Lymphangiosarcoma in a 3.5-year-old Bullmastiff bitch with vaginal prolapse, primary lymph node fibrosis and other congenital defects

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ABSTRACT

Lymphangiosarcoma is an extremely rare tumour in dogs with only 16 cases reported in the literature. Lymphoedema, which may be primary due to defects in the lymphatic system, or secondary to various other pathologies, often precedes malignancy. Of the 16 canine reports, only 1 dog was confirmed as having had prior primary lymphoedema due to aplasia of the popliteal lymph nodes. A case of lymphangiosarcoma is described in a 3.5-year-old purebred, Bullmastiff bitch which presented with vaginal blood 'spotting' for 3 weeks after cessation of oestrus, during which intromission by the male had been unsuccessful. During ovariohysterectomy a large multicystic, proliferative, spongy, fluid-filled, brownish-red mass surrounding the cervix and projecting into the abdominal space was removed with the cervix, and a diagnosis of lymphangiosarcoma made on histological and electron microscopic examination of the tissue. Ultrastructurally, no basement membrane or pericytes were found, only some of the neoplastic endothelial cells were linked by tight junctions while there were gaps between others, and neither micropinocytotic vesicles nor Weibel-Palade bodies occurred in the cells examined. Very few of the endothelial cells lining the many interlinking, tortuous maze of channels, stained slightly positive immunohistochemically for factor VIII-related antigen. The channels were filled mostly with serous fluid, and occasionally mixed leucocytes and some erythrocytes. The endothelium was often associated with underlying blocks of collagenous material, as well as loosely-arranged aggregates of lymphocytes, other mononuclear cells and occasional neutrophils in the connective tissue septae and more prominently perivascularly. The bitch was discharged on antibiotic treatment but returned 2 weeks later with apparent prolapsed vagina which failed to reduce over the next week. Laparotomy revealed the tumour to have spread extensively in the caudal abdomen to involve the broad ligament and the ventral rectal serosa, and the 'prolapsed' tissue was found to be expanded vaginal wall. The bitch was euthanased and necropsied, Histological examination confirmed lymphangiosarcomatous invasion of the submucosal and muscular layers of the retroperitoneal, traumatised, prolapsed part of the vagina, the urethra and the ventral rectal wall. The broad ligament was diffusely invaded with tumour which had proliferated into the caudal abdominal space, and 3 small intra-trabecular foci of tumour were found in the right popliteal lymph node near the hilus. Mitotic figures were generally scarce. There was mild subcutaneous oedema of the ventral trunk extending from the axillae to the inner proximal thighs, which had not been evident clinically, and the lymph nodes (peripheral more so than internal) microscopically showed marked trabecular and perivascular fibrosis especially in hilar regions. Other congenital defects were hepatic capsular and central venous fibrosis with lymphatic duplication and dilatation in all areas of connective tissue, ventrally-incongruous half-circular tracheal rings, and multifocal renal dysplasia affecting the right kidney. There was locally-extensive subacute pyelonephritis of the left kidney.

Key words: cervix, congenital defects, dog, histopathology, lymphangiosarcoma, lymph node fibrosis, lymphoedema, ultrastructure, vagina.

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INTRODUCTION

Lymphangiosarcoma is an extremely rare, generally aggressive malignant tumour which has been reported in humans[3,5,19,26], only 16 dogs[1,4,8,9,14–18,20,22,24,27,29], a similar number of cats[19,11,12,25,28], 2 horses[13,23], and a cow[21]. Lymphangiosarcoma in dogs, with comparison with that in humans, is reviewed in a companion article[30]. The tumour arises from lymphatic lining endothelium, often in the skin or subcutis, and was originally reported in humans by Stewart and Treves in 1948 in patients having had chronic lymphoedema of extremities after radical mastectomy for breast carcinoma, which had included lymph node resection and/or radiation, thereafter becoming known as 'Stewart-Treves' syndrome[3,5,19,26]. Lymphangiosarcoma in humans has also occasionally arisen following lymphoedema of other origins such as primary lymphoedema due to defects in development of the lymphatic system, or secondary to the likes of inflammatory disease, surgical procedures, trauma, idiopathic, congenital pathology or filarial infestations[5]. In most cases lymphangiosarcoma rapidly invades and infiltrates adjacent tissues and metastasises *via* haematogenous and lymphatic routes internally, often involving the chest, but other organs and cavities may also be involved[5,12,13,23,30]. The majority of reported feline cases, however, presented as tumours of the caudoventral abdominal wall[10–12,25,28]. Mean survival time after diagnosis and/or surgery is generally short in most species and the overall prognosis, as in humans, is considered poor[3] to extremely poor[26].

