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ABSTRACT

Green KT, Regazoli E, Olegário da Silva E, Scortecci Hilst CL, Wingeter Di Santis G., Myxoid liposarcoma in a dog, Onl J Vet Res., 17 (5): 218-226, 2013. A male, mixed-breed stray dog presented a voluminous, intramuscular mass in the thigh. On clinical examination, the mass was firm and painful. Fine-needle aspirates of the mass were examined cytologically and diagnosis was suggestive of a malignant mesenchymal tumor. Clinical signs progressed and the dog presented poor response to clinical treatment and was euthanized. Cut sections of the mass at necropsy revealed a white, multilobulated mass with scattered irregular areas of necrosis. Histopathological evaluation of the mass was compatible with myxoid liposarcoma. The myxoid liposarcoma subtype is the most common in dogs and is considered of intermediate malignancy with low metastatic potential. Evidence of necrosis observed macroscopically in this report is not a common finding in myxoid liposarcoma, indicating a poorer prognosis regardless of the subtype classification.

Key words: liposarcoma, thigh, dog.

INTRODUCTION

Liposarcomas are rare neoplasms in domestic animals (Wang et al., 2005) that originate from primitive mesenchymal cells (lipoblasts). Among domestic species, the dog is most frequently reported (Doster et al., 1986; Shive et al., 2006; Chang and Liao, 2008). In humans, the most common sites affected are the deeper soft tissues, including the thighs, gluteal region and retroperitoneum (Aceñero-Fernández et al., 2007; Roh et al., 2011;
Papacharalampous et al., 2012). In dogs, the subcutaneous tissue is more prone to the development of this neoplasm, however, may develop in the abdominal cavity and other extracutaneous areas (Messick et al., 1989; Vascellari et al., 2004; Shive et al., 2006). There is no reported sex and breed predisposition (Zwicker, 1970; Gross et al., 2005), however, in Shetland Sheepdogs has been most frequently observed (Goldschmidt and Hendrick, 2002).

Clinical signs are variable and early detection is usually delayed due to the fact that most tumors are painless and exhibit an insidious growth pattern usually in deep seated soft tissue (Fletcher et al., 2002; Roh et al., 2011). End stage signs of this pathology are pain and edema of the affected area, and weight loss (Torres et al., 2001). Diagnosis is made through cytological and histopathological evaluation, the latter being necessary for a definitive diagnosis (Loubignac et al., 2009).

Myxoid liposarcoma should be differentiated from other spindle-cell tumors such as: myxoma, myxosarcoma, myxoid peripheral nerve sheath and fibrosarcoma which share similar histomorphological characteristics (Gross et al., 2005). Liposarcomas are locally invasive, aggressive and rarely metastasize; however there are reports of metastasis in the lungs, liver, spleen and bones in both humans and dogs (McCarthy et al., 1996; Baez et al., 2004; Chang and Liao, 2008).

Due to the rarity of this neoplasm, the aim of this report is to describe a case of a well-differentiated myxoid liposarcoma arising from the left hind limb of a stray dog and determine its histopathological pattern, clinical manifestation, identify possible biological behaviour and potential prognosis with a literature review.

**Case Report**

An adult (age unknown) intact male, mixed-breed stray dog, was presented to the Veterinary Hospital of the Universidade Estadual de Londrina, in southern Brazil for evaluation of a mass located on the left hindlimb in the lateral region of the thigh. The owner reported that the animal was recently taken off the streets and the mass had been evident at the time. Clinical examination revealed a large, oval, firm and painful mass measuring 23 x 24 cm located on the lateral aspect of the proximal portion of the left hind leg (thigh) that extended to the ischium of the pelvis. These regions presented extensive edema that extended to the distal extremity, with lameness of the member. The animal was overweight, depressed and prostrated; other physical medical parameters were within normal range.

