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Primary Pulmonary Angiosarcoma in a Dog

Preeti Kumari Chaudhary, Hakhyun Kim, Daehwan Park, Dongwoo Chang, Ji-Houn Kang and Soochong Kim[1]

Department of Veterinary Medicine and Veterinary Medical Center, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk 28644, Korea

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Abstract : The prevailing discipline notes that primary pulmonary angiosarcoma is an extremely rare malignant tumor with almost grave prognosis when presented in a dog. No cases have been reported earlier as occurring in dogs. This is the first time we are reporting a case of primary lung angiosarcoma in a 12-year-old Yorkshire terrier breed dog, that will explore the clinical as well as histopathological features of the tumor as noted in a dog. In this case, radiography revealed a well-defined large soft tissue mass in the caudo-dorsal lung field across the left hemi-thorax. After necropsy, it is noted that the lung was found to have the blood-filled nodular lesions on its surface, as determined with no such lesions on other organs. Upon the histological examination, it showed the presence of an extensive necrotic hemorrhage with anastomosing vascular space. Later, the immunohistochemistry showed strongly positive CD31 cells confirming the endothelial origin of the tumor. This is the first report of canine primary lung angiosarcoma in the Republic of Korea.

Key words **:** pulmonary angiosarcoma, lung cancer, CD31, pathology, dog.

Introduction

Broadly speaking, angiosarcomas are rare soft tissue malignant tumor of endothelial origin representing less than 1% of all sarcomas in the world. The incidence of primary pulmonary angiosarcomas are the exceptional type of malignant angiosarcomas with multiple consolidations and innumerable, variably-sized anastomoshing blood-filled vascular spaces and vascular channels with vasoformative features. In this sense, it is known that lung angiosarcomas are usually metastasized from other sites of primary vascular angiosarcomas through hematogenous route. Thus, the occurrence of a primary pulmonary angiosarcoma is a very rare malignant vascular tumor with unclear clinicopathologic features, usually requiring a very aggressive course of management and treatment, and resulting in a grim prognosis.

Dogs are the most common host of this type of tumor, because of its anatomy or microvascular features, and it is known that it rarely occurs in cats, horses, cows, and sheep. Notably, the common primary visceral sites for the canine angiosarcomas include the regions of the spleen, heart, kidney, and liver. Other primary sites include cutis, lumbar muscles, larynx, retroperitoneal, peritoneum, or the breast regions.

It is emphasized that there are fewer than 31 cases of primary pulmonary angiosarcomas which have been reported in a human. No cases of the occurrence of primary pulmonary angiosarcoma in dog have been reported until this date. There is only one case reported mentioning the treatment of the primary pulmonary angiosarcoma in a dog with attenuated bacteria (10). However, no literature about the clinical and histopathological features of the disease has been explained up to now as seen in a literature review on this condition.

Because of the rarity, the understanding of the clinical significance of the primary pulmonary angiosarcoma in dogs is obscure, which functions to an obstacle which results in making the early diagnosis difficult. Various specific dog breeds such as Boxers, Basset hounds, St. Bernards, Scottish terrier, Bulldogs, Airedales, Weimaraners, Golden retrievers, Doberman pinschers, Labrador retrievers, English setters are more predisposed to the development of angiosarcomas. Additionally, older dogs between 8-13 years are also at a higher risk for developing this condition. The spayed female has five times greater risk of such vascular sarcomas than the intact female, and has the risk of 2.4 times higher even in neutered dogs than in an intact male dog to develop this condition (11).

It is noted that a comprehensive histopathological and immunohistochemical characteristics of the lesion are not yet established. There are difficulties in distinguishing canine angiosarcomas from hemangiosarcomas, especially when there is significant suffusion of the blood throughout the tumor (14). In those cases, the angiosarcomas have much less tendency to form endothelial-lined blood lakes and have severe edemas than the known presence of hemangiosarcomas (2). Identification of specific markers associated with primary pulmonary angiosarcoma using immunohistochemistry may help in the differential diagnosis of the lesion in some cases.

