Schweiz. Arch. Tierheilk.
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M. Kessler et al., Band 150, Heft 11, November 2008, 565–569
DOI 10.1024/0036-7281.150.11.565

Primary malignant lymphoma of the urinary bladder in a dog: longterm remission following treatment with radiation and chemotherapy

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Abstract

Primary (extranodal) malignant lymphoma limited exclusively to the urinary bladder is an extremely rare disorder in both humans and animals and has to be differentiated from malignant lymphoma cases where a systemic (multicentric) lymphoma has spread to the bladder. We report a case of a 3-year old female spayed mixed breed dog presenting with gross haematuria and dysuria and diagnosed with a primary B-cell high-grade lymphoma of the urinary bladder without involvement of any other site. After treatment with a combination of hypofractionated external beam radiation and cytotoxic chemotherapy, rapid and complete remission of the tumor occurred. At present the dog is alive and has been in remission for 52 months.

Keywords: dog, extranodal malignant lymphoma, urinary bladder lymphoma, chemotherapy, radiation therapy

Primäres malignes Lymphom der Harnblase bei einem Hund: Langzeitremission nach Bestrahlungs- und Chemotherapie

Ein primäres, ausschließlich die Harnblase betreffendes (extranodales) malignes Lymphom kommt bei Mensch und Tier sehr selten vor. Es ist von Lymphomformen zu unterscheiden, bei denen es im Zusammenhang mit der Ausbreitung eines systemischen (multizentrischen) malignen Lymphoms zu einer Tumormanifestation in der Harnblase kommt. Der Bericht beschreibt den Fall eines 3 Jahre alten weiblich kastrierten Mischlingshundes, der mit Makrohämaturie und Dysurie vorgestellt wurde und bei dem ein primäres B-Zell Lymphom von hohem Malignitätsgrad diagnostiziert wurde, das sich ausschließlich auf die Harnblase beschränkte. Nach Behandlung mit einer Kombination aus hypofraktionierter Bestrahlungstherapie und Chemotherapie kam es zu rascher und kompletter Remission des Tumors. Zum Zeitpunkt des Berichts lebt der Hund mit einer Remissionszeit von 52 Monaten.

Schlüsselwörter: Hund, extranodales malignes Lymphom, Harnblasenlymphom, Chemotherapie, Bestrahlungstherapie

Introduction

Malignant lymphoma is the most common haematopoietic neoplasia in the dog and occurs in a variety of clinico-anatomic forms. The vast majority of the patients show the multicentric form which affects multiple lymph nodes, spleen, liver, bone marrow and sometimes also additional organ systems. Malignant lymphomas which do not primarily affect the lymphatic organs are referred to as „extranodal", the most common ones being primary lymphomas of the eyes, kidneys, gastrointestinal system, central nervous system, nasal cavity, and skin (Valli et al., 2002). Other primary sites for extranodal malignant lymphomas have only rarely been reported and even less is known about their biological behaviour and response to therapy. In the dog, the majority of urinary bladder tumors are carcinomas with transitional cell carcinoma as the most common type. Malignant mesenchymal tumors, such as leiomyosarcomas, fibrosarcomas, or hemangiosarcomas make up less than 10% of all neoplasias (Meuten et al., 2004). Primary extranodal lymphoma of the urinary bladder is extremely rare in dogs and there are only a few reported cases (Strafuss and Dean, 1975; Van Noort, 1997; Maiolino and De Vico, 2000; Benigni et

al., 2006). To the authors' knowledge this is the first case report of a dog with a primary lymphoma of the urinary bladder undergoing multimodality treatment.

Case report

History

A 3-year old female spayed mixed breed dog was presented to Hofheim Animal Hospital with a 5 week history of haematuria, pollakisuria and polydipsia, a two day history of dysuria, anorexia and three episodes of vomiting. Physical examination revealed no abnormalities except for a palpable, painful mass in the caudal abdomen. All peripheral lymph nodes had no palpable abnormalities. A serum chemistry panel and standard haematological parameters were within the normal range. Urine sediment analysis revealed massive haematuria with some leucocytes and uroepithelial cells. A urine bacterial culture was performed and showed no bacterial growth.

Diagnostic imaging

Ultrasonographic examination of the abdomen revealed a large ill-defined mass infiltrating almost the entire bladder including the bladder neck and trigone area. The bladder lumen was almost lost and the bladder wall was up to 3 cm thick with loss of its typical layered ultrasonographic appearance (Fig.1). Except for a minimal bilateral distension of the ureters and the pelvis of both kidneys, the ultrasonographic appearance of the kidneys was normal. All other abdominal organs including the lymph nodes were unchanged on ultrasound. Lateral and ventrodorsal chest radiographs were found to be within normal limits and with no signs of systemic spread.

