Metastasized Leydig cell tumor in a dog

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Summary

We present the clinical findings, diagnosis and treatment of an 11-year old intact male Fox Terrier with a malignant Leydig cell tumor of the right testicle, which metastasized to the skeletal musculature of the left hind limb. The primary tumor and the metastasis were resected with narrow margins. The dog was treated with metronomic chemotherapy using thalidomide and dyclophosphamide. Local recurrence at the site of the metastasis and a pulmonary metastasis were present 30 months after surgery. The dog was euthanized.

Keywords: canine, Leydig cell tumor, malignant, metastasis, dog

Introduction

In dogs the prevalence of testicular tumors varies from 1 to 27% (Reif et al., 1979; MacLachlan and Kennedy, 2002; Grieco et al., 2008) depending on the study. Seminoma, Interstitial or Leydig cell tumor and Sertoli cell tumor are the most common types with a prevalence of 33.9%, 33% and 26.4% respectively (Nødtvedt et al., 2011). Interstitial cell tumors arise from Leydig cells. They are common in dogs and are also described in other species such as horses, cattle, cats, and man. Interstitial tumors usually develop in older animals. They can be uni- or bilateral, single or multiple in one testicle (MacLachlan and Kennedy, 2002). The occurrence of different tumor types in the same testicle has also been described (Grieco et al., 2008). Seminoma and Sertoli cell tumors are more common in cryptorchid testes than in scrotal testes (Reif et al., 1979; Nødtvedt et al., 2011). Leydig cell tumors are generally considered benign although malignant forms have been described. An irregular cell form and an increased mitotic rate histologically characterize these. The distinction between benign and malignant forms is based on histological criteria such as infiltrative growth and can be difficult to diagnose (MacLachlan and Kennedy, 2002). Metastasized Sertoli cell tumors and Seminoma have been described in dogs (Tennant and Kelly, 1992; Dhaliwal et al., 1999), but to our knowledge metastasis of Leydig cell tumor in the muscles has not yet been reported in a dog.

History and clinical examination

An 11-year old intact male Fox Terrier, 11.2 kg, was referred to the Small Animal Clinic, University of Zurich, with a rapidly growing mass in the left hind limb. The referring veterinarian had noted a small mass in the right testicle. A fine-needle aspiration (FNA) of the mass in the limb had been performed prior to referral. The mass consisted of spindeloid to oval cells with clearly demarcated intracytoplasmatic lipid vacuoles. Because the nuclei were round to oval with vesicular chromatin pattern, large irregularly formed nucleoli and moderate anisocytosis, anisokaryosis and anisonucleoliosis the diagnosis was spindle cell sarcoma, most likely a liposarcoma (Fig. 1). On physical examination a soft non-movable mass measuring 10 × 6 × 6 cm was palpated in the left hind limb. The right testicle contained a firm nodule of 1 × 1.5 cm. The dog was slightly lame (grade 1 out of 5) without showing any pain on orthopedic examination.

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Further examination

Blood chemistry and a complete cell count were within reference values. A CT-scan of the thorax, abdomen and both hind limbs revealed a poorly delineated space-occupying lesion caudal to the left femur that extended to the ischial tuberosity (Fig. 2). In transverse images, the area of the left limb measured 61.1 cm² at the point of major distension, which was 1.59 times larger than the contralateral side at the same level (38.35 cm²). After contrast media application a discontinuing rim-enhancement was visible. The mass showed heterogeneous contrast uptake with small cavities. There was no involvement of bones or lymph nodes. The thorax and abdominal cavity were normal. Amputation of the left hind leg with caudal hemipelvectomy was advised but the owner requested less invasive treatment. Surgery was therefore limited to debulking of the mass and bilateral orchiectomy.

Surgery and histology

Firstly, bilateral orchiectomy and scrotal ablation was performed than the mass was debulked. At surgery the mass was partially enclosed in a pseudocapsule. The mass extended beyond the pseudocapsule and infiltrated the surrounding muscles. A marginal resection, debulking was performed. The sciatic nerve was dissected free from the tumor. The limb was weight bearing on the day after surgery. The patient was discharged 2 days after surgery.

