Lymphangiosarcoma of dogs: a review

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ABSTRACT

Lymphangiosarcoma in dogs, an extremely rare tumour with only 16 cases reported in the literature, is reviewed. Lymphangiosarcoma in humans, also very rare, and known in post-mastectomy, chronically-lymphoedematous patients as 'Stewart-Treves' syndrome, is briefly outlined, as well as the various other causes of lymphoedema, both primary and secondary, which usually precede malignancy. Comparisons between human and canine lymphoedema are made when such references were found. The genetic links to primary lymphoedema and the manifestation thereof in humans are mentioned. Lymphangiosarcoma in the majority of human and canine patients is an aggressively malignant tumour with few patients surviving despite various attempted treatments. The tumour most commonly arises in the subcutaneous tissues and rapidly invades underlying tissues and may spread widely internally *via* haematogenous and lymphatic routes, with frequent pleural and chest involvement. The tumour has been reported mostly in medium- to large-breed dogs, in slightly more males than females, and in an age-range of 8 weeks to 13 years, with more cases aged 5 years and older. Methods of diagnosis, with the variations encountered, including routine histopathology, immunohistochemistry, electron microscopy, tissue culture characteristics and endothelial expression of glycoconjugates, are discussed.

Key words: diagnosis, dogs, genetics, lymphoedema, human, lymphangiosarcoma, review, treatment.

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INTRODUCTION

One of the very rare complications of chronic lymphoedema in humans is the development of lymphangiosarcoma, which is an aggressively malignant tumour[3,22].

This neoplasm arises from lymphatic lining endothelium, and was originally reported in humans by Stewart and Treves in 1948 in chronically oedematous extremities occurring mostly after radical mastectomy, which included lymph node resection and/or radiation for breast carcinoma. Lymphangiosarcoma arising in these circumstances thereafter became known as 'Stewart-Treves' syndrome[6,3,22,29]. The postmastectomy oedema in one report[6] preceded the multicentric, polymorphous, patchy, nodular to bullous, ecchymotic soft tissue malignancy in the subcutaneous tissue by an average of approximately 9.5 years but ranged from 1.5 to 26 years and neoplasia occurred in less than 1 % of cases. The lymphoedema in cases of lymphangiosarcoma not associated with mastectomy has usually been secondary to inflammatory disease, surgical procedures, or radiation[6], but other rare associations are with traumatic, idiopathic, congenital or filarial lymphoedema[13].

In some cases of lymphangiosarcoma in humans following lymphoedema, the lymphoedema was considered primary[6] and was present for an average of 21 years (range of 1.5 to 46 years) before malignancy. Primary lymphoedema may be defined as that caused by a primary abnormality or disease of the lymph-conducting elements of the lymph vessels or lymph nodes, leading to excessive accumulation of protein-rich lymph/plasma ultrafiltrate in the interstitial tissues[2,6]. Three groups are recognised where the functional abnormality and its cause is known, namely large-vessel abnormalities such as congenital aplasia, hypoplasia or obstruction of the thoracic duct or cisterna chyli; congenital lymphatic valvular incompetence and congenital aplasia or hypoplasia of peripheral lymphatics, which includes lymph node absence, hypoplasia or fibrosis[2,27]. Some humans with unilateral whole leg lymphoedema have been found to have small shrunken lymph nodes with an increased amount of fibrous tissue in the hilus, suggesting obstruction to lymph flow[2]. Many of the dogs reported with primary lymphoedema have had small or absent lymph nodes, the initial defect having been reported, as in humans, as fibrosis of the lymph nodes[8] and leading to secondary obstructive changes in lymph vessels due to chronic overdistension, loss of contractility and/or non-functional lymphatic valves. The remaining human cases either had a reduced number of lymphatics on lymphography, described as 'obliterated' lymphatics, and were possibly born with too few lymphatics (hypoplasia) if they manifested early clinically; or those manifesting later in life may have acquired obliterative disease of obscure cause – this latter group comprising the majority of lymphoedemas[2].