Histopathology and immunohistochemistry

A full thickness surgical bladder biopsy was performed and histopathologic examination revealed a relatively uniform population of small oval to round lymphoid cells with a diffuse (non-follicular) growth pattern. The cells had a moderate amount of pale cytoplasm and non-cleaved, hyperchromatic nuclei, a marked anisokaryosis and on average more than 3 prominent small nucleoli per nucleus. About 4-6 mitoses were seen per high power field (Fig. 2). Using the NCI Working Formulation the neoplasia was diagnosed as a high-grade diffuse small-cell non-cleaved malignant lymphoma (NCI, 1982). Classification according to the new WHO-classification scheme posed some difficulties but the characteristics of the tumor resembled those of an extranodal marginal zone malignant lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (Valli et al., 2002). A CD79a positive and CD3 negative immunohistochemical reaction identified the mass as a B-cell lymphoma (Fig. 3). Staging consisting

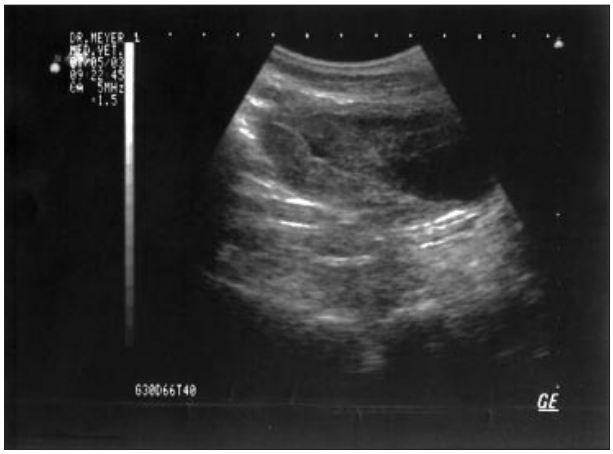

Figure 1: Longitudinal ultrasonographic image of the primary bladder lymphoma. Extreme thickening of large parts of the bladder wall due to an infiltrative and sonographically homogeneous soft tissue mass with loss of the typical layered appearance of the bladder wall.

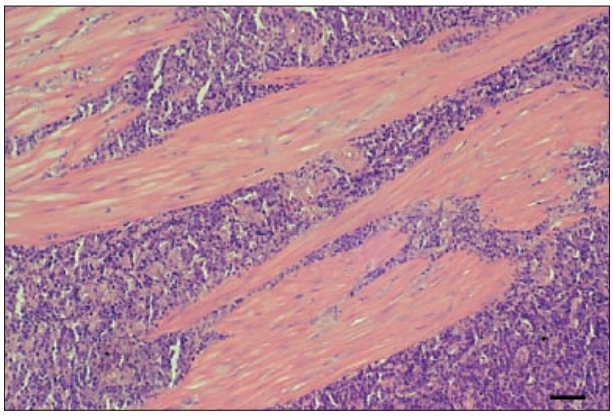

Figure 2: Full thickness biopsy of the bladder mass. Uniform, oval to round lymphoid cells with diffuse growth pattern infiltrating the bladder wall. HE, 10x. Bar = 100 µm.

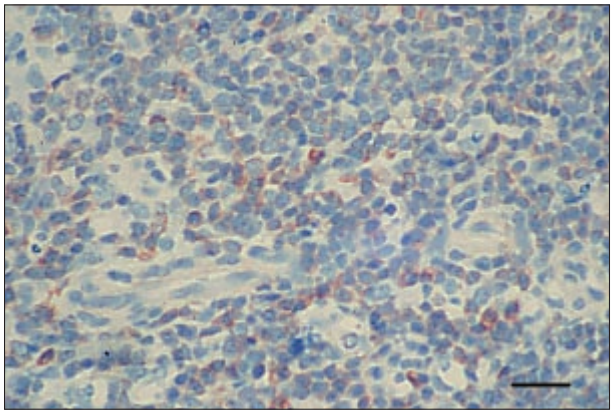

Figure 3: Immunohistochemistry of the bladder mass. Note the positive CD79a reaction which defines the tumor as a B-cell lymphoma. 40x. Bar = 50 µm.

of fine needle aspirates of liver, spleen and one peripheral (popliteal) lymph node as well as of a bone-marrow aspirate collected using a bone-marrow needle disclosed no detectable signs of systemic tumor spread.

