

PRIMARY RENAL LYMPHOMA IN TWO CATS: CASE REPORT

(Linfoma renal primário em dois gatos: relato de caso)

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ABSTRACT - Lymphoma is a hematopoietic neoplasia which occurs due to the proliferation of malignant lymphocytes. It can be present in different forms, including alimentary, mediastinal, multicentric and extranodal. In both cases described in this report, signs consistent with chronic kidney disease were present. An ultrasound-guided fine-needle aspiration was performed and suggested a lymphocyte neoplastic process. Both cats received prednisolone and life support treatment, with mild improvement. One cat was euthanatized and the other died spontaneously, five and seven days after onset of treatment, respectively. The kidneys were enlarged, whitish, irregular, with a firm mass in the cortex. Histopathology confirmed that the lymphoma was restricted to the kidneys.

Key words: round cells; extranodal; feline leukemia; kidney; lymphoid.

RESUMO - O linfoma é uma neoplasia hematopoiética que ocorre devido à proliferação de linfócitos malignos. Pode ser encontrado de diferentes formas, incluindo alimentar, mediastinal, multicêntrica e extranodal. Em ambos os casos descritos neste trabalho, estavam presentes sinais consistentes com doença renal crônica. Realizou-se punção aspirativa guiada por ultrassom que sugeriu um processo neoplásico de linfócitos. Ambos os gatos receberam prednisolona e tratamento de suporte, com melhora leve. Foi realizada eutanásia em um gato e o outro morreu espontaneamente, cinco e sete dias após o início do tratamento, respectivamente. Os rins estavam aumentados, esbranquiçados, irregulares, com massa firme no córtex. A histopatologia confirmou que o linfoma era restrito aos rins.

Palavras-chave - células redondas; extranodal; leucemia felina; rim; linfóide.

INTRODUCTION

Lymphoma is a heterogeneous group of hematopoietic neoplasms characterized by the clonal proliferation of malignant lymphocytes. It is originated from DNA mutations which occur during the primary differentiation of secondary lymphoid tissues (Argyle e Pecceu, 2016). Lymphomas correspond to 90% of all hematopoietic neoplasms in cats and can affect any organ that presents lymphocyte migration (Valli et al., 2000; Moore, 2013).

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Lymphomas are categorized, according to the topography, in alimentary, mediastinal, multicentric and extranodal (Ettinger, 2003; Sato et al., 2014). Extranodal lymphoma refers to disease confined to locations other than alimentary, mediastinal or multicentric sites and includes nasal, central nervous system, ocular, laryngeal, cutaneous and renal lymphoma (Taylor et al., 2009). Renal lymphoma can be primary or associated with multicentric or gastrointestinal involvement (Ettinger, 2003).

It is known that cats infected with Feline Leukemia Virus (FeLV) can be presented with a virus-induced lymphoma (Lutz et al., 2009; Weiss et al., 2010). These animals have a 62-fold more chances of developing lymphoma than those negative for the virus, while cats infected with the Feline Immunodeficient Virus (FIV) have about a five-fold increased risk of lymphoma development (Hartmann, 2012). FeLV has a direct oncogenic effect, while (FIV) can contribute to lymphoma formation due to its immunosuppressive effect (Weiss et al., 2010). Cats that are positive for FeLV have worse prognosis than negative cats (Taylor et al., 2009;).

The clinical signs of lymphoma are widely variable and unspecific, since they are associated with the affected organ; Cats with renal lymphoma often have signs of chronic kidney disease, and nephromegaly with a firm and irregular appearance (Moore, 2013). In most cases, the kidneys are bilaterally affected, and neurological signs can be present due to uremic state (Guimarães -Okamoto et al., 2016). Patients also have polyuria, polydipsia, azotemia and nonregenerative anemia or polycythemia (Moore, 2013). Specifically for renal lymphoma, ultrasound facilitates identification of diffuse infiltrative disease and it is also used to guide fine needle aspiration (FNA) cytology, which is highly sensitive and specific for renal lymphoma diagnosis. Cytology is less time consuming and a less invasive alternative to kidney biopsy (McAloney et al., 2018).