Hematological evaluation revealed a leukocytosis with a left shift neutrophilia. Serum biochemistry revealed increased alkaline phosphatase. Cytological analysis of fine-needle aspirates of the mass was suggestive of a malignant mesenchymal tumor with a neutrophilic inflammation process. Lateral radiographs of the thorax displayed a bronquial and interstitial mixed pattern and the presence of an oval radiopaque structure at the base of the heart compatible with soft tissue measuring 5 x 3 cm indicative of a possible metastasis.

Radiographs of the left femur (thigh) revealed a diffuse, irregular radiopaque structure compatible with soft tissue measuring 25 x 12 cm. The animal was treated with Tramadol®
3mg/kg, 1ml via SC and was subsequently discharged with follow-up anti-inflammatory treatment for 10 days. Two weeks after the initial consultation, the dog presented further progressive swelling, pain and edema of the member. Due to the lack of response to treatment and poor prognosis, the dog was euthanized and a necropsy was done.

Gross examination revealed a large, firm mass located in the proximal two-thirds portion of the left hind limb (thigh) and extended to the distal portion of the pubis measuring 25 cm in diameter. Edema was also observed in the pelvic region adjacent to the genital area. On cut section, the subcutaneous presented diffusely edematous and exuded a transparent fluid. The mass appeared multilobulated, admixed with a delicate fibrotic tissue, white to greyish in colour, shiny and greasy in aspect (Fig. 1 A, next page). On cut sections, scattered irregular areas that were soft and yellowish in colour, that exuded a mucoid substance of a similar colour compatible with necrotic areas were also observed along with haemorrhagic areas (Fig. 1 B). The mass was deeply attached to the underlying muscle fascia of the thigh.

Examination of the other organs revealed that the diaphragm presented a hernia. The hernial opening was located in the right dorsolateral region measuring 2cm in diameter and presented rough, irregular margins with adherence of the omentum. The omentum was dislocated into the thoracic cavity along with a small portion of the intestines. The liver presented moderate congestion with rounded borders, an irregular surface, and soft in consistency with areas of depression specifically in the left lateral lobe. Tissue samples from the mass were fixed in 10% neutral buffered formalin solution and routinely processed, sectioned to a thickness of 4µm and stained with hematoxylin and eosin (HE) for histologic evaluation.

Histopathological examination revealed a heterogeneous population of neoplastic cells, with a prominent population of lipoblasts in different phases of differentiation. These were admixed with highly cellular areas of well-differentiated adipocytes containing lipid vacuoles of variable sizes in abundant cytoplasm, dislocating the nucleus to the periphery and intermingled in a prominent myxoid stroma (Fig. 1 C). Other segments revealed plump, ovoid cells with sporadic pleomorphic giant multinucleated cells with large vesicular nuclei (an average of 2cells/10 x HPF) admixed a sparse collagenous matrix (Fig. 1 D); and stellate to spindle shaped lipoblasts containing few lipid droplets were scattered throughout the tumor accompanied by necrosis supported by a sparse fibrovascular stroma. Analysis revealed an average of 3 mitoses/x 400 field with several atypical mitotic figures. In replicate sections of tumor samples, multifocal areas of basophilic ground substance stained positively with Alcian blue (Fig. 1 E). Histopathological findings were consistent with a well-differentiated myxoid liposarcoma. Accentuated edema was observed in all extension of the dermis and hypodermis.

