Splenic malignant mesenchymoma in a dog – immunophenotypic features and clinicopathological ramifications: a case report

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ABSTRACT: A 13-year-old spayed bitch was referred for evaluation of an abdominal distension with a palpable, continuously growing mass. Abdominal ultrasonography revealed a 30 × 20 cm mass directly connected to the spleen. Surgical exploration confirmed the sonographic diagnosis with adhesions to the omentum and the liver. Pathohistological samples revealed well differentiated adipose tissue and variably differentiated collagenous and myxomatous tissue. Immunohistochemically, vimentin and in some regions alpha smooth muscle actin were expressed indicating smooth muscle differentiation. The results support the diagnosis of a malignant mesenchymoma composed of liposarcoma, mixosarcoma and leiomyosarcoma. No local recurrence or metastasis occurred during a nine month follow-up. So far, only two pathological retrospective studies describing the common prevalence and properties of canine splenic malignant mesenchymomas were found in the literature. However, this rare tumor entity has to be considered as a differential diagnosis in cases of large splenic masses.

Keywords: mixed sarcoma; mitotic index; immunohistochemistry; surgery; survival rate

Benign and malignant mesenchymal neoplasias are well described in the veterinary literature (Spangler and Culbertson 1992; Spangler and Kass 1997; Miller et al. 2005; Liptak and Forrest 2007; Eberle et al. 2012). Only a small number of case reports describe sarcomas, which were previously referred to as unclassified mesenchymomas with heterologous differentiation. These tumours consist of multiple cell types and matrix components of mesenchymal origin, including osteoid, chondroid, and collagen (Spangler et al. 1994; Dennis et al. 2011). Abdominal, thoracic, skeletal, and submandibular malignant mesenchymomas have been reported in dogs (McDonald and Helman 1986; Hahn and Richardson 1989; Robinson et al. 1998; Machida et al. 2003; Murphy et al. 2006; Petterino et al. 2010; Gomez-Laguna et al. 2012). These tumours have a slower growth rate, but tend to become very large (Moore et al. 1983). Morphologic classification of tumour microanatomy and immunohistochemistry are necessary for an accurate diagnosis (Adachi et al. 2003). Malignant mesenchymomas are more likely to be reported in older individuals (Spangler et al. 1994). Local recurrence and metastases in human and animal patients depend on the independent behavior of the constituent tissue present in the tumour (Schajowiez et al. 1966; Liwnicz and Ferreol, 1986; Hassan et al. 1994; Robinson et al. 1998; Machida et al. 2003; Gomez-Laguna et al. 2012).

This case report describes a canine splenic malignant mesenchymoma with liposarcomatous, mixosarcomatous and leiomyosarcomatous cellular composition.

MATERIAL AND METHODS

A 13-year-old, neutered, female Welsh Springer Spaniel presented with a two-month history of abdominal distension and a palpable mass in the mesogastrium. Preoperatively, the patient's status was assessed clinically and using laboratory testing. Survey three-view thoracic and abdominal ra-

diographs with abdominal ultrasound examination were performed to accurately evaluate the mass properties including infiltrative and metastatic potential. The patient was pre-medicated for surgery with morphine hydrochloride (0.3 mg/kg *i.v.*; Morphin, HBM Pharma, Slovak Republic) and diazepam (0.2 mg/kg *i.v.*; Apaurin, Krka, Slovenia), induced with propofol (1–6 mg/kg *i.v.*; Propofol-Lipuro 1%, B. Braun, Germany), intubated, and maintained with isoflurane in oxygen general anaesthesia. Amoxicillin/clavulanic acid (8.75 mg/kg *s.c.*; Synulox RTU, Pfizer, Czech Republic) was given pre-operatively to continue the initial therapy prescribed by the referring veterinarian. A splenectomy via a midline celiotomy with partial resection of the adhered omentum and a hilar lobectomy of the lateral hepatic lobe were performed using a harmonic scalpel (Ethicon G-110, Ethicon, USA) dissection and four metric polyglycolic acid (Safil, B. Braun, Germany) suture ligation with routine closure. Post-operative pain was controlled with morphine hydrochloride (0.2 mg/kg *s.c.*) every 6 h for the first 24 h after surgery. Adequate gross sections of nodular tissue, including interface area to adjacent parenchyma, were obtained from numerous sites and fixed in 10% neutral buffered formalin. Amoxicillin/clavulanic acid (Synulox 200, Pfizer, Czech Republic) was continued at 12.5 mg/kg *p.o.* every twelve hours and tramadol hydrochloride (Tramal, Grunenthal, Germany) at 3 mg/kg *p.o.* every eight hours for the next five days. Samples of necropsy tissue were processed for histopathology and immunohistochemistry and examined with standard immunohistochemical panel markers (Vimentin, Sigma; SMA, Dako; CD18, P.F. Moore; GFAP, Dako; S-100, ZYMED; CD31, Dako). At the third, sixth, and ninth month post-operative checkups, clinical exams that included three-view thoracic radiographs and ultrasound examination were performed to assess infiltrative or metastatic progression.