The 1st canine case was reported by Kelly in 1981[15], with only sporadic reports since then. Most cases were in medium to large breed dogs with ages ranging from 8 weeks to 13 years but with a slight majority in male dogs and dogs 5 years or older[30]. Only 1 canine case was related to primary congenital dysplasia of the lymphatic system, that being in a 4-year old Bouvier des Flandres described by Webb et al in 2004[29] with aplasia of the popliteal lymph nodes. However, lymphoedema in dogs due to primary lymphatic system dysplasia is recognised[7], the defect most commonly being small or absent lymph nodes, with lymph node fibrosis being reported as the initial defect, and leading to secondary lymphatic obstruction. Very few cases of lymphangiosarcoma arising from primary lymphoedema have been reported in humans[3]. Primary lymphoedema predominates in human pubertal females, suggesting an oestrogenic link[19] but a similar sex predisposition has not been found

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in lymphoedematous dogs[7].

Chronically lymphoedematous tissue is prone to recurrent infection due to it being protein-rich, as well as to the associated impairment of the local immune system and regional immunosurveillance[6,19,29,31]. Lymphangiosarcoma appears in most species to arise most commonly in anatomical regions having been lymphoedematous, whether of primary or secondary origin, and especially in humans, this is often of long duration[5]. This suggests that lingering protein-rich interstitial fluid and/or chronic physical pressure on lymphatic endothelium may be stimuli for neoplastic transformation[8].

CASE HISTORY

A 3.5-year old purebred Bullmastiff bitch with no apparent inbreeding in the 3 preceding generations and with no previous medical history of disease, was presented to the 2nd author 3 weeks after oestrus, during which the male had made unsuccessful attempts at mating due to unsuccessful intromission. She had then 'spotted' blood droplets from her vulva after cessation of oestrus, which had raised concern in her owner. At presentation she was playful, eating well, and with no systemic signs of disease. On clinical examination, rectal temperature was normal, the bitch was panting and all peripheral lymph nodes palpated (submandibular, superficial cervical and popliteal) were unremarkable. She was in good body condition but with a slightly dull haircoat. A mass in the caudal abdomen was palpated but not precisely located. The vulva appeared normal in size, with no fresh blood when examined, however blood was noticed when the dog moved around in the hospital kennel. Ovariohysterectomy was performed, during which the ovaries and uterine horns were normal in size and appearance, but the cervix was approximately 5 cm in diameter, due to a soft, proliferative, irregular, brown-red serosal surface with multiple fluid-filled cystic structures (Fig. 1). Most of the cervix was excised and submitted for histopathological examination, where a diagnosis was made of suspected lymphangiosarcoma, based on both H&E and immunohistochemical staining for factor VIII antigen. Scattered colonies of bacterial rods were seen under light microscopy in some sections in some of the more necrotic areas of tumour where there was also a predominance of neutrophils. The cervical mucosal glands were mildly distended, with some containing eosinophilic proteinaceous material with occasional red blood cells. The tumour did not extend to the cervical lumen, submucosa or subjacent inner 1/3 of smooth muscle. She was discharged on a week's course of broad spectrum antibiotics.

Fig. 1: **Serial transverse sections of post-ovariohysterectomy formalinised cervix with irregular lymphosarcomatous proliferation of outer mural and serosal regions.**

Approximately 14 days later the bitch was returned to the veterinarian due to development of an apparent vaginal prolapse; she was admitted for daily cleansing and attempts at reduction of the proplapsed tissue, which only illicited tenesmus and re-prolapse after each reduction. A laparotomy was performed 7 days after admission with the aim of performing an internal vaginopexy. During laparotomy, however, it was discovered that the prolapsed tissue was actually expanded vaginal wall, and similar fluid-filled friable red-brown cystic masses as had been found surrounding the cervix, were now evident involving the tissues around the stump of the vagina, and along the serosa of the base of the intra-abdominal rectum. The bitch was euthanased with an overdose of barbiturate while under general anaesthesia and necropsied the following morning.