The prognosis for lymphoma is reserved and one must consider the stage, anatomical location, histological grade, immunophenotype and comorbidities associated with the patient (Moore, 2013). Treatment in cats includes life support, as well as chemotherapy, radiotherapy and surgery according to lymphoma classification. In cats with renal lymphoma, the treatment of choice is chemotherapy, since usually both kidneys are affected, which makes surgery unviable (Moore, 2013). Antineoplastic agents such as cyclophosphamide, doxorubicin, vincristine, prednisolone, L-asparaginase (Taylor et al., 2009; Moore, 2013; Limmer et al., 2014) may be considered in chemotherapy protocols for lymphoma. Protocols must be performed according to the stage and clinical condition of each patient.

Primary renal lymphoma in cats is uncommon and having access to descriptions of clinical follow-up, along with satisfactory knowledge of clinical signs, especially in advanced stages of the disease, is important to assist the veterinarian in treating and understanding the evolution of this disease. Thus, two cases of primary renal lymphoma are reported, as well as laboratorial and post-mortem findings.

CASE REPORT

Two mixed-breed cats, a 3-year-old male and a 9-year-old female weighing 4,5 and 6,2 kg, respectively, were referred for medical care. Both animals were semi-domiciled and were presented with a history of apathy, fatigue, anorexia, polyuria and polydipsia for 30 days, which evolved to hypodipsia in the past week. The patients were treated in distinct moments and do not have any relationship between them).

Physical examination of the male cat showed rectal temperature of 37.2°C, pale mucosa, capillary refill time of 3 seconds, weak arterial pulse, tachypnea, 4/9 body condition score and estimated dehydration of 8%. The female patient had pale mucosa, 8/9 body condition score and estimated dehydration of 6%. In both patients, peripheral lymph nodes had no abnormalities on physical examination, but painful bilateral nephromegaly was present.

Complete blood count found leukocytosis with neutrophilia in the male cat and no abnormality in the female. Serum biochemistry found similar results for both animals, such as increased creatinine (5,4 and 6,2 mg/dL) blood urea (120 and 147 mg/dL) and phosphorus (8,3 and 8,5 mg/dL), respectively, for the male and female. Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were within normal ranges. A snap test (IDEXX®) for FIV and FeLV resulted positive for FeLV in both animals.

In both cats, abdominal ultrasound examination found enlarged and irregular right and left kidneys, with a thick and hyperechoic cortical layer, echogenic renal medulla and decreased corticomedullar differentiation. Renal diverticula and pelvis were dilated and there was presence of a moderate subcapsular effusion (Figure 1).

Urine samples were obtained by cystocentesis. Urinalysis showed hematuria and isosthenuria (urine specific gravity of 1.010 and 1.012 in the male and female, respectively).

Renal ultrasound-guided fine-needle aspiration was performed in both patients and went uneventfully. A large number of round cells with moderate anisocytosis and anisokaryosis was present. These cells had a scarce, well-delimited and basophilic cytoplasm. The nucleus was wide, round and with a dense chromatin. There were also

groups of polygonal, cohesive cells demonstrating mild anisocytosis and anisokaryosis, which suggested a malignant neoplastic process originated from lymphocytes.