RESULTS

On physical examination, the dog was alert but slightly tachypnoic (32 breaths per minute) with pale pink mucous membranes and a prolonged capillary refill time (CRT) of three seconds. The cranial abdomen was distended, with a non-painful solid mass occupying most of the cavity. The complete blood count (CBC) revealed a leukocytosis with neutrophilia (23×10^9/l, reference range 3 to 12×10^9/l); mild, microcytic (54 fl, reference range 60–77 fl) and hypochromic (29 g/dl, reference range 32–37 g/dl) regenerative anaemia (red blood cells 5×10^{12}/l, reference range 5.5–8.5 $\times 10^{12}$/l; hematocrit 0.32 l/l, reference range 0.37–0.55 l/l; absolute reticulocyte count 150×10^9/l), and mild thrombocytosis (510×10^9/l, reference range 200 to 500×10^9/l). Basophilic stippling and polychromatophilic cells without fragmentation were present in blood smear samples and there was no autoagglutination. Serum biochemical analysis revealed a mild hypoalbuminaemia with a slight elevation in alkaline phosphatase (ALP) – 3.2 μkat/l, reference range 0.3–2.5 μkat/l). The urinary sediment findings were unremarkable. Concerning differentials, such findings indicated internal and probably chronic bleeding into body cavities or even the mass itself. Survey abdominal radiographs indicated a large, circumscribed, soft tissue mass that displaced surrounding organs. Examination of thoracic radiographs revealed no apparent pulmonary metastasis or effusion. Sonographically, the splenic tumour was identified as a cavitated mass of mixed echogenicity that appeared to be attached to the omentum and liver. The generally homogenic liver was compressed from the left side by a 3 cm hyperechogenic mass on the lateral left lobe and a less well-defined hypoechoic rim. The other organs were within normal limits or were only partially visualised with a small amount of free peritoneal fluid, which was confirmed as haemorrhagic by abdominocentesis.

Surgery revealed distended and aberrant omental vascular trunks wrapped around a splenic mass that haemorrhaged into the peritoneal space. Remaining abdominal viscera appeared grossly normal. Results for cytological evaluation of the regional lymph nodes were unremarkable. The resected, 3.5 kg, oval-shaped spleen contained firm nodules with glistening white and yellowish cut surfaces; some nodules were filled with a mucinous secretion (Figure 1). The liver mass was of a soft consistency with a smooth surface, and was well circumscribed from the rest of the parenchyma.

The dog recovered uneventfully and was discharged two days after the surgery. There were no complications during the convalescence period, and the tumour did not recur or metastasise during the nine-month follow-up according to regular examinations performed every three months. The dog remained free of signs of clinical disease relating to the tumour until eleven months after the surgery, when it developed acute onset of respira-