Macroscopic necropsy findings

The body condition of the bitch was good, with the only external abnormalities being the prolapsed vaginal tissue which was erythematous, haemorrhagic and ulcerated, and the evidence of abdominal midline surgery (Fig. 2). Subcutaneous tissues of the ventral trunk, caudo-ventral abdomen and inner thighs were mildly oedematous, and perivaginal and perirectal deep tissues were oedematous and haemorrhagic. The inguinal lymph nodes appeared to be congested with moderate perinodal oedema; however, lymph node size of all peripheral and internal abdominal nodes was unremarkable.

The caudal abdomen internally showed diffuse red-brown, soft, irregular, serous-fluid-filled neoplastic tissue involvement

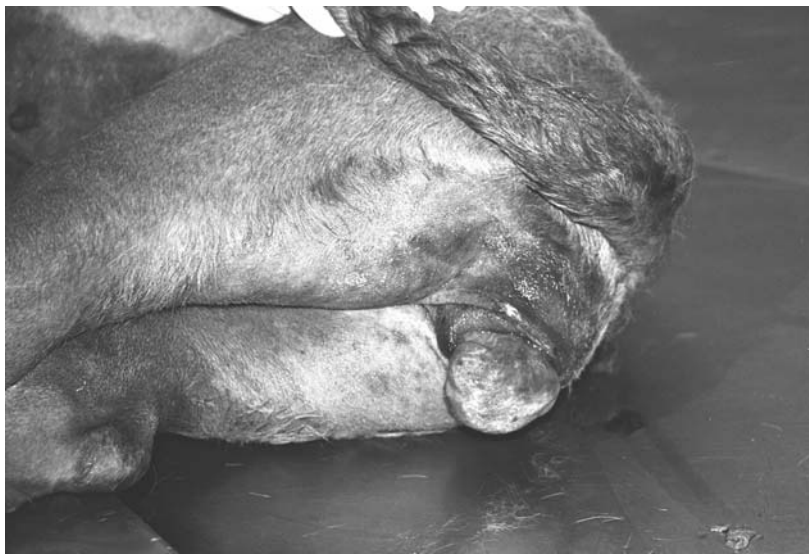

Fig. 2: **Traumatised prolapsed portion of vagina due to mural invasion by lymphangiosarcoma.**

of the broad ligament , the stump of the vagina and a locally-extensive, elliptical, plaque-like area (10 × 4 cm) of the intra-abdominal ventral rectal serosa (Fig. 3), as had been seen involving the cervix submitted previously for histopathology. The bladder wall was contracted with marked serosal congestion and mural muscular hyperplasia. The remaining genital tract along with bladder and rectum, were dissected out completely, including all surrounding retroperitoneal, intrapelvic tissues, and fixed in 10 % buffered formalin.

Other pathological findings of note were moderate size-discrepancy between left and right kidneys, with the right kidney being firm, pale, irregular and apparently fibrotic, and at least 1/3 smaller than the left. A large wedge-shaped area of medullo-cortical necrosis was situated in the middle of the left kidney (Fig. 4). There was mild mitral valvular endocardiosis with mild left ventricular eccentric hypertrophy and moderate left papillary muscular hypertrophy. The tracheal cartilaginous rings were all narrow and each petered out at the ventral midline of the trachea, with successive cartilaginous half-circles alternating with each other. Being a brachycephalic breed, there was mandibular prognathism and also mild bilateral internal hydrocephalus. On faecal flotation, a few *Ancylostoma caninum* eggs were found.

Microscopic findings

With routine haematoxylin and eosin (H&E) staining, the intra-abdominal areas of tumour involving serosal surfaces of the cervix, broad ligament, and ventral rectum comprised numerous interlinking channels lined discontinuously by elongated, variable-sized, spindle-shaped cells with plump oval to round vesicular nuclei and prominent, large and mainly single nucleoli (Fig. 5). In places these cells piled up on each other and there was invasion into the *tunica muscularis* layers of both rectum (Fig. 6), urethra and reproductive tract and in several areas also into the submucosa, with the cells mostly lining small open, vacant spaces, and surrounding bundles of muscle fibres and small regular blocks of collagen, in this way dissecting its way into tissues. Several of the neoplastic cells appeared multinucleated (2 or more nuclei were counted), or were piled up alongside each other with indistinct cell borders. Mitotic figures were generally scarce, ranging from 0 in most fields, to up to 4 in some high-power fields (×40) in more anaplastic regions of the tumour, and some of the mitoses were bizarre. The channel lumens mostly