In humans, primary lymphoedema has been classified into hereditary and non-hereditary, with the oedema in hereditary cases present at birth or in early childhood (Milroy's Disease), with late onset between the 1st decade and puberty (Meige's disease), or, exceptionally, after age 35 years[3]. Non-hereditary primary lymphoedema may also occur at birth or later in life[3]. Genetic mapping of the autosomal dominant form of hereditary primary lymphoedema (Milroy's disease) suggests a mutation that inactivates the vascular endothelial growth factor C receptor (VEGFR-3) tyrosine kinase signalling mechanism felt to be specific to lymphatic vessels[22,33]. This was recently used immunohistochemically to show up lymphatic-origin vessels in normal skin and vascular tumours of lymphatic origin[16,30]. Other congenital lymphoedemas mostly cluster in families, with an autosomal dominant pattern of transmission and involving various genes, locus heterogeneity and/or environmental determinants[22,33]. 'Lymphoedema – distichiasis' syndrome in humans is an autosomal dominant disorder characterised by lymphoedema of the lower limbs, together with a 2nd row of eyelashes growing from the meibomian glands, as well as other developmental defects, including cardiac defects, cleft palate and extradural cysts. This suggests a gene defect with pleiotropic effects acting during development[33]. Apart from the

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VEGFR-3 gene mutation, a 2nd gene, *FOXC2*, which directs development of a variety of embryonic tissues, was identified[33]. It is also known that an inactivated 2nd X chromosome or else the Y chromosome is necessary to prevent XO Turner syndrome in man[33]. It is hypothesized that a gene or genes expressed from non-inactivated portions of the inactive X or the Y chromosome are involved in the development of the lymphatic system, and a deficiency of the product of this gene is responsible for the Turner syndrome phenotype, which includes peripheral lymphoedema[33]. Down syndrome (trisomy 21) may occasionally present with foetal cystic hygroma, lymphoedema and intestinal lymphangiectasis, in addition to anomalies of the blood vessels and heart[33].

Primary lymphoedema may manifest at any phase of life but most commonly appears at puberty in humans. However, acquired lymphoedema is much more common[28,33], occurring secondary to especially parasitic (filarial) and other infections, and less commonly to cancer invasion, cancer treatment (surgery and irradiation) and trauma[33]. Primary lymphoedema predominates in human females with an estimated ratio of 10:1 (females to males), suggesting oestrogenic involvement[22]. Exogenous (as in oral contraceptives) or endogenous oestrogen (at puberty) appears to stimulate lymphangioma and other angiotumour growth[33]. A similar sex predisposition was not apparent in reports of dogs with lymphoedema[8].

Any condition diminishing lymphatic contractility, whether primary or acquired, will also result in lymphoedema[2,8]. Lymphatic contractions are stimulated by noradrenaline, serotonin, prostaglandin F2 alpha, thromboxane B2 and endothelin; they are inhibited by haemoglobin and haem-containing proteins and oxygen free radicals[27]. Lymphatic endothelium can also automodulate contractions by the local production of nitric oxide[27]. Lymphatic propulsion is generated primarily by intrinsic smooth muscle contractility of the lymphatic truncal wall, which beats rhythmically and independently of respiration and cardiac activity[33]; only larger lymphatics have a thin muscular wall.

Very rarely, with only 12 cases having been reported in humans[3] and 1 case confirmed in a dog[31], lymphangiosarcoma has arisen in cases of primary lymphoedema.

Very occasional postmastectomy cases of lymphangiosarcoma had no clinical history of lymphoedema, or oedema had subsided several years prior to onset of the tumour[6]. Roentgen therapy either pre- or post-operatively may play a role in the pathogenesis of lymphangiosarcoma in humans due to aggravation of lymphatic occlusion, but some cases had no radiation therapy, or the tumour arose in the contralateral non-irradiated limb[6]. Lymphangiosarcoma is known to extend rapidly in the subcutaneous tissues distally, circumferentially and proximally, with infiltration along the deep intramuscular fascial septae, and with lymphatic and haematogenous metastases to the thoracic wall, pleura and lungs most frequently, but few organs may be spared. Mean human survival time was just over 1.5 years with a range of 2 months to 5.5 years[6] and overall prognosis is considered poor[3,13] to extremely poor[29].