Therapy

Due to the lack of information on the treatment of localized urinary bladder lymphoma in the dog, a combination therapy consisting of bladder irradiation and chemotherapy was recommended to the owner. A computed tomography (CT) study was used as a basis for radiation treatment planning (Fig. 4). The urinary bladder was treated with 15 Gray (Gy) administered in 3 weekly fractions of 5 Gy each, using a ^{60}Cobalt teletherapy unit. The treatment was performed with the patient in dorsal recumbency using one ventral port of 8.5 × 12 cm (source surface distance 76 cm; dose rate 64.6 cGy/min). The bladder was emptied using a transurethral catheter immediately prior to each radiation treatment to minimize variations in bladder size and to ensure inclusion of the entire target volume in the radiation field.
All tumor-associated clinical symptoms subsided after the first radiation treatment. One week after the third fraction ultrasonography of the bladder confirmed complete remission of the tumor. There were no clinically relevant side effects to this treatment. The radiation was followed by a polychemotherapy protocol consisting of four cycles of vincristine (Cellcristin, Cell pharm), L-asparaginase (Asparaginase Medac, Wedel), cyclophosphamide (Endoxan, Baxter), cytosine arabinoside (Ara-Cell, Cell Pharm) and doxorubicin (Doxo-Cell, Cell Pharm) over a period of six months according to a previously published protocol (Kessler and Kandel, 2004; Tab 1). Cyclophosphamide was replaced by chlorambucil (Leukeran, Baxter) after the first cycle to avoid the risk of hemorrhagic cystitis secondary to cyclophosphamide. There were mild and self limiting gastrointestinal side effects following each doxorubicin application. Follow up examinations including abdominal ultrasonography, standard haematological parameters, serum chemistry profile and urinalysis performed initially on monthly, later on 3- and 6-monthly intervals revealed no recurrence of the neoplasia or any other signs of systemic spread. At present, the dog is alive, in complete remission and has been free of symptoms for 52 months.

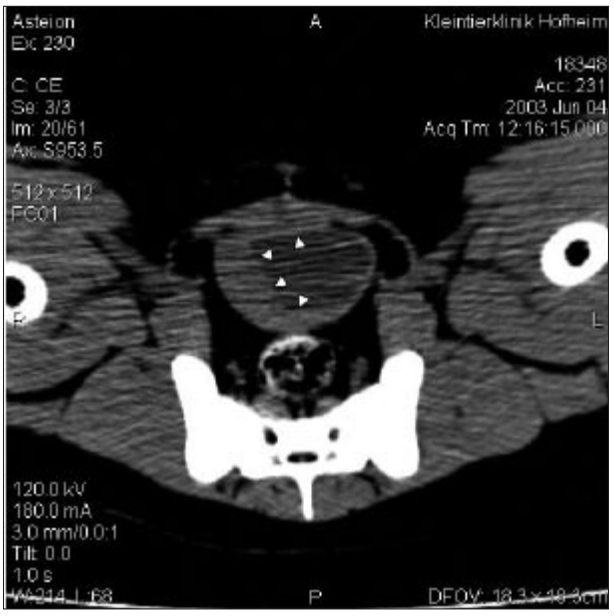

Figure 4: CT scan of the pelvis and urinary bladder for radiation planning. Large soft tissue mass (40 HU) encompassing large parts of the urinary bladder wall (arrows). Transverse image 3mm (120kV, 180 mA), soft tissue window.

Table 1: Chemotherapy protocol used to treat primary lymphoma of the urinary bladder (Kessler and Kandel, 2004). Four cycles of chemotherapy were administered. After completion of each cycle, there was an interval of 14 days before the start of the new cycle.

Drugs and dosages	Day in cycle 1	4	10	20-24	32	40
Vincristine 0.65-0.7 mg/m² BSA iv	*					
L-Asparaginase 10.000 IE/m² BSA im		*			*	
Cyclophosphamide 200 mg/m² BSA orally (1st cycle)			*			
Leukeran 1.4 mg/kg orally (cycles 2–4)						
Cytosin Arabinoside for 4 days 3 times daily 60 mg/m² BSA sc				*		
Doxorubicin 28–30 mg/m² BSA over 20 min iv						*

BSA: body surface area (in m²)