Histologically the testicular mass was composed of solid cell nests supported by a fine fibrovascular stroma. In some areas neoplastic cells bordered directly on blood filled, vascular lacunae. The neoplastic cells were polyedric to ellipsoid with a moderate amount of eosinophilic cytoplasm, round to oval nuclei with vesicular chromatin pattern and one often clearly demarcated nucleolus. There was low to moderate anisocytosis and anisokaryosis. Only one mitotic figure could be found in the entire mass. Large areas of necrosis were scattered though the parenchyma of the tumor. Some neoplastic cells showed clear demarcated fatty vacuoles in their cytoplasm (Fig. 3a). Few tumor emboli were found in blood vessels of the plexus pampiniformis. The left testicle was free of disease. The histological appearance of the mass in the left hind limb was similar to that in the right testis but the mitotic rate was 6 mitotic figures in 10 fields taken with the 40×-objective.

A special staining with Prussian blue following a routine protocol was performed on both masses. Neoplastic cells in the right testicle as well in the left hind limb showed mild depositions of ferric oxide (Fe (3+)) (Gross et al., 2005).

Immunohistochemistry

Immunohistochemistry using a polyclonal anti-S100 antibody (Code No.H0066, Dako®) on both masses was performed to exclude a highly differentiated liposarcoma. Two 3 μm thin paraffin sections were mounted on positively charged glass slides and boiled in a microwave with citrate buffer (S2031, Dako®) for 30 min. For antigen retrieval and further processing endogenous peroxidase was blocked ( Peroxidase Blocking Reagent, S2001, Dako®) for 5 min. at room temperature. Afterwards, the ChemMate kit was applied (ChemMateTM, Detection
Kit, rabbit, mouse, code No. K5003, Peroxidase, Dako®) as described by the manufacturer. AEC was used as chromogen. Both neoplasms showed no signal using S100 antibody. Therefore the diagnosis was Leydig cell tumor with metastasis to the left hind limb (Fig. 3b).

GnRH-stimulation test and preputial smear

A GnRH-stimulation test (de Gier et al., 2012) was performed 9 days after surgery, to detect hormonal activity of the remaining tumor cells. The dog received busrelin (Receptal®, MSD Animal Health GmbH, Luzern, Switzerland) in a dose of 0.4 µg/kg intravenously. Plasma concentrations of testosterone and estradiol were less than 0.1 ng/ml and between 5.2 and 7.3 pg/ml respectively. Estradiol concentration were slightly higher than the cut-off value (5.8 pg/ml) proposed by de Gier et al. (2012). No sings of cornification of preputial mucosal cells were detected in the preputial smear (Dreimanis et al., 2012).

Metronomic chemotherapy

Adjuvant treatment consisted of metronomic chemotherapy consisting of dyclophosphamide (10 mg/m² every second day) and thalidomid (4.46 mg/kg once daily) per os, for life (Burton et al., 2011; Marconato et al., 2011). The owner was instructed how to administer the chemotherapeutic agent cyclophosphamide as well as the thalidomide safely. After 26 months, the owner decided to discontinue chemotherapy without our knowledge. Thirty months after surgery the dog was presented to the referring veterinarian because of a growing mass in the scar measuring 3 × 3 × 1 cm. FNA, thoracic radiographs and abdominal ultrasound were performed. Cytology confirmed recurrence of the Leydig cell tumor. Chest x-ray revealed a single nodule in the lung and abdominal ultrasonography showed multiple nodules in the spleen. The owner requested euthanasia.

Discussion

In men malignant Leydig cell tumors are rare with 15–20% of patients having metastatic disease at the time of diagnosis. Retroperitoneal lymph nodes are most frequently involved (70%). Other metastatic sites are the liver (45%), the lungs (40%) or the bones (25%) (Bertram et al., 1991; Al-Agha and Axiotis, 2007; Vasilakaki et al., 2011). Histological differentiation of benign from malignant Leydig cell tumor is challenging (Cheville et al., 1998; Al-Agha and Axiotis, 2007; Vasilakaki et al., 2011). Malignant Leydig cell tumors are treated by orchiectomy and retroperitoneal lymphadenectomy because this tumor does not respond favorably to chemotherapy and/or irradiation. The mean survival time ranges from 2 months to 17 years in men (Al-Agha and Axiotis, 2007).

In our canine patient the cytological diagnosis differed from the final histological diagnosis. This is not unusual as FNA gives an incorrect diagnosis in 15% of soft
tumor in a dog

A. Togni et al.

References


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A. Togni et al.


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