Chronically lymphoedematous tissue is prone to recurrent infection, microbial growth being encouraged by the surplus protein-rich interstitial fluid. Lymphatic dysfunction also impairs local immune response and regional immunosurveillance [7,22,31], sometimes being referred to as 'immunodysregulation'[33]. In chronic lymphoedema, macrophages are dormant, no longer functioning to lyse the large amount of protein in the interstitial fluid; this includes a deficiency of collagenase, which is produced by macrophages[7]. Benzo-pyrones are a group of drugs that have been successfully used to treat experimental lymphoedema in dogs and spontaneous lymphoedema in humans. The group has multiple actions but the main one is stimulation of macrophages, which therefore promotes proteolysis, after which protein fragments can be reabsorbed directly into the blood stream. These drugs are active orally and topically, are inexpensive, and include coumarin, diosmin and rutin[7,31]. They have been reported to be free of side-effects[7]. However, in one American multicentre study, 6 % hepatotoxicity was observed in humans[15,19]. Lymphoedema secondary to irradiation has recently been reported to respond to treatment with sodium selenite in humans[19] and 1 paper described temporary post-mastectomy success with quanethidine used intravenously as a regional sympathetic block[7]. A hypothesis explaining the success of quanethidine suggested that improved perfusion resulting from vasodilatation facilitated drainage of extracellular fluid.

Most therapeutic modalities for lymphangiosarcoma have had little or no effect in humans and wide local excision or intensive radiation or both, regional intra-arterial perfusion with chemotherapeutic agents, or early radical amputation are recommended if diagnosis is made early. Delay in diagnosis has contributed to the relatively poor response to treatments. Occasional patients are long-term survivors, with tumour morphology not appearing to influence prognosis[4,6]. Therapeutic consensus has not been reached in human medicine on account of the rarity of the tumour. In metastatic or locally advanced tumours use of more recent cytotoxic drugs known to be effective on soft tissue tumours may be considered[13].

DIAGNOSIS

The characteristic normal histological lymphatic phenotype has been designated as staining negative for PAL-E (vesicular component in blood vessel endothelium), PECAM, CD34, basement membrane components laminin and Type IV collagen and von Willebrand's factor (vWf or factor VIII-related antigen), and positive for VEGFR-3, alkaline phosphatase, 5'endonuclease, podoplanin, junctional protein desmoplakin, LYVE-1 (a homologue of the hyaluronan receptor CD44)[33], vimentin[26] and proliferating cell nuclear antigen (PCNA)[26]. However, these staining characteristics may vary with species, vessel calibre, stage of embryonal development, level of gene expression and a variety of physiological as well as pathological conditions, such as neoplasia[33]. They may also not stay persistent in tissue culture[33], where cells may be positive for von Willebrand factor (vWf) and also express antithrombin 3 and MHC1 on the cell surface[33]. In tissue culture, characteristic overlapping cell junctions have been noted in normal and lymphangioma-derived endothelium and tight junctions are rare; VEGFR-3, fibronectin, F-actin, *Ulex europaeus* ligand (UEA-1, a lectin of human and canine[5] blood vascular endothelium), and Weibel-Palade bodies have been documented, whereas chemical enzyme markers such as 5'endonuclease, adenylate and guanylate cyclase enzymes are lost[33].

Endothelial expression of glycoconjugates has been studied in normal human vascular and lymphatic endothelium, normal dog vascular endothelium, human and canine haemangiosarcoma[5], a canine lymphangiosarcoma using only UEA-1 and *Arachis hypogaea* (PNA)[26] (neither vascular endothelium nor LAS cells were positive for UEA-1, but vascular endothelium picked up PNA), and a canine lymphangiosarcoma using 20 lectins to compare differences in phenotypic characteristics with 4 canine haemangiosarcomas[5]. In the latter study, only the lymphangiosarcoma stained with Con A, UEA-1, PNA, RCA-1 and sWGA, whereas PHA-E only stained the haemangiosarcomas. With BSL-1, BSL-II, SJA, PHA-L and ECL there was no stain-

ing of any of the tumours tested, and the remaining lectins stained both tumour types[5].

LYMPHANGIOSARCOMA IN DOGS

Various well-known veterinary texts have described lymphangiosarcoma in dogs as rare[18,25,32] to extremely rare[21] and could only refer to the few cases reported at the time of publication of their texts. In current research of the literature for the purpose of this review, only 16 reported canine cases were found[1,5,9,10–12,14,17,20,23,24,26,30,31], the 1st being in 1981 by Kelly *et al.*[12], with sporadic case reports since then. Only one of these was reported as the 1st confirmed case of lymphangiosarcoma associated with primary lymphoedema due to congenital lymphatic system dysplasia[31]. This was a 4-year-old spayed female Bouvier des Flandres described by Webb *et al.* in 2004[31], which had aplasia of the popliteal lymph nodes, and which had manifested hind limb oedema from the age of 8 weeks. It had a lymphangiosarcomatous inguinal mass, which had been noticed only 45 days prior to referral.