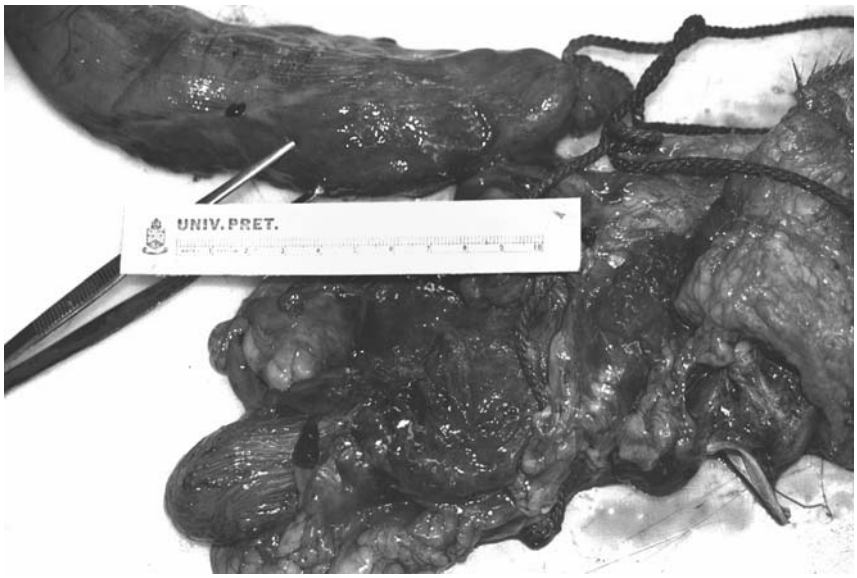

Fig. 3: **Stump of uterus, broad ligament and ventral rectal serosal involvement with lymphangiosarcoma 3 weeks after ovariohysterectomy.**

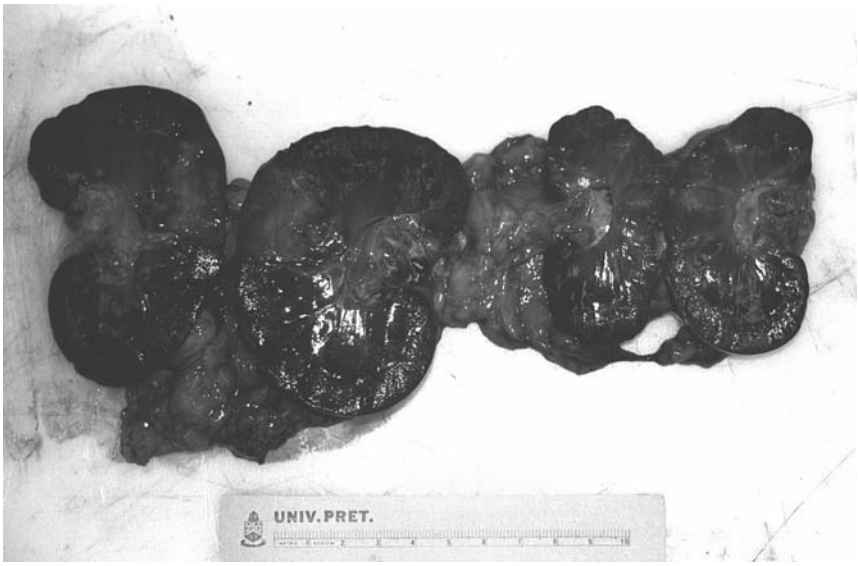

Fig. 4: **Shrunken right kidney due to multifocal cortical dysplasia; focally-extensive wedge of pyelonephritis of non-dysplastic left kidney.**