In what follows, there is no standard treatment for the disease. In the past, the surgical removal of locally located lesions, chemotherapy, and radiotherapy have been performed in

[1]Corresponding author.
E-mail : skim0026@cbu.ac.kr

humans (3) but still have an unfavorable prognosis in those identified cases of the disease.

Here, for the first time, we report a case of a primary pulmonary angiosarcoma in a Yorkshire Terrier breed spayed bitch, which will contribute to the understanding of a thorough description of the ongoing clinical and pathological literature of the lesion.

Case

A 12-year-old spayed bitch with complaint of experiencing difficult respiration was admitted to Veterinary Medical Center, Chungbuk National University, South Korea and had the history of gastrotomy, MGT resection, pyometra, and inflammatory bowel disease. Under physical examination of the patient, forceful inspiration, crackle sound on right thorax without a cardiac murmur, and bilateral epiphora and discharge were observed at that time. A thorough blood analysis showed the presence of neutrophilia, monocytosis, increased BUN, hypoalbuminemia, and increased CRP. At that time, the radiological examination showed a well-defined large soft tissue mass in the caudo-dorsal lung field across the left hemithorax, though the margin of mass was ill-defined in the left lateral view due to the positioning effect (Fig 1). It was shown that the cardiac axis was shifted to the right thorax because of the mass effects. Additionally, it is noted that this mass caused effacement of adjacent soft tissue structures in the lateral view, especially in the caudo-dorsal lung field. Upon review, the left cranial lung lobe was collapsed and deviated cranially though air filled bronchi which are shown. The cause was suspected to produce a mass effect which is common in sarcomas, because of the presence of solid masses type of object. The patient was temporarily diagnosed with a benign lesion based on the overall left-sided hypertrophy and right-sided displacement of the heart. Further abdominal ultrasonography showed no remarkable findings at that time.

A macroscopic examination after necropsy revealed the presence of several diffused reddish-brown or dark red nodular lesions on the surface of the lung of size 10 cm × 7 cm (Fig 2), as were found in the primary or metastasized lung angiosarcoma. The lung was diffusely hemorrhagic. No metastases were found at that time.

The lung tissue was stained with H&E stain routinely and was reviewed. A histopathological examination revealed well formed interanastomosing irregular blood vessels lined by plump and protruding atypical endothelial cells (Fig 3A and B). The tumor infiltrate had abundant various sized vascular spaces filled with blood cells. Later an immunohistochemis-

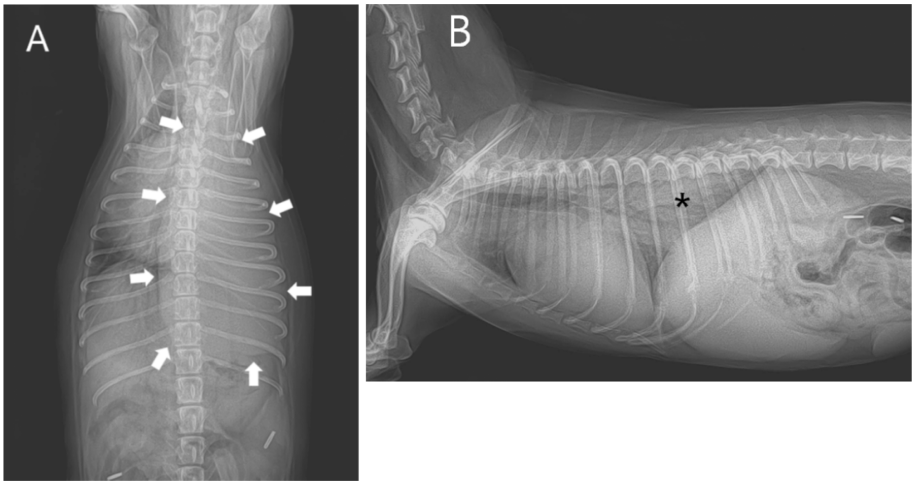

Fig 1. Radiological findings of the pulmonary tumor. Across the left hemithorax, there was a well-defined large soft tissue mass (arrowhead) in the caudodorsal lung field, though the margin of mass (asterisk) was ill-defined in the left lateral view due to the positioning effect (A: dorsoventral view, B: left lateral view).