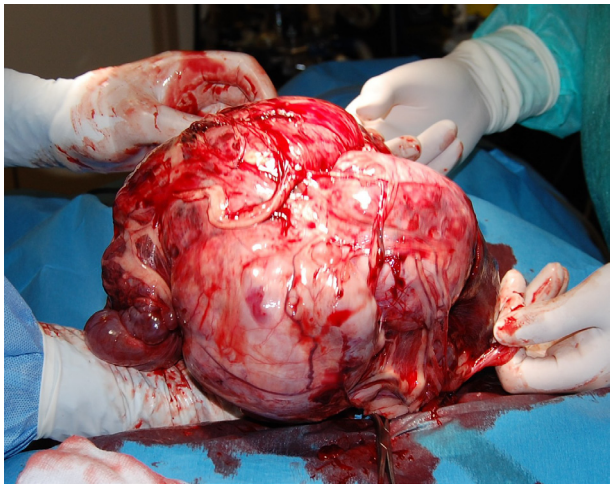

Figure 1. Splenic mesenchymoma: Intraoperative view of mass representing 1/6 of the whole dog weight (21 kg)

tory distress and depression. The referring veterinarian diagnosed scattered metastasis throughout the lungs and the dog was euthanised. A necropsy was not performed.

The histopathological examination revealed a highly pleomorphic mesenchymal tumour. Large areas of well-differentiated adipose tissue, smooth muscle tissue, and variably differentiated fibrous tissue with a prominent myxomatous matrix were present (Figure 2). Spindle-shaped cells with mild anisokaryosis had a mitosis rate of 10 per 10 high power fields (hpfs; Figure 3). Variably large foci of necrosis were present. The regions with differentiation into adipose tissue and smooth muscle cells exhibited minimal signs of malignancy; mitoses were infrequently observed and were 1/10 hpfs. There was variable congestion and mild haemosiderosis within the splenic parenchyma. Lymphoid follicles were usually small and non-reactive. Immunohistochemical labelling of serial sections diffusely expressed Vimentin and in regions with smooth muscle differentiation, alpha-smooth muscle actin. Neoplastic cells did not express CD18, GFAP, S-100, or CD31 antigens; there was no evidence of a vascular component, histiocytic proliferation, or proliferation with peripheral nerve sheath differentiation. The presence of the heterogeneous combination including myxosarcoma, leiomyosaroma and liposarcoma in a single splenic mass defined it as a malignant mesenchymoma. The hepatic mass consisted of solid areas of well differentiated but heavily vacuolated hepatocytes showing moderate anisocytosis and rare mitoses (2/10 hpfs). Lobular structures including portal triads were rarely identified with widespread necrotic areas and haemorrhages. Signs of invasive growth were absent, and a delicate fibrous capsule, moderately compressing adjacent hepatic tissue, was observed. Hepatic mass findings led to a diagnosis of hepatocellular adenoma.

DISCUSSION AND CONCLUSIONS

This report describes a case of canine splenic malignant mesenchymoma. Diagnosis was based on

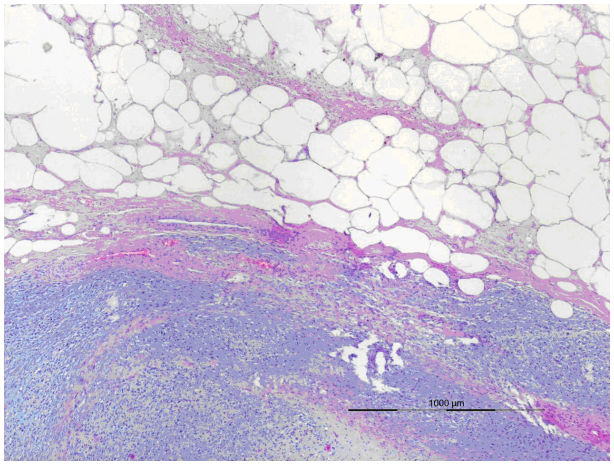

Figure 2. Splenic mesenchymoma: Areas of well differentiated liposarcomatous tissue which, similar to leiomyosarcomatous tissue, resemble a normal adult mesenchymal tissue with myxosarcomatous matrix of the intermediate histological grade