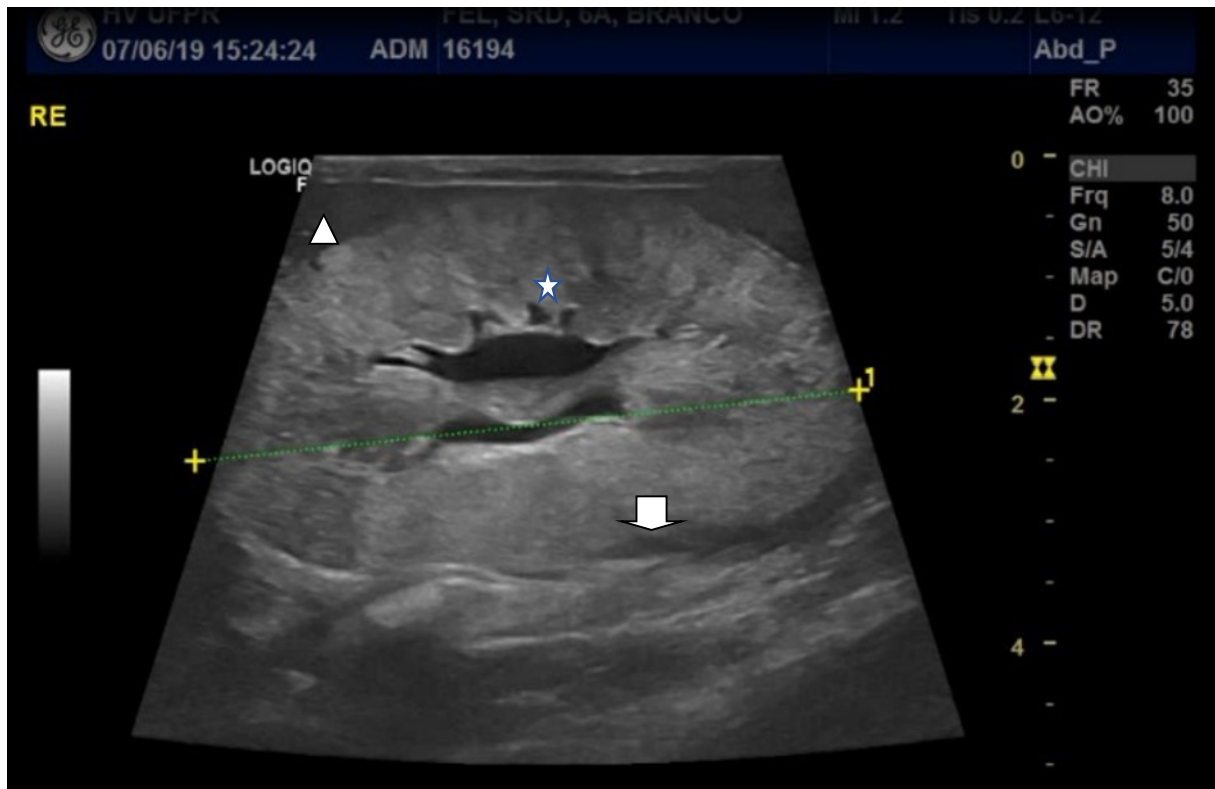


Figure 1 – Ultrasonographic image of the left kidney of a cat with primary renal lymphoma. The kidney is enlarged, with loss of corticomedullar definition (arrowhead), irregular parenchyma, areas of heterogeneous echogenicity (star) and subcapsular effusion (arrow).

Both animals were treated with fluid therapy, ondansetron (0,22 mg/kg, TID, SQ), omeprazole (1 mg/kg, BID, IV), maropitant citrate (1 mg/kg, SID/ IV) and prednisolone (2 mg/kg SID PO). The female cat also received dipyrone (15mg/kg, SID, IV).

The male cat showed improvement of appetite on the first day of the treatment, however, chemotherapy was not authorized by the owner. On the second and third days of treatment, there was worsening of clinical signs and on the fifth day, euthanasia was requested by the owner

The female cat received chemotherapy (vincristine 0.7 mg/m² as part of CHOP protocol – vincristine, cyclophosphamide, doxorubicin, and prednisolone) (Thamm, 2019) leading to a rapid improvement of clinical signs. However, on the seventh day of treatment, the animal died spontaneously due to the progression of clinical signs. The

addition of doxorubicin to the chemotherapeutic protocol would only be considered if a decrease in serum creatinine concentration could be achieved. Due to the concern that the nephrotoxicity of doxorubicin could worsen renal function, the COP protocol (vincristine, cyclophosphamide and prednisolone) would be an alternative treatment for these cats.

Both animals were submitted to necropsy. Macroscopically, there was bilateral kidney enlargement with a whitish and irregular surface. The corticomedullar definition was moderately attenuated with reddish and radiated areas at the cortical. The renal pelvis was moderately dilated and a firm whitish mass was present at the cortex (Figure 2).



Figure 2 – Cat kidneys with primary renal lymphoma. The kidneys are irregular, enlarged and whitish. There is attenuation of corticomedullar definition, reddish and radiated areas on the cortical layer and a whitish, firm mass on the cortex (arrow).