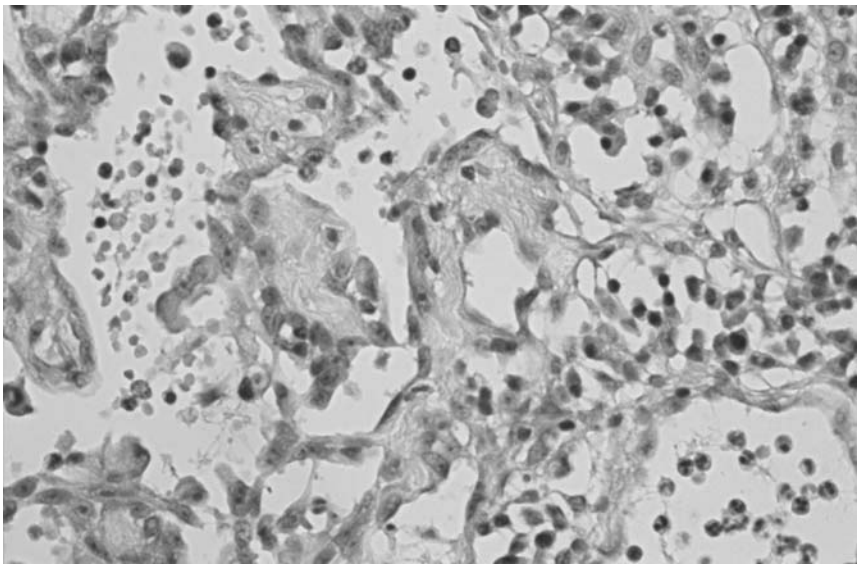

Fig. 5: **Extra-cervical lymphangiosarcoma showing neoplastic endothelial cells lining fluid-filled channels containing occasional leucocytes** (H&E, ×20).

appeared empty but within some there was pale amorphous eosinophilic material, while others contained haemolysed blood or a few intact red blood cells, and/or scattered lymphocytes and plasma cells as well as occasional neutrophils. The interstitial stromal areas were oedematous, sometimes haemorrhagic and with moderate numbers of loosely aggregated mononuclear round cells (lymphocytes, plasma cells and macrophages), variable numbers of neutrophils, and there was fairly marked interstitial mononuclear perivascular cuffing. Vascular endothelium of blood vessels supplying the areas of tumour was hypertrophic with nuclei being plump and vesicular. Many blood vessels within the interstitium displayed neutrophilic leucostasis and some areas of tumour were necrotic.

Retroperitoneally, lymphangiosarcoma was found multifocally throughout smooth muscle and fibrous connective tissue of the wall of the vagina including the caudal proplapsed region, along with marked vascular congestion, haemorrhage and oedema affecting especially the traumatised prolapsed part. This region had overlying mucosal ulceration and necrosis and chronic-active subluminal granulation tissue. The neoplastic cells made rudimentary scattered, poorly-connecting or large inter-connecting channels, extending in parts right up to the ulcerated mucosa. Similar scatterings of lymphocytes and plasma cells as seen in the abdominal regions of the tumour were present in the intervening tissues and most channels were empty or contained only a few red blood cells. The outer smooth muscle layers of the urethra were also invaded by tumour, and 3 small trabecular foci of lymphangiosarcoma were found in the right popliteal lymph node near the hilus (Fig. 7).

Immunohistochemical staining of the tumour with factor VIII-related antigen showed strong positive granular intracytoplasmic staining of all vascular endothelial cells in the interstitial tumour stroma, but only very few neoplastic lymphatic endothelial cells had very slight cytoplasmic granular positivity (Fig. 8).The left mandibular (right was not sampled), left and right inguinal, left and right popliteal, sublumbar and supra-rectal lymph nodes as well as a small node in the region caudo-dorsal to the cervical area had atrophic cortical lymphoid tissue and moderate to marked trabecular and perivascular fibrosis especially involving medullary and hilus regions; this latter change being more prominent in the peripheral than the intra-abdominal nodes (Fig. 9). Medullary sinuses and trabecular lymphatics in all nodes were

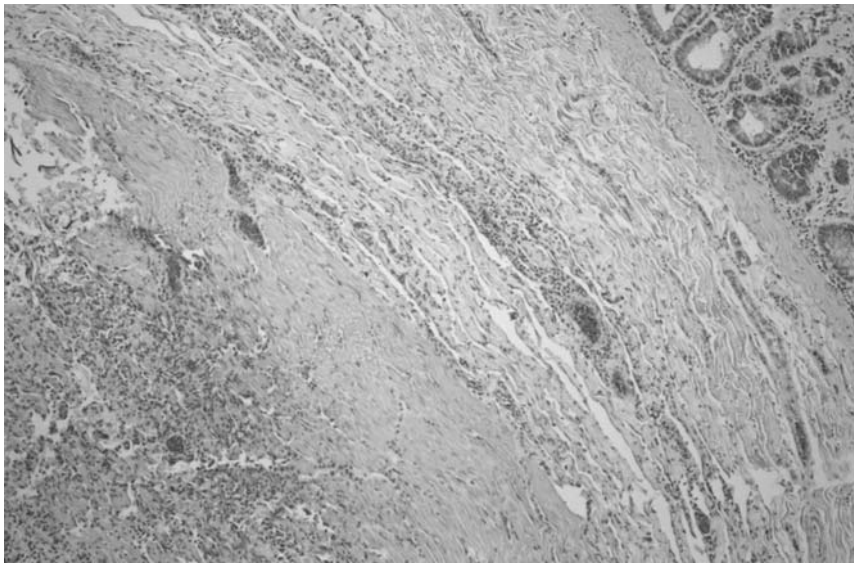

Fig. 6: **Rectal serosal, muscular tunic and submucosal invasion by lymphangiosarcoma** (H&E, ×4)**.**

