

Case Report

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Massive lymphangiosarcoma in a dog: a case report

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A 12-year-old neutered male Golden Retriever presented with a progressively enlarging mass in the submandibular region. Histopathological diagnosis confirmed lymphangiosarcoma with metastasis to the liver and spleen. The pleomorphic neoplastic endothelial cells of the tumor grow directly on bundles of dermal collagen, forming numerous clefts and interconnecting channels that are devoid of conspicuous hematic elements. As lymphangiosarcoma is an uncommon malignant neoplasm, the number of previously reported cases and information of the tumor is limited. The present report describes the clinical history and histopathological diagnosis of a progressive lymphangiosarcoma in the submandibular region with metastases in a dog.

Keywords: angiosarcoma; lymphatic; endothelial cells; canine; metastasis; LYVE-1

Lymphangiosarcoma is a rare tumor arising from lymphatic endothelial cells in both humans and animals [1]. Dogs in the literature with lymphangiosarcoma range from 8 weeks to 13 years of age, and most reported cases occurred in medium to large breeds with no sexual predisposition [2-4]. Lymphangiosarcoma in dogs typically presents as a poorly demarcated subcutaneous mass or focal swelling with edema tissues. Lesions have been commonly reported to originate in the subcutaneous tissue in the inguinal and axillary regions; thoracic cavity; mediastinum; limbs; ventral cervical and midline areas [2,3,5]. However, information regarding the treatment of lymphangiosarcoma is limited, and the prognosis is considered to be poor in both humans and animals because of its aggressive and infiltrative characteristics [6]. Although it has been described in dogs, cats, and horses, the number of reported cases of lymphangiosarcoma is limited in veterinary medicine [1,2,7,8]. This case report describes the clinical history and histopathological features of a progressive and metastatic lymphangiosarcoma in the submandibular region of a dog.

A 12-year-old neutered male Golden Retriever was presented to the animal hospital with a history of a progressively enlarging mass in the submandibular region, which had rapidly grown for approximately 1 month. Complete blood count and serum biochemistry analyses were within the normal ranges for the species but revealed anemia. Radiographic and computed tomographic (CT) analyses were performed for the examination of other organs and detection of metastasis. The mass was biopsied for histopathological diagnosis. The biopsied tissue was fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin wax. The samples were sectioned 4- μ m thick, stained with hematoxylin and eosin

(H&E), and Masson's trichrome (MT). Immunohistochemistry (IHC) was performed using anti-lymphatic vessel endothelial receptor-1 (LYVE-1; Abcam, UK), and examined microscopically.

On radiographical analysis, a round shaped soft tissue opacity mass sized 9.8×8.7 cm was identified at the ventral to the basihyoid bone with moderate enlargement of the retropharyngeal lymph node (Fig. 1), which was confirmed to be associated with both left mandibular lymph node and left retropharyngeal lymph node on CT images (Fig. 2A and B). Multiple oval-to-round hypoattenuating nodules of varying size were found in the hepatic and splenic parenchyma on CT images (Fig. 2C and D). Grossly, the biopsied tumor mass with whitish cut surface consisted of necrotic center and hemorrhage. Histopathologically, the pleomorphic neoplastic cells proliferated, dissecting the collagen and forming numerous collagen clefts and channels which were identified in MT staining (Fig. 3A and B). Although there were numerous necrotic cell debris with hemorrhage at the center of the biopsied mass, the anastomosing channels did not contain erythrocytes. The cells lining the clefts and channels were oval to spindle shaped nuclei with prominent nucleoli (Fig. 3C). Individual neoplastic cells with indistinct borders had a scant eosinophilic cytoplasm. A few mitotic figures were found and the mitotic count was 6 per 10 high power field. In IHC, the neoplastic cells lined arborizing channels was immunopositive for LYVE-1 (Fig. 3D), a specific marker for lymphangiosarcoma. Based on the histological findings, the mass was diagnosed with lymphangiosarcoma.

Lymphangiosarcoma is an uncommon, highly malignant, and infiltrative neoplasm that replaces and effaces the dermis and subcutis [9,10]. They occur as poorly defined fluctuant or edematous dermal masses that are often wet on cut surfaces and exude a clear serous to milky fluid [1,5]. Histopathologically, the neoplastic endothelial cells grow directly on bundles of edematous dermal collagen, dissecting them and forming nu-

merous clefts and channels. The majority of interconnecting channels are devoid of conspicuous hematic elements [1,4]. The malignant tumor lining the cleft and channels have increased cellular and nuclear pleomorphism with hyperchromatism and few mitotic figures [1]. In this case, diagnosis was achieved by histopathological examination, which showed features similar to those described in literatures about lymphangiosarcoma. Contrary to the common characteristics of lymphangiosarcoma that mitoses are not evident [1], a few mitotic figures were found in this dog, which was supposed to be related to the intense and rapidly progressive neoplastic proliferation, with distant metastases, of the tumor for 1 month. In dogs with lymph-