Multifocal necrosis accompanied by hemorrhage and calcification was also observed with sheets of inflammatory cells consisting primarily of lymphocytes in the adjacent muscle tissue. Immunohistochemistry assay (IHC) was performed on formalin-fixed, paraffin-embedded tissue sections using the monoclonal antibodies anti-vimentin (V9, 1:100, Invitrogen®) and anti-cytokeratin (AE1/AE3, 1:100, Biocare®). The evaluation of IHC detected expression of only the vimentin antibodies, indicating a tumor of mesenchymal cells (Fig. 1F).
Figure 1- Myxoid liposarcoma in a dog. A- Multilobulated mass involving the lateral region of the left thigh (white arrow), head of the femur (star). B- Cut section of the mass demonstrating scattered irregular areas of necrosis and mucoide substance exuding from the mass (arrows) and hemorrhagic areas. INSET-Fine-needle aspirate of the mass in the left thigh of the dog. Note the presence of pleomorphic mesenchymal cells with ample cytoplasm with variable numbers of lipid vacuoles intermixed with eosinophilic matrix and occasional neutrophils. Giemsa stain, Objective 40x. C-Extensive areas of atypical lipoblasts admixed with well-differentiated adipocytes in a prominent myxoid stroma. Hematoxylin & Eosin, Objective 10x. D-Multinucleated giant cells with significantly pleomorphic (arrow) admixed adipocytes within a sparse collagenous matrix. Hematoxylin & Eosin, Objective 40x
E- Replicate sections of the well-differentiated tumor markedly stained with Alcian Blue. Alcian Blue, Objective 10x. F- LPS with neoplastic cells showing strong cytoplasmic immunoreactivity (DAB 40X) and the inset showing negative cytokeratin immunostaining (DAB 20X).

DISCUSSION

Liposarcomas are one of the most common soft-tissue sarcomas in humans accounting for up to 20% of these cases (Aceñero-Fernández et al., 2007; Roh et al., 2011; Asano et al., 2012; Papacharalampous et al., 2012). On the contrary, in domestic animals liposarcomas are rare (Messick et al., 1989; Hendrick et al., 1998; Baez et al., 2004). Most reports have been described in dogs frequently arising from the subcutis (Doster et al., 1986; Hendrick et al., 1998; Baez et al., 2004; Kwon et al., 2007) and in humans the thighs, buttocks and retroperitoneum are sites most commonly reported (Fletcher et al., 2002; Roh et al., 2011). This tumor frequently occurs in middle-aged dogs and adults (Zwicker et al., 1970; Doster et al., 1986; Roh et al., 2011) and males are slightly more prone to develop liposarcoma (Roh et al., 2011; Papacharalampous et al., 2012). However, we were unable to determine the exact age of the dog in this report because it was a stray animal. On physical examination, it was determined that the animal was an adult with a probably 8 years old. Nevertheless, there is a report in younger animals (2 years old) being affected (Baez et al., 2004). In our case the mass involved the deep seated soft tissue of the thigh - appendicular region; which has a lower occurrence. This tumor is more frequently reported in the subcutis of axial region in dogs.

There are no known or established the aetiology of liposarcoma in domestic animals. In cats, feline leukaemia virus infection has been associated with the development of liposarcoma (Stephens et al., 1983). In dogs, there are two reports of liposarcoma development due to foreign bodies (McCarthy et al., 1996; Vascellari et al., 2004) and one of which was related to old trauma. In laboratory experiments, mice implanted with microchips developed sarcomas including liposarcomas (Elcock et al., 2001). It may be assumed in this case that the dog suffered from a trauma in the past, evidenced by a fibrotic lesion on the diaphragmatic hernia. It may be deduced in our case, that trauma may be the possible instigator factor that lead to the formation of this neoplasm in the thigh. Literature reviews in humans have demonstrated that they may also develop liposarcoma due to recurrent trauma (Dubin and Chang, 2006) although its prevalence is low (0).

There is no classical clinical presentation of this pathology. In 10 to 15% of human cases, patients exhibit signs of pain, hypersensibility, weight loss and other functional alterations usually due to compression of adjacent structures associated with the growth of the mass (Torres et al., 2001; Papacharalampous et al., 2012). However, edema is a frequent sign occurring during the later course of the disease, as seen in the case of the dog reported here.

