter proliferate, with few tortuous and small diameter tubules. Pax-8: shows mild multifocal immunostaining in tubular epithelial cells and blastema cells. WT-1: mild multifocal immunostaining in blastema cells. AE1-AE3: severe multifocal immunostaining in renal tubule epithelial cells. Bar 50 µm.

Immunohistochemistry

Immunohistochemistry was performed using cytokeratin AE1/AE3, PAX-8, and WT-1 in neoplastic tissue. Tissue-block sections of the kidney were processed following antibody supplier recommendations. Briefly, the sections were deparaffinized and rehydrated, then treated with 3% hydrogen peroxide in methanol for 5 minutes to block endogenous peroxidase activity. Tissue sections were incubated for 30 minutes with normal nonimmune serum to reduce nonspecific staining. All reagent incubations were performed at room temperature. Heat-induced epitope retrieval (HIER) was used for all three markers (citrate buffer [pH 6.0] for cytokeratins AE1/AE3 and PAX-8; EDTA buffer [pH 8.0] for WT-1) (Table 1). Immunoreaction visualization was achieved using diaminobenzidine tetrahydrochloride and hydrogen peroxide (0.03% in 50 mM Tris-HCl, pH 7.6) for 10 minutes. Sections were rinsed in tap water, counterstained with hematoxylin, dehydrated through graded alcohol, cleared in xylene, and mounted using DPX.

Table 1. Immunostaining methodology for Cytokeratins (AE1/AE3), PAX8 and WT1 performed on tissue-block sections of kidney.

Antibody	Type Antibody	Dilution	Incubation	Pretreatment	Source Antibody
Cytokeratins (AE1/AE3)	Monoclonal-Mouse	1:100	60 min.	HIER- Buffer citrate-pH 6.0	Dako
WT1	Monoclonal-Mouse	1:100	90 min.	EDTA- Buffer-pH 8.0	Dako
PAX-8	Monoclonal-Mouse	1:100	90 min.	HIER- Buffer citrate-pH 6.0	Sigma -Aldrich

HIER: Heat Induced Epitope Retrieval.

WT-1 showed mild immunostaining in blastema cells and was scarce in epithelial cells. PAX-8 exhibited moderate immunostaining in blastema cells and mild staining in renal tubule cells. Cytokeratin AE1/AE3 demonstrated severe multifocal immunostaining in renal tubule epithelial cells and scarce staining in glomeruli (Figure 4).

Discussion

This case was diagnosed as a mixed-type nephroblastoma based on its morphological characteristics and the use of immunohistochemistry, which identified a triphasic component composed of epithelial, mesenchymal, and blastema-derived cells. Another pattern described in canine nephroblastoma is the blastemal type (Simpson et al., 1992; Chen et al., 2018); other previous reports do not specify the subtype (Montinaro et al., 2013; Araujo et al., 2020; Richardson, 2020). The usual appearance of nephroblastoma in humans is the mixed type, in which the stromal, blastemal, and epithelial portions are proportionally distributed (Al-Hussain and Akhtar, 2014). In humans, other described patterns include epithelial, stromal, regressive, and anaplastic forms (Vujanic, 2009). A major limitation in dogs with nephroblastoma is that its rarity does not allow for correlation between morphological subtype and prognosis (Chen et al., 2018). Additionally, renal neoplasms are uncommon in dogs (Bryan et al., 2006). For these reasons, this type of neoplasm is limited to case reports, and it is not possible to determine a typical age of presentation. Some studies include animals older than five years (Bryan et al., 2006; Araujo et al., 2020), while other reports describe this neoplasm in young animals under six months of age (Baskin and De Paoli, 1977; Montinaro et al., 2013).

In this case, immunohistochemistry was used to confirm the diagnosis due to the rarity of this presentation in dogs and to further characterize the cell types involved in the neoplasm, demonstrating its renal origin. Cytokeratin AE1-AE3 was used because it is valuable in diagnostic pathology; it is classified as a pancytokeratin due to its ability to detect both low- and high-molecular-weight cytokeratins in epithelial cells (Shen et al., 2012). Cytokeratins have been previously used in the diagnosis of nephroblastoma, with expression observed in the epithelial component (Simpson et al., 1992; Chen et al., 2018). In this case, severe immunostaining was observed in renal tubule epithelial cells.

WT-1 is a transcription factor associated with Wilms tumor (nephroblastoma) in humans; it is essential for kidney development (Kreidberg et al., 1993). In spinal nephroblastoma cases in dogs, WT-1 has been previously used, demonstrating immunostaining mainly in blastema cells and occasionally in other cells in nine out of eleven cases (Brewer et al., 2011).

In this case, mild multifocal immunostaining was observed in blastema cells, supporting the usefulness of this marker in nephroblastoma in dogs. PAX-8 and PAX-2 are transcription factors involved in embryonic kidney development (Lechner and Dressler, 1997). In this case, PAX-8 immunostaining was mild and multifocal, primarily in epithelial and blastema cells. This marker has been previously used in dogs with renal cell carcinoma, showing immunostaining in up to 98% of reviewed cases (Peat et al., 2017), and has also proven useful for detecting nephroblastoma (Chen et al., 2018).

Based on the SIOP classification, this case was classified as grade II (intermediate risk); similarly, in the NWTSG classification, it also corresponds to grade II. In humans, complete tumor resection under this classification is associated with a good prognosis, even when chemotherapy is administered for a short period (Kaste et al., 2008). In dogs with nephroblastoma, no clear correlation has been established between histological grade and prognosis (Chen et al., 2018). In humans, surgery is the primary and most effective treatment, with a potential cure in select cases (Kaste et al., 2008). Similarly, in dogs with renal neoplasms, surgery remains the only treatment that significantly improves survival (Bryan et al., 2006). At the time of this report, the patient remains alive with no clinical evidence of metastasis or local recurrence 48 months after nephrectomy, as confirmed by radiology and ultrasound examination.

Conclusion

This report demonstrates the usefulness of cytokeratin AE1-AE3, WT-1, and PAX-8 immunohistochemistry in the diagnosis of nephroblastoma in dogs. Additionally, it applies the SIOP and NWTSG classifications based on morphological characteristics, confirming the diagnosis of a mixed-type nephroblastoma. Given the rarity of this neoplasm, it is necessary to implement these classifications in canine cases to identify possible prognostic indicators, which could contribute to improved clinical decision-making, early diagnosis, and treatment. To date, no previous reports of canine nephroblastoma in Colombia have incorporated complementary immunohistochemistry to support the final diagnosis.

Declarations

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Conflicts of interest

The authors declare no conflict of interest regarding the authorship and/or publication of this article.

Author contributions

Clinical examination, diagnosis, surgery, and patient management: Johanna M. Fonseca-Matheus and Xavier L. Jaramillo-Chaustre. Histopathology, literature review, and manuscript writing: Diego F. Rincón-Alarcón. All authors revised the final version.

Use of artificial intelligence (AI)

No AI or AI-assisted technologies were used during the preparation of this work.

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