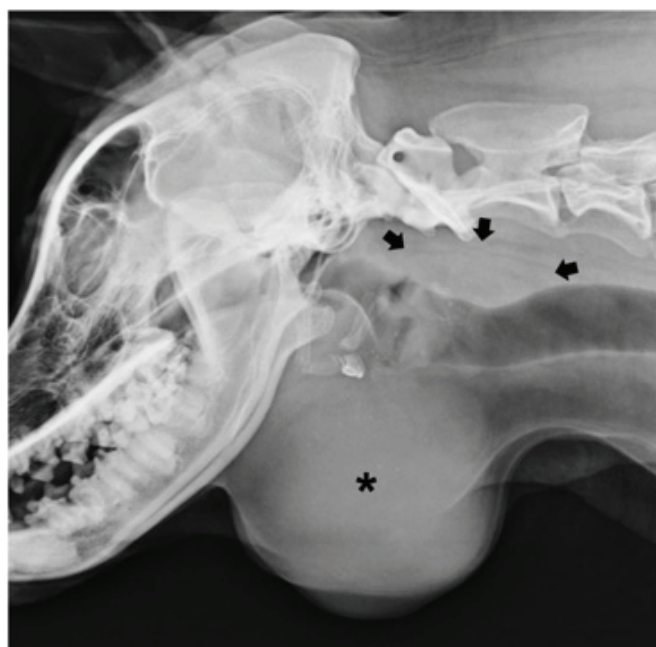


Fig. 1. The lateral head and neck radiograph. A round shaped soft tissue opacity mass (asterisk) sized 9.8×8.7 cm² at the ventral to the basihyoid bone. In addition, the moderately enlarged retropharyngeal lymph node is identified, which also leads to ventral indentation of the dorsal tracheal margin (arrows).

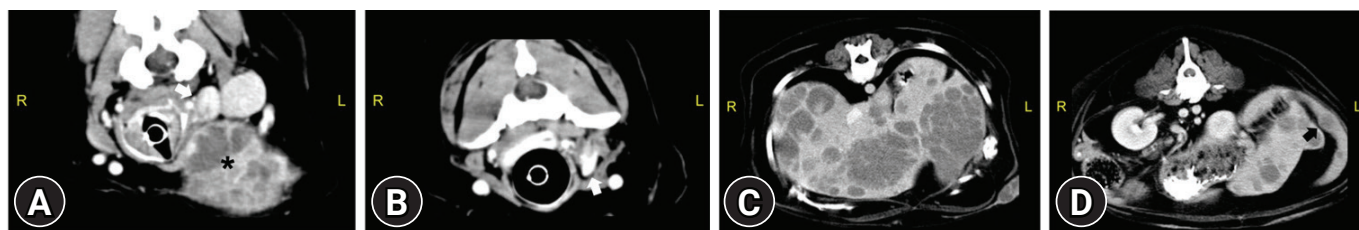


Fig. 2. Post-contrast transverse computed tomography images of the submandibular region and the abdomen. (A) The left mandibular lymph node (arrow) is moderately enlarged which is associated with heterogeneously contrast enhanced soft tissue mass (asterisk). (B) The mass extends caudally to the left retropharyngeal lymph node (arrow). (C, D) Multiple oval-to-round hypoattenuating nodules of varying size are shown, which have no contrast enhancement in the entire hepatic lobes (C) and spleen (arrow) (D).

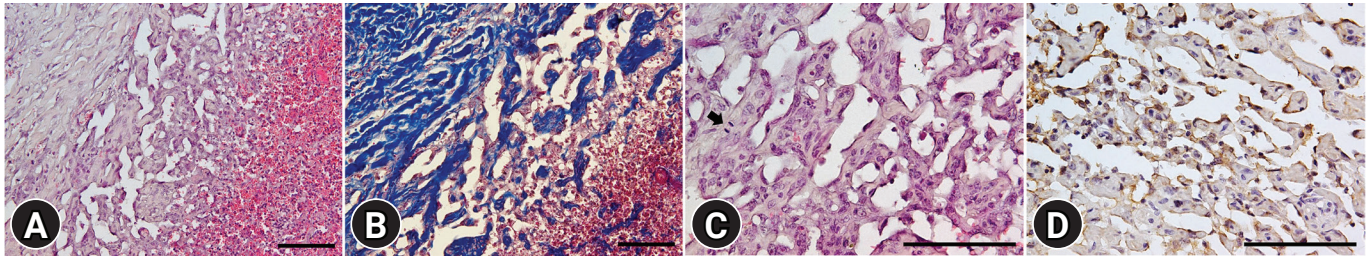


Fig. 3. Histological examination of the mass. (A) Pleomorphic neoplastic cells formed numerous collagen clefts and channels. Most of the channels had no blood, although the center of the mass was necrotic with hemorrhage on the right side of figure (H&E) (B) Numerous collagen clefts and channels are confirmed blue by Masson's trichrome staining. (C) Note spindle shaped nuclei with prominent nucleoli. Anaphase mitotic figure is found (arrow) (H&E). (D) Neoplastic cells immunopositive for lymphatic vessel endothelial receptor-1, which is a specific marker expressed on moderately to well-differentiated lymphatic vessels. Scale bars: 100 μ m.

angiosarcoma, complete blood cells count and serum biochemistry are usually within normal reference ranges; however, there are some reports of anemia in dogs with lymphangiosarcoma as our case [3].