Table 1 summarises the 16 canine cases of lymphangiosarcoma reported, giving breed, sex, age, duration of signs or lesion before referral or diagnosis, site/s of lesion, and metastasis if it occurred. Of the cases reported, 7 were female[5,10,12,23a,23b,26,31], of which 2 were recorded as having been spayed[23a,31], and 9 were male[1,9,11,14,17,20,23c,24,30], of which 3 had been neutered[5,9,14]. Their ages at presentation for the tumour ranged from 8 weeks to 13 years, with 9 dogs being 5 years or older.

The majority presented with subcutaneous oedema involving the trunk (inguinal, axillary, thoracic, mammary, limb/s, head or neck) with only 2 of the 16 having had no clinical oedema[11,26]. Baseline haematological and serum chemistry values at presentation were in most cases within normal limits, except for the Toy poodle[20] which had a seemingly unrelated bleeding tendency, and the terrier cross[14]. In the terrier cross there was severe pleural effusion, inappetance and chronic cutaneous drainage from the skin tumour. Later, this animal developed neutrophilia, hyponatraemia, hyperkalaemia, hypochloraemia, hyperaldosteronaemia, azotaemia and hypoproteinaemia[14].

Histopathological examination of formalin-fixed specimens of either the presenting mass, oedematous skin and subcutaneous tissue, or internal fluctuant masses, was diagnostically definitive in all cases presenting with such clinical signs, with the typical picture of neoplastic lymphatic endothelial cells lining channels devoid of blood. Where this was done early after presentation, it saved numerous other tests, which were perhaps helpful but not diagnostic. Immunohistochemistry for factor VIII-related antigen performed on formalin-fixed biopsied tissue was mostly weakly positive in the 5 cases in which it was done[1,5,9,11,24]; vimentin was clearly positive in the 3 dogs in which it was performed[5,9,24] , and cytokeratin was negative in the Doberman pinscher reported by Sagartz[24]. Lectin histochemistry was done on tissues from the poodle[5] post mortally and compared with 4 haemangiosarcomas from other dogs, RCA-1 labelled the lymphangiosarcoma the most intensely and with the widest distribution as opposed to PHA-E which labelled the haemangiosarcomas. Transmission electron microscopy was performed on tissues from the Doberman pinscher reported by Sagartz[24] and showed numerous micropinocytotic vesicles and a continuous basal lamina.

Other commonly-performed tests included radiography (mentioned in 13 of the 16 cases), as well as the more specialised radiographic techniques of sialography[10], angiogram[9], lymphangiogram[30], and retrograde urethrogram[14]. Ultrasound examination[1,9,20,30,31], echocardiography[9,20], lymphoscintigraphy[9,3], fine needle aspiration or thoracocentesis[9,10,–12,14,20,23,30], culture[10,12,20] and electrocardiogram[1] were also variably performed. Other tests and techniques were done depending on clinical variations, attempts to exclude other differential diagnoses, or attempts to surgically alleviate symptoms, according to the specific cases.