Discussion

Primary (extranodal) lymphoma of the urinary bladder in humans is defined as a malignant lymphoma limited exclusively to the bladder with no other sites affected and no previous history of lymphoma in the patient. This form of lymphoma is differentiated from „non-localized lymphoma“ in which lymphomatous infiltration of the bladder occurs as a manifestation of a systemic (multicentric) lymphoma. It is also differentiated from „secondary lymphoma“ where there is a previous clinical history of a successfully treated malignant lymphoma elsewhere in the body followed by a recurrence of the tumor in the urinary bladder (Kempton et al., 1997; Leite et al., 2004). In human patients, non-localized and secondary lymphomas make up the bulk of the cases with urinary bladder

involvement and necropsy studies have shown that about 10-20% of the non-Hodgkin's lymphoma patients ultimately develop secondary bladder involvement (Bates et al., 2000; Leite et al., 2004). In contrast, primary lymphoma of the bladder is exceedingly rare and represents less than 1% of all vesical tumors and only 0.2% of all extranodal lymphomas with less than 100 cases reported over the last 40 years worldwide (Ohsawa et al., 1993; Kempton et al., 1997; Leite et al., 2004). In human patients the most common types of primary malignant lymphomas of the bladder are those arising from the mucosa-associated lymphoid tissue (MALT-type lymphomas) and diffuse large-cell lymphomas (Isaacson, 1992; Kempton et al., 1997; Thieblemont et al., 2000). MALT-lymphomas are low-grade centrocytic lymphomas and are of B-cell origin. They initially arise from the marginal zone around reactive follicles and secondarily invade epithelial tissue (Thieblemont et al., 1995). Diffuse large-cell lymphomas of the bladder are high-grade lymphomas usually also of B-cell origin and make up about 20% of all bladder lymphoma cases (Fernandez Acenero et al., 1996; Leite et al., 2004). Transformation of MALT-lymphomas into high-grade diffuse large-cell lymphomas has been reported (Fernandez Acenero et al., 1996; Bates et al., 2000). Lymphomas of T-cell origin are very rare in the bladder of both humans and dogs (Mourad et al., 1998; Maiolino and De Vico, 2000). The most commonly reported clinical signs in humans with a primary urinary bladder lymphoma are irritable bladder symptoms and gross haematuria. The tumor occurs 6.5 times more frequently in women than in man and the mean age of affected patients is 64 years (range, 20-85 years) (Leite et al., 2004). The great majority of patients with MALT-type or diffuse large-cell bladder lymphomas are treated with chemotherapy, radiotherapy or both (Tsang et al., 2001; Leite et al., 2004). The response to treatment is generally rapid and cure rates of over 80% for diffuse lymphomas and almost 100% for MALT-type lymphomas have been reported (Leite et al., 2004).

A search of the veterinary literature resulted in only five canine and three feline case reports of malignant lymphoma of the urinary bladder and some of these had to be considered „non-localized" or „secondary" lymphomas (Strafuss and Dean, 1975; Van Noort, 1997; Maiolino and De Vico, 2000; Benigni et al., 2006).

The radiographic and sonographic findings in dogs with lymphomas involving the urinary bladder are similar to those of other bladder neoplasms and thus cannot be used to make the presumptive diagnosis of malignant lymphoma (Benigni et al., 2006). Sonographically they appear as heterogeneous mural or lobular masses with mucosal and/or submucosal infiltration (Maiolino and De Vico, 2000; Benigni et al., 2006). Ureteral distension is frequently present and could also be demonstrated in our case (Maiolino and De Vico, 2000; Benigni et al., 2006). In all reported canine cases, including the case described here, the presenting complaint was gross haematuria and abdominal pain, which is similar to the findings in humans. The age of the patients ranged between 2 and 7 years (Maiolino and De Vico, 2000; Benigni et al., 2006). Because none of the reports from the veterinary literature gave detailed information on therapy, we chose a combination of radiation and chemotherapy for the treatment of our case, similar to the treatment strategy in humans. In order to avoid bladder fibrosis or other side effects from radiation therapy the total dose delivered was below that reported in protocols for bladder irradiation in humans (Tsang et al., 2001; Shipley et al., 2003).

Classification of the neoplasia according to NCI criteria was easily achieved, but classification according to the newly established WHO guidelines was found difficult. Like in the corresponding human disease (Isaacson, 1992), MALT lymphomas in animals are usually characterized as low-grade CD79a positive small cell lymphomas arising from the marginal zone of lymph follicles, but subtypes composed of cells with higher malignancy grade have been described (Valli et al., 2002). In the case presented, cell size, shape, localisation and immunophenotype were compatible with a MALT-lymphoma, but tumor grade was unusually high. Additional to these histopathologic features there were also some striking similarities with the corresponding human disease regarding clinical features and response to therapy. It is concluded that this type of extranodal lymphoma may have a similarly favourable prognosis as the human counterpart and radiation and chemotherapy can lead to a complete and durable remission.

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Received: 7 January 2008
Accepted: 19 May 2008