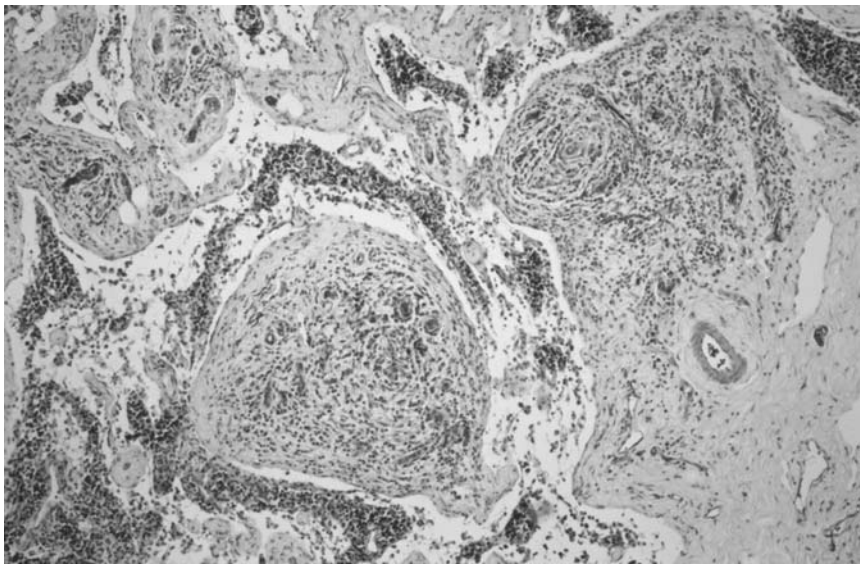

Fig. 7: **Trabecular foci of lymphangiosarcoma** (H&E, ×4) **of the right popliteal lymph node.**

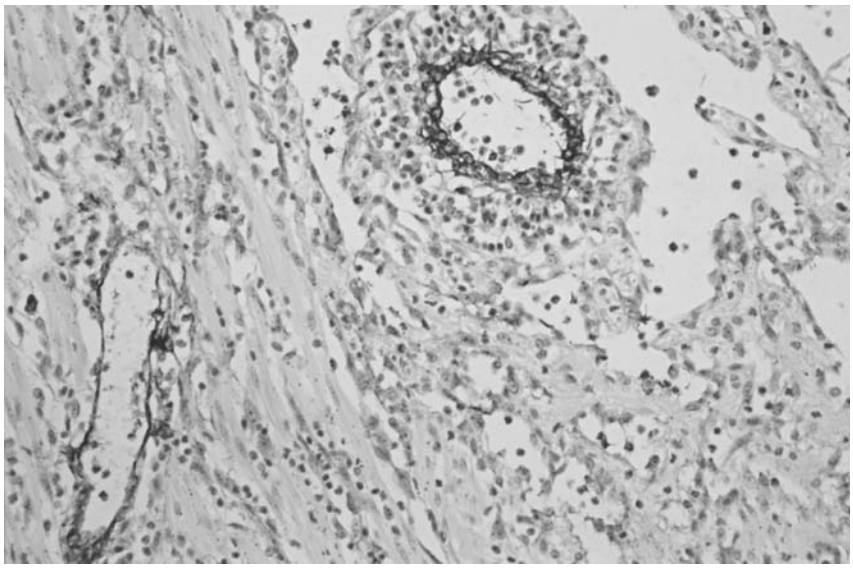

Fig. 8: **Factor VIII-related antigen immunoperoxidase staining of lymphangiosarcoma** (×10) **showing strong vascular endothelial positivity but negligible neoplastic endothelial staining.**

distended due to oedema, as well as with red cells in the caudal intra-abdominal nodes, and sinus histiocytosis was common. Some nodes (mandibular and inguinal) had a moderate amount of intracellular melanin pigment at the cortico-medullary junctions and others had intracellular haemosiderin; evidence of prior blood breakdown. The sublumbar lymph node showed perinodal/extracapsular tumour invasion. Unfortunately, skin from the oedematous area of the ventral trunk was not sampled.