Five dogs were recorded as having had pleural effusion[1,9,12,14,23] and 2 had chylothorax[20,30]. All dogs except 1 Poodle[26] and 1 Toy poodle[20] were medium- to large-breed dogs. Golden retriever[10,30] and Doberman pinscher[5,24] were the only breeds represented twice each. Tumour growth was generally rapid once it either appeared for the 1st time, or started enlarging or spreading, with the duration prior to presentation or referral being from 3 weeks to 6 months, despite the duration of prior lesions, which in some cases was up to a few years[12,23b,31]. Exceptions to this were a Poodle[26] and a Rhodesian ridgeback[1], which both showed gradual tumour progression over years. The only cases which were apparently successfully treated without recurrence by the time of publishing, were the Poodle[26] (with successful surgical excision), and a Siberian husky[11], where recurrence after excision occurred but was subsequently successfully treated with doxorubicin. However, neither of these animals had presented with subcutaneous oedema. The 8-week-old Doberman pinscher puppy[24] with lymphangiosarcoma affecting the left inguinal subcutis underwent surgical excision of the mass, which also contained a testis, epididymis and lymph node. The tumour involved the deep dermal and subcutaneous inguinal tissues as well as 1 pole of the excised lymph node. Following surgery the right hind limb became oedematous and painful, and some large subcutaneous vessels were observed along the ventral body wall extending to the right axilla. This puppy was then experimentally treated with a morpholino-doxorubicin derivative, FCE 27362 for 6 treatments (18 weeks). After the 1st treatment, full use of the right hind limb resumed and the incisional discharge ceased; 6 weeks later the axillary swelling had completely disappeared. After the 6th treatment the pup was clinically normal apart from a small area of residual fibrosis at the surgical site. At 7 months of age he developed parvoviral enteritis, which was successfully treated, but at 8 months septic polyarthritis led to euthanasia. Cosmetic necropsy revealed a fibrotic scar and gelatinous subcutaneous fat in the left inguinal region, and the left axillary lymph node adhered to the thoracic wall. Well-differentiated lymphangiosarcoma was diagnosed histologically at the site of original tumour (left inguinal) and in the left axillary lymph node, therefore treatment had not been curative. All other treatments described in the canine reports were merely palliative and did not alter the course of the malignancy. These included rutin[30,31]; antibiotics such as cephalexin, enrofloxacin, norfloxacine, or tetracycline[1,5,9,12,14,17,20,23a,30,31]; diuretics[9,12,30]; corticosteroid such as prednisolone[1,9,12,14,17]; antihistamine[9]; butorphenol[20]; L-thyroxine (this Golden retriever had been on L-thyroxine from 6 months of age)[30] ; surgery (surgical excision of tumour or related tissues)[5,11,14,23a,24,26]; enzymes[12] and drainage or aspiration[12,14,23a,23b].

Factor VIII-related antigen (fVIII) immunopositivity is not always present in lymphatic endothelium, as mentioned previously[33], and most of the canine lymphangiosarcomas were reported to stain only slightly as compared with the vascular endothelium in the same sections or controls. Meuten stated that although fVIII immunopositivity has traditionally been considered diagnostic for haemangiosarcoma, many haemangiosarcomas will not stain for fVIII, and some lymphangiomas and lymphangiosarcomas will[18]. This is borne out by the variable presence of Weibel-Palade bodies in lymphangiosarcoma cells[33].

Lymphangiosarcoma generally spread extensively from the primary subcutaneous

Table 1: **Summary of reported canine cases of lymphangiosarcoma.**

Breed	Sex	Age	Duration of lesion	Site/s of lesion	Spread or metastasis
Great Dane[12]	Female	2,5 y	12 mo L shoulder swelling. 55 d post-injury LF	L shoulder + fore limb, axilla oedema SC, PE	Lungs + pleura, regional lnn, kidney, bone marrow, spleen (many small)
Golden retriever[10]	Male	7 mo	4 mo	Mass under chin	Recurred 6 w post surgery; after 7 mo mandible invasion, 2–3 mm mets in regional lnn + lungs (?PE)
Pointer[23a]	Female (spayed)	13 y	4–5 mo	Lobulated fluid inguinal mass from vulva to medial right thigh	PM (euthanased); pelvic canal to kidneys
Chow chow[23b]	Female	5 y	27 mo; 4 mo enlarged	SC oedema left axilla, L/R mammary, PE	Spleen – multiple 8 mm foci in capsule
English pointer[23c]	Male	11 y	5 mo + 2 mo progress	SC oedema preputium, R hind	Sublumbar, pelvic canal
Doberman pinscher[5]	Female	1 y	6 mo, gradual growth of mass	Swelling SC L axilla, axilla + prescap ln	Mediastinal lnn
Irish setter[17]	Male (castrated)	5 y	3 w+	Left thorax SC mass oedema, ecchymoses (?trauma)	Extension to brisket, R thorax. Euthanased, PM. Liver, kidneys, spleen?
Terrier cross[14] (22.7 kg)	Male (castrated)	13 y	18 w, acute onset	SC prepuce, ventral abdomen, hindlimbs, scrotum. PE	Euth., no PM. ?Thorax
Poodle[26]	Female	11 y	6 y	SC mass R chest + mammary. No oedema	None seen
Toy poodle[20] (3.4 kg)	Male	10 y	3 w progr. Cough/dyspnoea, bleeding tendency [occ. cough since pup; tracheal collapse; 5 m previous chest trauma]	Cranial mediastinum + ln LAS; secondary truncal SC oedema, Chylothorax	None found on PM (euthanased). Widespread lymphatic hypertension (lnn dilated sinuses and haemorrhage)
Doberman pinscher[24]	Male	8 w	3 w (7mo – parvo, 8 mo septic poly-arthritis; euthanased)	Left inguinal SC oedema	Inguinal + axillary ln, R axilla, tunica albuginea testis, ventral body wall. PM – L inguinal + L axillary ln
Rhodesian ridgeback[1]	Male	11 mo	38 mo ongoing, gradual; + 3 acute episodes	RF SC, skeletal muscle oedema/LAS 3 y later PE	PM – pancreas, spleen, liver, lung, extra-caps kidney, omentum, mesentery, mediastinum
Chesapeake Bay retriever[9]	Male (castrated)	3 y	2 mo – acute oedema, later dyspnoea	SC oedema head, neck, cranial trunk; PE	?Chest. No PM Diffuse SC LAS of oedematous areas
Golden retriever[30]	Male	8 y	2 mo	Pulmonary pleura; persistent chylothorax	None on PM
Siberian husky[11]	Male	9 y	6 mo	SC L cervical mass. No oedema	None. Recur 3 w post surgery. Remission chemo 8 mo+
Bouvier des Flandres[31] [primary lymphoedema]	Female (spayed)	4 y	Hindlimb oedema from 8 w old; inguinal mass 45 d prior to referral	Inguinal mass (L); hindlimb oedema; lymphorrhea; popliteal lnn absent	Unknown: euthanasia due to seizures, head tilt 8 w post-operative. No PM