Bilateral histological examination of both cats' kidneys demonstrated non-delimited neoplastic proliferation constituted of round cells with moderate anisocytosis and anisokaryosis. The cytoplasm was scarce, eosinophilic and moderately delimited. The nucleus was round, central and had a dispersed chromatin, with one or two nucleolus, compatible with renal lymphoma. There was also diffuse and moderate thickening of the bowman capsule (Figure 3). Immunohistochemistry was performed on the renal neoplastic tissue for evaluation of CD20 (1: 1000, polyclonal) expression for B-cells and CD3 (1: 500, polyclonal) for T-cells. There was no CD-20 or CD-3 expression, therefore, it was not possible to confirm the lymphoma cell type.

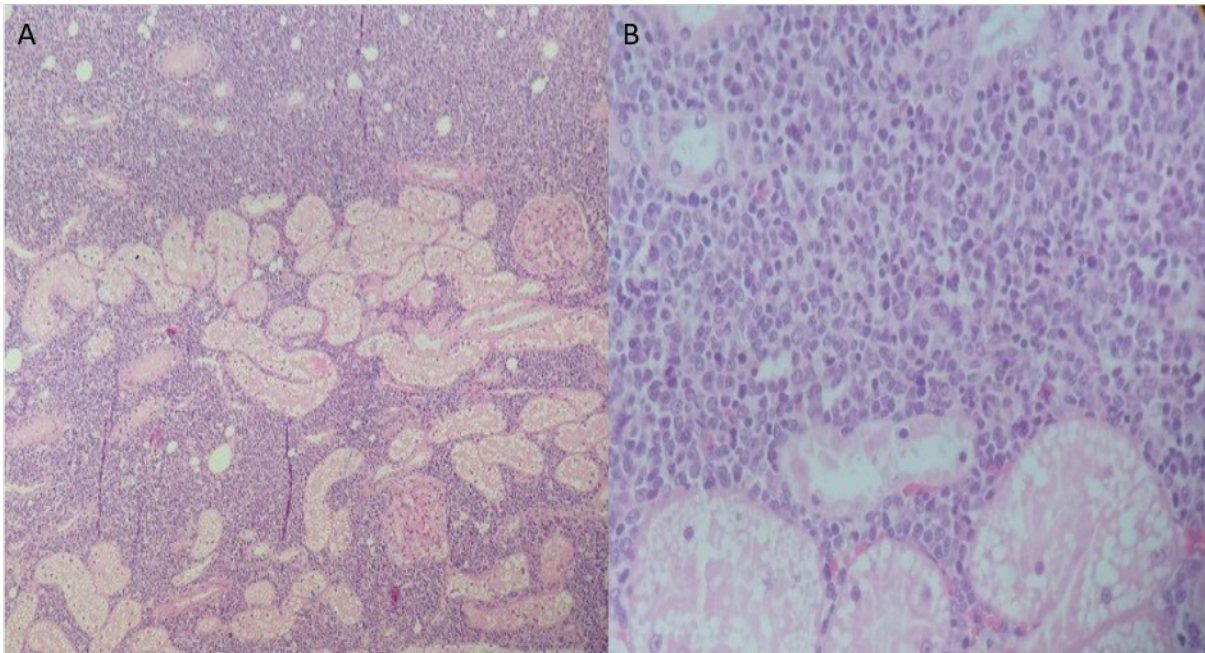


Figure 3 – Feline lymphoma, kidney. (A) Infiltration of neoplastic cells, expanding to the parenchyma and around the renal tubules. H&E, 20x. (B) Sheets of round cells showing moderate anisocytosis and anisokaryosis, with a scarce and moderately delimited cytoplasm and a round central nucleus. The diagnosis was high-grade lymphoma. H&E, 40x.

DISCUSSION

Despite lymphoma being the most common feline hematopoietic malignancy, the incidence of renal lymphoma is low, as shown in a study in which of 740 cats with lymphoma, only 3.6% had renal lymphoma (Williams et al., 2021). Cats with renal lymphoma exhibit classic signs of chronic kidney disease due to the infiltration of neoplastic cells. Apathy, anorexia, weight loss, polydipsia, polyuria, and dehydration are common clinical findings. In late stages, as in the present cases, the animals can have hypodipsia as uremia worsens (Bartges, 2012; Moore 2013). Ultrasound examination is the main tool for detecting abdominal masses, including kidney neoplasms, in addition to assisting in the collection of fine-needle aspiration (Garcia et al., 2012). The cats reported here had similar clinical signs and ultrasonographic abnormalities and were submitted to the aforementioned procedure.