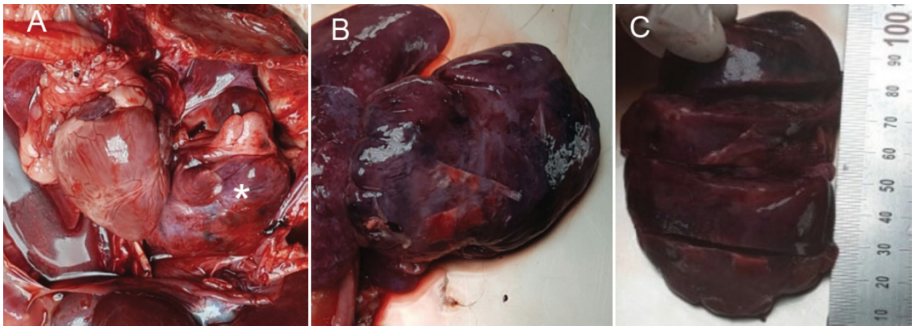

Fig 2. Macroscopic appearance of the lung. A) The lung was diffusely hemorrhagic. B) The whole surface of the lung showed multiple blood-filled reddish-brown and dark-red nodular lesions. The nodules were fused to each other forming a relatively-marginated tumor mass. C) The tumor masses were size 10 cm × 7 cm.

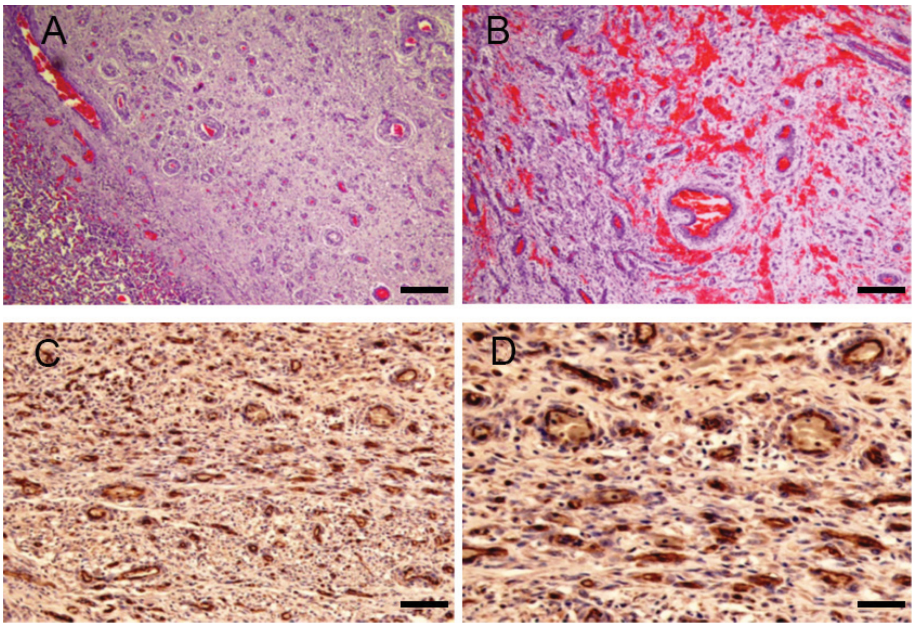

Fig 3. Histopathological observation of the lung lesions. A) The lung was mostly replaced by solid areas of vascular spaces. H&E stain. Scale bar = 100 μm B) Blood vessels were lined by plump and protruding endothelial cells. Moderate to extensive areas of hemorrhage and large vascular lumina filled with blood cells were found. H&E stain. Scale bar = 50 μm. C and D) Immunohistochemical staining of the lung lesions. The tumor cells were shown as strongly positive for anti-CD31 antibody. The stain showed diffuse strong membranous staining of the tumor cells, indicating the endothelial origin of tumors (Scale bars C = 100 μm, D = 50 μm).

