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NEOPLASTIC DISEASE

Comparative Pathology of Canine Soft Tissue Sarcomas: Possible Models of Human Non-rhabdomyosarcoma Soft Tissue Sarcomas

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Summary

Comparative analyses of canine and human soft tissue sarcomas (STSs) are lacking. This study compared the histological and immunohistochemical (labelling for desmin, smooth muscle actin [SMA], CD31, pancytokeratin, S100 and CD34) appearance of 32 archived, formalin-fixed, paraffin wax-embedded canine STS tumour specimens by board-certified veterinary and medical pathologists, both blinded to the other's interpretations. Comparison between the veterinary and human diagnoses revealed a generally consistent pattern of interpretation with few notable variations. Most tumours (13/32) were judged to display similar histomorphological appearance to human low-grade spindle cell sarcomas, appearing non-distinctive and morphologically of a fibroblastic/myofibroblastic type. Five canine cases resembled human liposarcoma, but with atypical desmin-positive epithelioid cells present. Five canine cases resembled human spindle cell sarcoma with myxoid features and two additional cases resembled human myxofibrosarcoma. Seven canine cases were noted to resemble human undifferentiated sarcoma. Findings in the present study demonstrate that canine STSs display histological and immunohistochemical features similar to their human equivalents. Because of these cross-species similarities, a particular opportunity exists to understand the biology and treatment of human STS by potentially including dogs as clinical models.

Keywords: comparative pathology; dog; man; soft tissue sarcoma

Pet dogs affected with spontaneously arising tumours are increasingly recognized as a clinically relevant model for studying similar tumours in man (Hahn *et al.*, 1994; Paoloni and Khanna, 2008; Pang and Argyle, 2009; Gordon and Khanna, 2010; Rankin *et al.*, 2012; Dickerson *et al.*, 2013). In contrast to people, soft tissue sarcomas (STSs) in dogs are considered relatively common and have been estimated to account for 8–15% of all cutaneous and subcutaneous tumours in the dog, with a standardized annual incidence rate of 122 cases per 100,000 dogs (Dobson *et al.*, 2002). As in man, canine STS represents a number of mesenchymal neoplasms with similar histological features and expected biological behaviours (Dobson *et al.*, 2002; Liptak and Forrest, 2007). Despite these recognized clinical similarities between human and canine STS, comparative studies focussing on this disease entity have been lacking in the peer-reviewed literature. This may be due to the complex and evolving nature of STS subtype nomenclature, which often relies on

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immunohistochemical, molecular and/or genetic tests, which are not available routinely in veterinary medicine (Folpe and Cooper, 2007; Thway, 2009; Dennis *et al.*, 2011; Taylor *et al.*, 2011). Therefore, a comparative analysis of human and canine STS should necessarily begin with standard histological techniques to attempt identification of canine STS subtypes that approximate their human counterparts. Therefore, the aim of the present study was to compare the histological and immunohistochemical characteristics of canine STS with their human STS correlates. Our hypothesis was that canine STSs would display histological and immunohistochemical features similar to their human equivalents.

Medical records from dogs seen at the Oregon State University Lois Bates Acheson Veterinary Teaching Hospital between 2007 and 2012 were searched to identify cases of histologically confirmed canine STS. All original histological diagnoses were derived from histopathology reports generated by the board-certified veterinary pathologist at the time of the original surgery or biopsy procedure. As per current veterinary diagnostic convention, specific STS subtypes included for the present study were fibrosarcoma, myxosarcoma, liposarcoma, malignant fibrous histiocytoma, peripheral nerve sheath tumours (neurofibroma, neurofibrosarcoma and schwannoma), spindle cell tumour and vascular wall tumours such as haemangiopericytoma (HPC). The following subtypes were specifically excluded: histiocytic sarcoma, lymphangiosarcoma, haemangiosarcoma, synovial cell sarcoma, leiomyosarcoma, osteosarcoma, rhabdomyosarcoma, sarcomas involving the oral cavity and brachial plexus nerve sheath tumours (Hendrick *et al.*, 1998; Dennis *et al.*, 2011). Each tumour was chemotherapy naïve, radiation naïve and arose spontaneously within an individual client-owned dog, with no dog contributing more than a single tumour to the study.

Routine haematoxylin and eosin (HE)-stained slides were prepared from paraffin wax-embedded, formalin-fixed tumour biopsy samples. Additional positively charged slides were prepared for immunohistochemical analysis of expression of desmin, smooth muscle actin (SMA), CD31, pancytokeratin (CK), S100 and CD34. Details of the immunohistochemistry (IHC) methodology are given in Table 1.

Board-certified human (AM) and veterinary (DEM) pathologists reviewed the resultant slides independently without knowledge of the original pathology reports. Pathologists reviewed HE sections for each case, excluding cases not consistent with the canine STS subtypes listed above. Mitotic index was determined by DEM and LS who counted mitotic figures in 10 arbitrary ×400 microscopical fields for viable areas within each neoplasm. Review of the IHC slides was performed following completion of the initial histomorphological review.

Grading of immunohistochemical labelling was approximated by light microscopy performed using a five-point scale: 0, no immunoreactivity within neoplastic cells; 1, minimal immunoreactivity with 5−10% of neoplastic cells displaying moderate to marked positive labelling; 2, mild immunoreactivity with 10−25% of neoplastic cells displaying moderate to marked positive labelling; 3, moderate immunoreactivity with 25−75% of neoplastic cells displaying moderate to marked positive labelling; 4, marked immunoreactivity with 75−100% of neoplastic cells displaying moderate to marked positive labelling. Control tissues for each antibody were strongly positive: desmin and SMA on muscle tissue, CD31 in and CD34 on vascular endothelium and S100 on nerve tissue.

The electronic medical records search and histopathological review identified 32 cases of canine STS, with the following subtype distribution: spindle cell tumour or STS ($n = 14$), fibrosarcoma ($n = 4$), myxosarcoma ($n = 5$), liposarcoma ($n = 4$) and HPC ($n = 5$). There were no predispositions in gender (16 neutered males, 13 neutered females, two entire males and one entire female), age (median 10.5 years, range 2−16 years) or breed (15 mixed breed dogs, four Labrador retrievers, three German shepherd

Table 1
Summary of immunohistochemical methodology

Marker	*Manufacturer*	*Antibody identification*	*Dilution*	*HTAR*
Desmin	Dako, Carpinteria, California, USA	M0724	1 in 50	+
Smooth muscle actin	Dako	M0851	1 in 30	−
CD31	Dako	M0823	1 in 50	+
Pancytokeratin	Dako	Z0622	1 in 500	−
S100	Dako	Z0311	1 in 400	+
CD34	Santa Cruz Biotechnology, Dallas, Texas, USA	SC-7045	1 in 80	+

HTAR, high temperature antigen retrieval at pH 6.0.