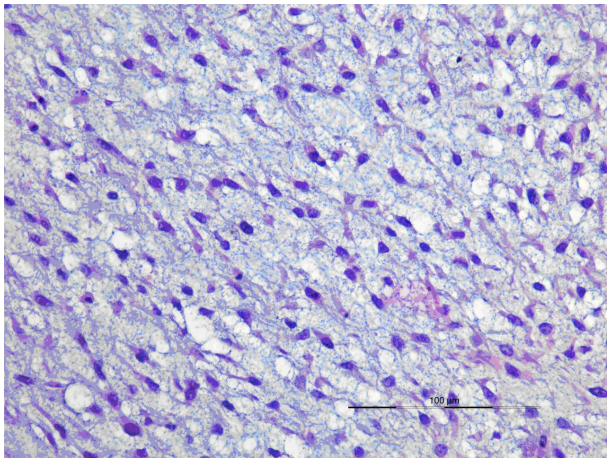

Figure 3. Splenic mesenchymoma: Areas of spindle-shaped cells with prominent myxomatous matrix, partly resembling a myxosarcomatous component, which showed the highest number of mitoses

clinical, histopathological, and immunophenotypic features. Two pathology studies have described the prevalence and properties of splenic malignant mesenchymomas in dogs (Spangler and Culbertson 1992; Spangler et al. 1994). Relevant cases with similar phenotypic features were not found in the human literature. Although this rare tumour showed divergent phenotypic differentiation in this study, the surgery contributed to prolong survival and there was no evidence of tumour infiltration or metastases during the 9-month follow-up period. Sonographic evidence of multiple nodular splenic changes is often associated with malignancy, but is not specific for any particular disease (Hanson et al. 2001; Ballegeer et al. 2007). Mesenchymomas represent 4% of all splenic malignancies (Spangler and Kass 1997); however, the relative size and morphological appearance makes it difficult to differentiate malignant mesenchymomas from other mesenchymal tumours (Johnson et al. 1989; Spangler et al. 1994). Pre-operative sonographical evidence of local spread in regional lymph nodes or other organs is important to determine prognosis in aggressive malignant sarcomas. Evidence of spread was hard to determine because of the large size of the tumour. Pre-operative cytological samples were not taken because of limitations in overall correspondence between the cytological and histopathological findings for liver and splenic nodular masses (O'Keefe and Couto 1987; Kuntz et al. 1997; Wang et al. 2004; Bellegeer et al. 2007). Therefore, apart from stopping the bleeding and providing a palliative relief of discomfort, the surgery was also utilised as a diagnostic tool. The staging system for canine soft tissue sarcoma includes clinical criteria and histological grading.

Mesenchymoma prognosis depends on the site of the primary tumour as well as on the biological behaviour or histological grade of its subcomponents (Adachi et al. 2003). A high mitotic index and regional or distant metastases are prognostic for low life expectancy. In this case, the results indicated the presence of two sarcomatous histological forms with a low grade (MI 1/10 hpfs, reference range 0–9/10 hpfs) and one with an intermediate grade (10/10 hpfs, reference range 10–19/10 hpfs). Areas of fibrosarcomatous differentiation with prominent myxomatous features were the only parts of the tumour with a remarkable number of mitoses and isolated necrosis (less than 50%). Metastases were not found at the time of diagnostic workup (including the surgery), which improves the prognosis with a significant increase in survival time. These were also not observed during a nine month follow-up period, but were reported as the reason of the clinical deterioration and euthanasia of the dog eleven months post-operatively. This finding corresponds to the previously documented biological behavior of such neoplasms (Spangler and Culbertson 1992; Spangler et al. 1994). Adipose tissue, myxomatous matrix, and spindle, fusiform, or stellate-shaped cells were features that correspond exactly to the characteristics of a mesenchymoma reported by Spangler et al (1994). The metastatic rate reported in this pathological study was 57% and tumour-related deaths were at 83%. Findings from the other documented primary tumor sites indicate high metastatic rate (McDonald and Helman 1986; Hahn and Richardson 1989; Robinson et al. 1998; Murphy et al. 2006; Gomez-Laguna et al. 2012). With respect to the described metastatic potential of various soft tissue sarcomas (Liptak and Forrest 2007), two individual tumour components (myxosarcomatous and liposarcomatous) have generally low metastatic potential and one (leiomyosarcomatous) moderate, mostly to the lungs, which corresponds to findings published by Kuntz et al. (1997), but also to the liver, spleen, kidney, mesentery and lymph nodes. In the literature the development of sarcomatous metastases is related to the mitotic rate (Kuntz et al. 1997). In our patient, only the myxosarcomatous component was prominent (MI 10/10 hpfs), indicating the unpredictable behavior of these tumours (Moore et al. 1983) and validating previous findings (Adachi et al. 2003), where clinical outcome was not affected only by specific immunophenotypes, but also by their characteristics and site of the tumour. We confirm at least a moderate metastatic potential of splenic mesenchymoma and find that our findings correspond to those of Spangler et al. (1994).