In humans, myxoid liposarcoma (LPS) corresponds to 10 to 35% of liposarcomas being the second most common subtype (Fletcher et al., 2002; Loubignac et al., 2009; Roh et al., 2011) and in dogs the most common subtype (Messick et al., 1989). Myxoid liposarcoma is characterized by of the presence of lipoblasts in different phases of differentiation admixed
well-differentiated lipocytes in an abundant mucinous stroma within an extensive capillary network (Fletcher et al., 2002). The myxoid subtype includes the category formerly known as round cell liposarcoma, with the former and the latter representing low and high grade variants, indicative of the well and poorly differentiated components respectively of this subtype (Fletcher et al., 2002; Loubignac et al., 2009). This round cell component is characterized by highly cellular areas of round cells arranged in solid sheets with no integration of a myxoid stroma.

In humans, the World Health Organization (WHO) recognizes five subtypes of liposarcomas: well-differentiated, dedifferentiated, myxoid (including round cell variant), pleomorphic and mixed liposarcoma (Fletcher et al., 2002). This classification is important in predicting the biological behaviour and clinical course of this neoplasm and aids in determining survival and metastasis rates. The biological behaviour of these tumors is associated with its differentiation cellular. Well-differentiated liposarcomas have a better prognosis and lower metastatic potential and pleomorphic liposarcomas exhibit poorly differentiated cells and are more aggressive. In domestic animals, the World Health Organization (WHO) scheme recognizes only three subtypes of liposarcoma: well-differentiated, myxoid and pleomorphic (Hendrick et al., 1998). In a retrospective study in 56 dogs with liposarcoma, histologic subtype did not affect or influence the overall survival time in dogs, conversely to humans, histopathological subtype influences directly on the prognosis, survival time, local recurrence and metastatic potential (Baez et al., 2004). However, in dogs, pleomorphic liposarcomas are more prone to metastasize than their more differentiated counterparts (Baez et al., 2004). In this case the histopathological findings were based on the WHO classification system for domestic animals (Hendrick et al., 1998) and diagnosed as a well-differentiated myxoid liposarcoma.

The histologic criteria for myxoid liposarcoma are a combination of lipoblasts, lipocytes, spindle cells and stellate cells; a prominent myxoid stroma and a delicate anastomosing vascular pattern (Hendrick et al., 1998; Gross et al., 2005). This heterogenic population of cells and a myxoid ground substance were observed in the case reported here, however the anastomosing vascular pattern characteristic of myxoid LPS was not noted. This may be presumed to the chronicity and prolonged evolution of the clinical signals as demonstrated by foci of necrosis. According to Gross et.al (2005), occasional pleomorphic giant multinucleated cells may be observed in myxoid liposarcomas. Conversely, in our case the indice was greater with at least 2 cells per 40 x high power field (HPF). This could indicate a continuum to a more pleomorphic variant of liposarcoma, as the latter as a marked number of pleomorphic giant multinucleated cells. As such, this continuum could indicate the transition of the myxoid variant to a more aggressive form of the tumor. Nonetheless, the pleomorphic variant of liposarcoma does not produce mucin or collagen.

Differential diagnoses for myxoid liposarcoma include myxosarcoma which is characterized by the presence of primitive pleomorphic fibroblasts arranged in stellate or spindle cells admixed abundant mucinous stroma. Myxoid liposarcomas are also characterized by a spindle or stellate population and mucinous stroma however differs from myxosarcoma and myxoma due to presence of atypical lipoblasts with cytoplasm containing multiple lipid droplets and well-differentiated lipocytes. In contrast to myxoid liposarcoma, fibrosarcoma
produces variable amounts of mature collagen with spindle cells arranged in interwoven or interlacing bundles at times forming the herringbone pattern. The spindle cell population present a scant cytoplasm, elongated to oval nuclei with inconspicuous nucleoli. Myxoid peripheral nerve sheath is distinguished from myxoid liposarcoma by the presence of spindle cells arranged in concentric whorls and palisades embedded in a collagen stroma (Gross et al., 2005). Anaplastic spindle cell sarcoma lacks cytoplasmic lipid vacuoles. It should be noted that histopathological evaluation is essential for the definitive diagnosis of liposarcoma and immunohistochemistry trials can help to discard other tumor types especially in cases of poorly differentiated tumors.