In humans, most lymphangiosarcomas arise in regions of chronic lymphedema following radical mastectomy, which includes lymph node resection or radiation for breast carcinoma, and present as multiple nodules that invade the pleura and lungs with pulmonary metastases [11-13]. As in humans, it has been shown that lymphangiosarcoma in dogs appears to arise most commonly in anatomical regions with a history of lymphedema, suggesting that the lingering protein-rich interstitial fluid and chronic physical pressure on the lymphatic endothelium may stimulate neoplastic transformation [13]. However, because a few cases of canine lymphangiosarcoma were not associated with prior lymphedema, it is uncertain whether lymphedema is a definitive cause of the tumor [13,14].

Diagnosis of lymphangiosarcoma can be challenging because of its histological similarity to hemangiosarcoma. Tumors of both the lymphatic vascular endothelium (lymphangiosarcoma) and the blood vascular endothelium (hemangiosarcoma) are invasive, and non-encapsulated masses composed of elongated-to-plump spindle cells forming arborizing channels [2,9]. Compared with hemangiosarcoma, the irregular neoplastic vascular channels of lymphangiosarcoma are generally characterized by a paucity or complete lack of erythrocytes [5,9]. The presence of stromal edema with lymphoplasmacytic infiltration supports a diagnosis of lymphangiosarcoma [15]. However, occasionally, microscopic differentiation between lymphangiosarcoma and hemangiosarcoma with typical H&E staining alone, which is traditionally based on the presence or lack of erythrocytes within the vascular spaces, can be problematic because both angiosarcomas display overlapping histomorphological features [3,9]. IHC is recommended to definitively diagnose tu-

mors of vascular origin. LYVE-1 and prospero-related homeobox gene-1 (PROX-1) are specific positive markers of the lymphatic endothelium [9]. LYVE-1 is exclusively expressed on moderately to well-differentiated lymphatic vessels and absent in blood vessel. PROX-1 is expressed for differentiation towards the lymphatic vasculature and is expressed exclusively in the lymphatic endothelial cells at all stages of development [2,9]. Therefore, LYVE-1 can be a first choice to detect lymphangiosarcoma and PROX-1 should be used in conjunction with LYVE-1 in poorly-differentiated vascular tumor [9]. Consequently, the mass in the present case were identified to be originated from lymphatic endothelium through the IHC using anti-LYVE-1. Several studies have used transmission electron microscopy to describe ultrastructural differences between the lymphatic vasculature and the blood vasculature. Lymphangiosarcomas have a discontinuous or absent basement membrane, fewer micropinocytotic vesicles and intercellular junctions, with lack of surrounding pericytes. On the contrary, hemangiosarcomas have a continuous basement membrane, many micropinocytotic vesicles and intercellular junctions, and surrounding pericytes [2,9]. However, considering the cost and sample preparation, the routine application of electron microscopy is precluded in the diagnostic setting [9].

Although the optical treatment of lymphangiosarcoma is not well established, aggressive local therapy with either surgical excision or a combination of surgery and chemotherapy, or radiation, is often recommended. Surgery requires a wide surgical margin, but the poorly defined borders and highly infiltrative growth of the tumors make complete excision difficult [3]. Adjunctive cytotoxic chemotherapy for lymphangiosarcoma should be considered based on a moderate to high risk of metastasis to the local lymph nodes and other internal organs [3]. Previously reported cytotoxic chemotherapeutic agents include doxorubicin, carboplatin, vinorelbine, and lomustine, metro-

nomic agents with chlorambucil, meloxicam, and cyclophosphamide [2]. Chemotherapy using toceranib, chlorambucil and non-steroidal anti-inflammatory drugs was proposed for the resolution of a recurrent mass [6]. Recently, treatment of lymphangiosarcoma with toceranib, a selective inhibitor of several receptor tyrosine kinases including vascular endothelial growth factor receptor, has been considered to be effective in dogs with relapsed disease by inhibiting lymphangiogenesis [3,6,16].

The present report describes a case of canine lymphangiosarcoma with metastases to the lymph nodes, liver, and spleen. Although the number of reported cases of lymphangiosarcoma is limited, this tumor may be more prevalent than recognized, as it is likely that other cases of lymphangiosarcoma have been diagnosed but not reported, or have gone undiagnosed or misdiagnosed, which may be associated with properties of the tumor including the short survival time and similarity to hemangiosarcoma [2,3,9]. Lymphangiosarcoma should be considered as a differential diagnosis in cases of progressive and non-resolving edematous lesions with no detectable underlying causes [13]. Histopathological examination of this unusual tumor may allow for more accurate diagnosis and treatment.

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