As both cats tested positive for FeLV, the relationship between the virus and the occurrence of primary renal lymphoma raises concerns. Because it is a virus incorporated into the host's genome, it can trigger oncogenes that lead to the development of lymphoma (Hartmann, 2012). The frequency of FeLV-positive individuals among cats with

renal lymphoma varies across studies, from 25 to 100% (Henry et al.; 1999; Seguela et al., 2008; Voccia, 2016; Cristo et al., 2019). Conversely, one study showed most cases of mediastinal and central nervous system lymphomas are positive for FeLV, but in cases of multicentric and renal lymphoma they are usually negative (Moore, 2013). Indeed, it must be considered that the variation in the degree of association of FeLV with the development of lymphomas among studies is probably due to the efficient preventive management of the disease (vaccination) in several countries in which decrease of such association has been noticed (Cristo et al., 2019). These authors (Cristo et al., 2019) evaluated cats with lymphoma in Brazil and found that 56.6% of cats with lymphoma were FeLV-positive, pointing out the need of preventing and controlling the factors associated with infection in our country. Thus, in the present report, taking into account the variations described in the literature, the fact that the two cats tested positive for FeLV could be a coincidence, due to the absence of vaccination programs at a national level, without necessarily FeLV having direct connection with the tumor. The other hypothesis is that FeLV actually triggered lymphoma in one or both cats, when considering, for example, the young age of the male cat.

In the case of cats with renal lymphoma, cytology in association with imaginological, clinical, laboratory findings and compatible clinical history could be highly suggestive (Valli et al., 2000; McAloney et al., 2018). For this reason, the treatment was initiated.

The treatment of renal lymphoma must be individualized, considering the clinical condition and comorbidities. Radiotherapy is rarely used to treat lymphoma, as it is usually a disseminated systemic disease; Further studies are needed to evaluate the effect of radiotherapy in uncommon locally spread lymphoma in cats (Thamm, 2019). Multidrug chemotherapy is often used for a higher chance of success (Vail et al., 2007; Taylor et al., 2009; Williams et al., 2021). Currently, the recommended protocol for high-grade lymphoma is the combination of vincristine, cyclophosphamide, doxorubicin and prednisone (CHOP protocol) (Taylor et al., 2009; Limmer et al., 2014; Williams et al., 2021). Doxorubicin should be included in this protocol preferably in cats with normal renal function (Moore, 2013), since it has been demonstrated that progressive increases in the concentration of serum creatinine and risk factors were associated with the use of doxorubicin in cats (Kopečný et al., 2020). Regarding corticosteroid administration, when comparing two protocols in cats with renal lymphoma, no statistical difference was found

in median survival time for cats being treated with corticosteroids alone or receiving an L-CHOP, and additional studies are necessary to define the ideal protocol (Williams et al., 2021). On the present study, the advanced stage of the disease at the time of diagnosis most likely contributed to a poor prognosis, regardless of the initiation of any therapeutic protocol.

The cases described here could only be confirmed as primary renal lymphoma post-mortem. Histological evaluations of other organs were negative for lymphoma. The immunohistochemistry to evaluate the presence of B and T-cells resulted negative and the determination of lymphoma cell type was not possible. Although renal lymphoma appears to be mainly B cell in origin, some cats have T cell renal lymphoma, and also the null cell lymphoma was described (Moore, 2013). Therefore, for both cases of the present study, additional immunohistochemical tests using other markers or molecular tests to define the neoplastic cell involved would be needed. However, it was not possible to carry out these analyzes and it is certainly a limitation of this work.

Both cases had a late-stage presentation since clinical signs were present for at least 30 days and progressively deteriorated. Late diagnoses contribute to poor treatment results (Taylor et al., 2009; Bound et al., 2011), especially in patients with azotemia, in which complications can be progressive and fatal. Early diagnosis is presumed to lead to a better prognosis and a gradual clinical response to chemotherapy

CONCLUSION

Primary renal lymphoma should be included in the differential diagnosis of cats with chronic kidney disease. Late-stage diagnosis is probably associated with a poor prognosis.

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