Other significant histopathological findings included severe ascending purulent pyelonephritis of the left kidney, with occasional adjacent areas of subacute lymphoplasmacytic interstitial nephritis and fibrosis. There was multifocal renal cortical dysplasia of the small left kidney, displaying typical foetal glomeruli, interstitial fibrosis, scattered rudimentary tubules, protein casts and little inflammatory change.

The liver revealed moderate pericentral to midzonal hydropic cytoplasmic change in hepatocytes, as well as moderate to marked multifocal central venous fibrosis with venous and especially lymphatic duplication, and lymphatic dilatation in several portal triads as well as in areas of capsular fibrosis. There was peri-arteriolar lymphoid sheath (PAL) lymphocyte depletion in the spleen with prominent ellipsoids surrounding each PAL.

Ultrastructural findings

Electron microscopy of the intra-abdominal tumour revealed slit-like spaces lined by spindle-shaped cells, with some nuclei exhibiting prominent nucleoli (Fig. 10). No basal lamina was found lining the spaces and pericytes were also absent in the sections screened. Some of the neoplastic cells were joined by tight junctions (Fig. 11), while others had large gaps between them. Pinocytotic vesicles and Weibel-Palade bodies could not be demonstrated in the tumour cells examined. Lymphocytes and neutrophils were found within some of the cell-lined spaces as well as in the interstitium.

DISCUSSION

This case appears to be the 2nd report of lymphangiosarcoma in a dog related to primary congenital dysplasia of the lymphatic system – the 1st being that in a 4-year old spayed female Bouvier des Flandres, which had aplasia of the popliteal lymph nodes, and which had manifested hind limb oedema from the age of 8 weeks[29]. It had a lymphangiosarcomatous inguinal mass which had been noticed only 45days prior to referral.

The bitch reported currently was not

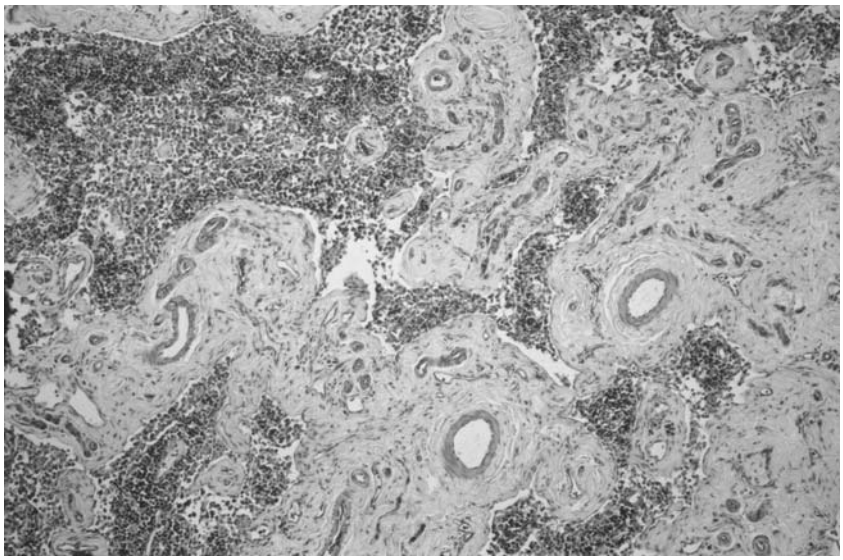

Fig. 9: **Right popliteal lymph node** (H&E, ×4) **showing marked medullary and hilar trabecular and perivascular fibrosis.**

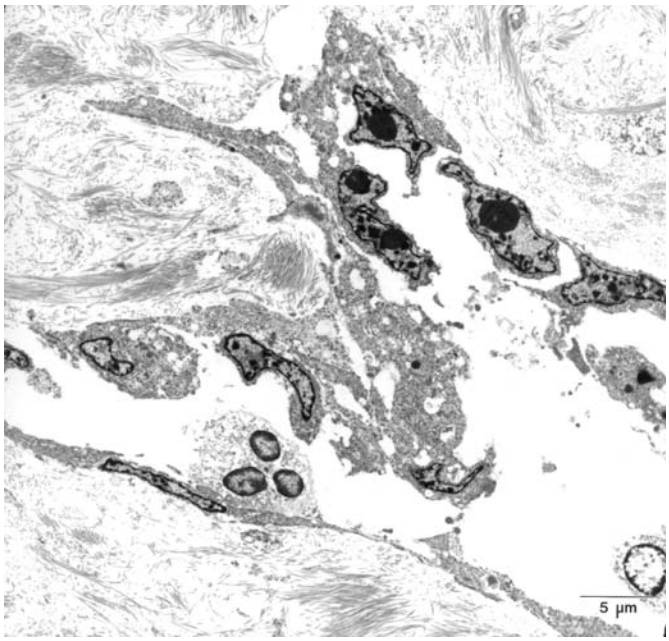

Fig.10: **Ultrastructure of lymphangiosarcoma showing spaces lined by neoplastic cells. Note prominent nucleoli, gaps between some of the cells and absence of a basal lamina.**