The described behaviour of individual components in the presented tumour and its primary site could predictably exhibit local infiltrative growth. Moreover, a large tumour size represents a risk factor for local recurrence despite a lower histological grade. Radiotherapy in malignant mesenchymomas is useful in primary sites, where the risk of postoperative local recurrence is high due to micro-invasion of residual cells, especially when the surgery is performed only within tight margins (Murphy et al. 2006). Chemotherapy has been reported in mesenchymomas as an attempt to decrease the likelihood of metastatic spread (Robinson et al. 1998; Murphy

et al. 2006), or to achieve a partial regression of the disease (Hahn and Richardson 1989). However, the insufficient number of cases and unspecified approach to complex cell element origins and their differentiation make a definitive conclusion regarding its effectiveness elusive. Further, the owners refused any adjuvant therapy in this case, which could have further minimised the repercussions of the disease and may have prolonged survival time. Therefore, we presumed that complete splenectomy with wide margins of omental resection would itself be sufficient to prevent or at least postpone local relapse. In the follow-up period we did not observe splenic mesenchymoma size to be important for local recurrence or as a prognostic factor for disease-free interval; however, owing to the lack of post-mortem examination this assessment could not be completely proven. Regardless of the chosen type of management, splenic mesenchymomas require longer follow-up periods.

Survival rates for soft tissue sarcomas are necrosis-dependent, and metastases as well as tumour-related deaths are more likely when the mitotic rate is 20 or more mitotic figures per 10 hpfs (Kuntz et al. 1997). The median survival rate of surgically treated mesenchymal sarcomas with varied differentiation and localisation, with or without adjuvant therapy, is recorded in months. The survival time of eleven months in our patient is in accordance with the pathological evidence describing splenic primary mesenchymal neoplasms, where mesenchymomas showed the longest median survival rate of twelve months (Weinstein et al. 1989; Spangler and Culbertson 1992; Spangler et al. 1994). The documented survival in mesenchymomas is affected by younger patient age (Addachi et al. 2003), primary localisation in the liver (McDonald and Helman 1986), vasoinvasive metastasis (Robinson et al. 1998) and late diagnosis and treatment (Kaneko et al. 2006).

Hepatocellular adenomas are non-aggressive, usually single, smooth tumours of variable size with little clinical significance (Stalker and Hayes 2007). These tumours do not considerably differ from nodular hyperplasia or interfere with normal hepatic function, unless acting as a diffuse multilobulated burden (Cave et al. 2003; Eves 2004;). Immunostaining with monoclonal antibody (MoAb) hepatocyte paraffin 1 (Hep Par 1) contributes to differentiate canine hepatocellular tumours from other neoplasms (Ramos-Vara et al. 2001). Sonographic findings of atypical target lesions exclude a differential diagnosis of hepatic malignancy (Cuccovillo and Lamb 2002; Irausquin et al. 2008). However, any occurrence of a hepatic mass together with a splenic mass increases the likelihood of a malignant process and a poor prognosis (Neer 1996). Metastases originating from splenic tumors are 2.5 times overrepresented in the liver (Liptak 2007). An absence of cytological and biopsy results indicating morphology and surgical margins was the reason, why a complete removal of the involved lobe was chosen. Complete surgical resection was reported to be curative (Eves 2004; Liptak 2007).

The splenic mass reported here was a mixed sarcoma – a mesenchymoma. This type of tumour is characterised by the presence of three mesenchymal tissue components, of which two including leiomyosarcoma and liposarcoma, resemble well-differentiated adult-like features of low grade malignancy, and one of myxosarcomatous origin represents an intermediate histological form. When complete excision with sufficient margins is performed, surgical resection can lead to prolonged survival. This type of splenic tumour is likely to metastasise. However, insufficient clinical reports about rates of metastasis and the behaviour of specific histological subtypes for different primary sites limit the debate on adjuvant therapeutic treatment, which could be beneficial. This case had a good short-term clinical outcome, but the long-term prognosis was unfortunately poor.

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