try was performed using rabbit polyclonal anti-CD31 antibody (Abcam), and the tumor cells revealed strong reactivity with anti-CD31 antibody confirming the endothelial origin (Fig 3C and D). The tumor was diagnosed both histologically and immunohistochemically as a primary pulmonary angiosarcoma.

Discussion

The prevailing discipline notes that primary pulmonary angiosarcomas are very rare conditions, and characterized by the insidious growth and extensive local invasion of multiple blood-filled irregular margin nodules in the lungs. By this token, an early pulmonary angiosarcoma diagnosis may be difficult because of the unspecific respiratory manifestations. There are no symptoms specific or special gross characteristics that would differentiate these nodules from any other lung cancers. However, the progression of the disease and histopathology of angiosarcoma in a dog can resemble the same or similar condition as seen in humans. The angiosarcoma has various patterns of growth including papillary, spindled and epithelioid morphologic histological features (4). Thus, histopathology and immunohistochemistry can lead to a definitive diagnosis of the disease.

In the present case, a crackle sound with forceful inspiration, a feature of human pulmonary angiosarcoma, was auscultated on the right-side thorax of the patient. Histologically, the tumors were cellular with hemorrhage and necrosis all around the section. In this case, there was the presence of enlarged irregularly branched, tortuous, malformed and anastomosing vascular spaces pooled with blood clots as found by others in angiosarcomas (7,8).

The pleomorphic and different patterns of nucleus and nucleoli in canine angiosarcoma are related to pathological features of pulmonary angiosarcoma as seen in humans. However, these features might not be pathognomonic in most cases. One of the differentiative features of angiosarcoma from hemangiosarcoma, may be that there is more of a tendency to form endothelial-lined blood lakes in hemangiosarcoma, than with the angiosarcoma as seen in the dog.

In this case, the CD31 serves as a specific and most probably reliable endothelial marker used in the diagnosis of angiosarcoma of endothelial origin, and may lead to a misdiagnosis if reacted with other antigens instead of CD31 (9). The present case was strongly positive to the immunohistochemical reaction when reviewed using an anti-CD31 antibody.

As seen, the atypical endothelial cells crowd along the interanastomosing vascular channels and may form papillary projections similar to that of papillary endothelial hyperplasia in the lung parenchyma. In what follows, the capillary, cavernous, or slit-like vascular spaces may be seen in low-grade tumors whereas solids sheets of epithelioid or spindle cells with malignant features of pleomorphism, large vesicular and hyperchromatic nuclei, abundant pale cytoplasm and high mitotic activity may be observed in high-grade angiosarcomas (12).

The incidence of an angiosarcoma may be an heritable feature, or etiology may include previous radiation treatment, environmental carcinogens like vinyl chloride, phenylethyl hydrazine, arsenic, etc. (1,5). Treatment is not 100% successful in these cases, but angiosarcomas can be sensitive to radiotherapy, chemotherapy using a combination of doxorubicin/ifosfamide and the use of docetaxel/gemcitabine (13).

In conclusion, it is shown that pulmonary angiosarcomas are extremely rare and should be carefully evaluated to

exclude other neoplastic lesions like lymphangitis carcinomatosa, pseudoangiomatous carcinomas, Kaposi's sarcoma and epithelioid hemangioendothelioma which can be differentiated by histology and the review of immunohistochemical markers, and should be differentiated from extrapulmonary metastases (6,12). Primary pulmonary angiosarcoma can be confused with thromboembolic and plexiform lesions of pulmonary hypertension, which tend to form intravascular papillae and anastomosing vascular channels, but these lack cytologic atypia, mitoses and confinement of lesions to vascular lumina.

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