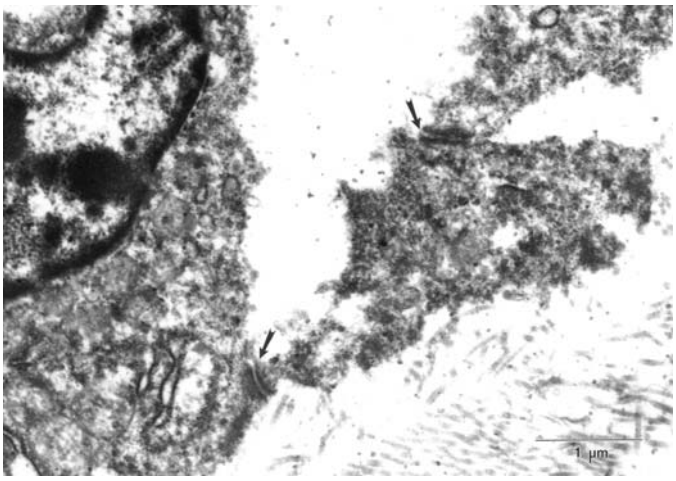

Fig.11: **Electron microscopic scan of lymphangiosarcoma showing tight junctions** (arrows) **between neoplastic cells and absence of a basal lamina.**

apparently recently inbred according to her pedigree papers, which registered the previous 3 matings on both dam and sire side. She had appeared healthy up to the time of the recent oestrus, apart from a mild hookworm infestation which may have been the cause of the dull haircoat at the time of initial presentation. The 1st sign of any problem had been the failure of intromission by the male during that oestrus due to narrowing of the vaginal lumen, and thereafter the vaginal blood 'spotting'. She had the unusual presentation of post-ovariohysterectomy vaginal prolapse due to progressive tumour invasion of the wall, making attempts at reduction impossible. The small foci of tumour in the trabeculae of the right popliteal lymph node may possibly have arrived there due to back pressure reflux from the intra-pelvic tumour. Subcutaneous oedema of the ventral trunk and medial hind limbs was relatively mild at necropsy and had never been noticed clinically. It may be speculated that the lymph node fibrosis affecting internal abdominal lymph nodes may have caused an underlying low-grade clinically unobtrusive oedema of the reproductive tract which may have worsened under the hormonal influence of oestrogen during oestrus, and these cumulative factors may have been the trigger for neoplasia.

Lymph node fibrosis has been mentioned as a primary lymph node anomaly in humans[2] and in dogs with primary lymphoedema[7], where the small shrunken lymph nodes have an increased amount of fibrous tissue in the hilum[2], much like that found in this case. This bitch also had other congenital anomalies including hepatic lymphatic and vascular derangements, unilateral renal dysplasia and abnormally-formed tracheal cartilaginous rings. Similar genetic studies as in man, for example, in which the *FOXC2* and *VEGFR-3* gene autosomal dominant mutations were found in human 'lymphoedema-distichiasis' syndrome[31], 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), has been ascribed to congenital or acquired abnormalities of the central abdominal or thoracic collecting ducts[2]. Unfortunately specific macroscopic and microscopic examination of abdominal and thoracic lymphatic trunks were not done in the bitch of this report. Very occasional human postmastectomy cases of lymphangiosarcoma had no clinical history of lymphoedema, or oedema had subsided several years prior to onset of the tumour[5].

More attention focussed on possible abnormalities of the lymphatic system in future cases of canine lymphangiosarcoma is warranted. Lymphatic neoplasia should be considered as a differential diagnosis in all cases of non-resolving lymphoedema, this case being unusual in that the primary site involved the reproductive tract and presented as failure to breed and vaginal prolapse after ovariohysterectomy. Most other cases have presented 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, skin, or subcutaneous tissue and careful investigation of pleural or abdominal tissue oedemas with effusions in dogs and other species is recommended for diagnosis of lymphangiosarcoma.

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