In the present report, at necropsy, scattered areas of necrosis were observed. In human literature, most authors are in agreement that necrosis is an indicator of a poorer prognosis (Loubignac et al., 2009; Roh et al., 2011; Haniball et al., 2011; Asano et al., 2012) influencing overall survival time and metastasis and in some cases increases the aggressiveness of liposarcoma (Guillou et al., 1997). Gross evidence of tumor necrosis is uncommon in myxoid LPS (Fletcher et al., 2002) and the replication of necrosis macroscopically in various studies have been inconsistent, as such, should be confirmed microscopically (Guillou et al., 1997; Coindre, 2006). Radiographic images such as ultrasound and computed tomography are recommended to evaluate the extension of tumor necrosis to differentiate lipoma from its malignant counterpart liposarcoma; the latter is more vascular and invasive in adjacent organs (Loubignac et al., 2009). It may be concluded in our case, that the presence of gross necrosis is indicative of a progressive and chronic clinical case of liposarcoma and though a diagnosis of myxoid liposarcoma is of intermediate malignancy, the presence of necrosis macroscopically and microscopically made for a poorer prognosis and as such, makes treatment more difficult and reduces the chances of a possible cure.

In humans, myxoid LPS located in the extremities are more prone to metastasize to extrapulmonary sites (Baez et al., 2004; Chang and Liao, 2008) and associated with a greater survival time in relation to pulmonary metastasis. Extrapulmonary sites reported in human and veterinary literature include the retroperitoneum, subcutaneous soft tissue, epidural space, bone, spleen, liver and serous membranes of the pleura, pericardium and diaphragm and kidney (Torres et al., 2001; Wang et al., 2005; Chang and Liao, 2008; Loubignac et al., 2009; Asano et al., 2012; Papacharalampous et al., 2012). The specific reasons of this occurrence is unclear, however authors assume that the abundance of adipocytic tissue in these regions may be the contributing factor (Asano et al., 2012). In our case, the tumor was located in the deep-seated soft tissue of the muscles of the thigh, however metastasis was not observed. It should be noted that in this case, that the radiographic evaluation of the thoracic cavity was suggestive of metastasis. At necropsy, only the dislocation of the omentum into the thoracic cavity via the hernial opening in the diaphragm was observed. This indicates in cases with suspicion of metastasis, along with the X-ray evaluation other complementary radiographic examinations such as computed tomography should be done to confirm metastasis and invasion into adjacent tissue and organs, which could change the long-term prognosis.

Wide excision surgery or amputation of the member affected are possible treatment methods utilized in prolonging survival time (Baez et al., 2004) and a widely accepted
treatment method in veterinary and human medicine (Torres et al., 2001; Chang and Liao, 2008; Loubignac et al., 2009; Asano et al., 2012; Papacharalampous et al., 2012). One study demonstrated that early and wide surgical excision were key elements in prolonging survival time in dogs on average 3.25 years while marginal and incisional excision correspond to 1.5 and 0.5 years respectively (Baez et al., 2004). Adjuvant treatment with chemotherapy and radiotherapy are debatable in both veterinary and human literature as both treatments have limited effect on liposarcoma (McCarthy et al., 1996; Baez et al., 2004; Asano et al., 2012), however, some studies have shown that chemotherapy may delay local recurrence and metastasis (Asano et al., 2012; Campbell et al., 2012).

In the present report the mass also involved the regional distal of the pelvis, which indicates that all the neoplastic tissue could not be removed surgically in its entirety. Not removing the tumor completely increases the possibilities of local recurrence and metastasis. In this case prognosis was poor due to the location, invasion and extension of the mass and presence of necrosis. Clinical signs, laboratory and radiographic exams are not conclusive for diagnosis. The histopathological evaluation is fundamental for the definitive diagnosis and classification of liposarcoma.

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