Key to abbreviations: L, left; R, right; LF, left fore; RF, right fore; LAS, lymphangiosarcoma; PM, *post mortem*; SC, subcutaneous; PE, pleural effusion; ln, lnn, lymph node/s; progr, progressive; chemo, chemotherapy; mets, metastases; haem, haemorrhage; occ, occasional; caps, capsule; d, day/s; w, week/s; mo, month/s.

site to involve underlying muscle and surrounding soft tissues, or by occasional local invasion into abdominal tissues[23a,23c]. Once the tumour became noticeably active, it seemed to spread rapidly, invading surrounding tissues, and, on occasion, metastasized or extended internally, with pulmonary or mediastinal involvement being relatively frequent[1,5,10,12,20,30], but with abdominal organs also being affected in several individuals[1,5,12,17,23a–c].

Some cases had quite possibly metastasized but necropsy was not performed[9,14,31].

DISCUSSION

Similar genetic studies as in man, for example where the *FOXC2* and *VEGFR-3* gene autosomal dominant mutations were found in human 'lymphoedema-distichiasis' syndrome[33], would be an interesting comparative exercise in dogs with multiple congenital defects which include dysplasia of the lymphatic system. The origin, in humans, of some simple lymphoedemas or chylous refluxes, as in chylothorax, chylous ascites, chyle reflux into limb lymphatics, in the kidneys (chyluria) and the uterus and vagina (chylo-metrorrhagia), have been ascribed to congenital or acquired abnormalities of the central abdominal or thoracic collecting ducts[2]. In the 2 canine cases in Table 1 where thoracic duct ligation was done, no obvious abnormalities had been found in those structures during the procedure[20] or on prior lymphangiogram[30].

Lymphangiosarcoma in both humans and the dogs reported to date appears to arise most commonly in anatomical regions where there has been prior lymphoedema,

whether of primary or secondary origin. Lymphoedema is often of lengthy duration, especially in humans, suggesting that the lingering protein-rich interstitial fluid might be a stimulus for neoplastic transformation. However, a few cases of lymphangiosarcoma in both man and dogs have not been associated with prior lymphoedema. It has been shown that *in vivo* transplantation of lymphangiosarcoma to the extremity of a lymphoedematous limb was more successful than transplantation to a healthy limb, suggesting also possible local immunodeficiency and/or chronic physical pressure on lymphatic endothelium to be factors in tumorigenesis[9].

Lymphatic neoplasia should be considered as a differential diagnosis in all cases of non-resolving lymphoedema, most cases usually presenting with subcutaneous oedema or a fluctuant subcutaneous mass and/or clinical signs related to thoracic effusion. Early, and if necessary repeated, biopsy and histopathological examination of any non-resolving oedematous mass in dogs is recommended for diagnosis of lymphangiosarcoma.

It is quite likely that other cases of lymphangiosarcoma have been diagnosed but not reported, or have gone undiagnosed or misdiagnosed. Of those reported, specific examination of the lymphatic system in general was often not mentioned. More attention, focussed on possible abnormalities of the lymphatic system in future cases of canine lymphangiosarcoma, is warranted.

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