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Case Report

A case of hepatic leiomyosarcoma with osteosarcomatous differentiation (malignant mesenchymoma) in a dog

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Abstract: A rare spontaneous hepatic leiomyosarcoma with osteosarcomatous differentiation was observed in a female beagle dog and its morphological and immunohistochemical characteristics were examined. Upon necropsy, an endoceliac mass originating from the liver was detected, which was composed of hematoid fluid-filled cysts and white to grayish solid tissue. There were no macroscopic findings in other organ systems. Histopathologically, the hepatic mass consisted of two different mesenchymal components. One form was spindle cells arranged in interlacing fascicles immunohistochemically positive for smooth muscle actin (SMA) and smoothelin, indicating leiomyosarcomatous differentiation. The other form was composed of short spindle cells positive for S-100 and was producing various amounts of eosinophilic osteoid and trabecula-like matrices positive for osteocalcin, indicating osteosarcomatous differentiation. In addition, invasive growth in the hepatic parenchyma and cell atypia were observed. Based on these findings, the mass was diagnosed as hepatic leiomyosarcoma with osteosarcomatous differentiation (malignant mesenchymoma), which might be derived from undifferentiated mesenchymal cells. (DOI: 10.1293/tox.2019-0065; J Toxicol Pathol 2020; 33: 33–37)

Key words: leiomyosarcoma, osteosarcoma, mesenchymoma, dogs

A malignant mesenchymoma is a rare tumor in dogs and is defined as a tumor of mesenchymal origin that is characterized by multiple mesenchymal tissue components differentiating into unrelated malignant cell types. We encountered a spontaneous hepatic malignant mesenchymoma in a 6-year-old female beagle dog. In the present case report, we describe morphological and immunohistochemical characteristics of the lesion, and discuss the nomenclature and the possible pathogenesis of the hepatic mesenchymoma.

A female beagle dog purchased from Covance Research Products Inc. (Denver, PA, USA) had been reared at the Drug Safety Research Laboratories of Takeda Pharmaceutical Company Limited (Osaka, Japan) until found dead at the age of 6 years without showing any apparent clinical symptoms. The animal had been housed individually in a metal cage set on racks in an animal room controlled with the following conditions: temperature at 20–26°C, a 12-h light/dark cycle, and humidity at 40–80%, which were approved by the Experimental Animal Care and Use Committee of Takeda Pharmaceutical Company Ltd. The animal had been fed a solid diet, had free access to water, and had not been engaged in any non-clinical experiment.

Upon macroscopic examination, a large endoceliac mass (approximately 20 × 10 × 10 cm) originating from the left lateral hepatic lobe was observed (Fig. 1). No adhesion was noted in other abdominal organs such as pancreas, spleen, or the gastrointestinal tract. On cross section of the endoceliac mass, hematoid fluid-filled cysts and white to grayish solid tissue with sporadic gritty areas were observed. In addition, hematoid ascites had accumulated. No metastases were grossly observed in the lymph nodes, lungs, or thoracic or abdominal cavities, and there were no macroscopic findings in other organ systems.

The hepatic gross lesion and lungs were fixed in 10% (vol) neutral buffered formalin, embedded in paraffin, and sectioned and stained with hematoxylin and eosin (H&E). For differential diagnosis, sequential sections from the hepatic lesion were immunohistochemically stained with anti-porcine vimentin mouse monoclonal antibody (diluted 1:500, clone: V9, Santa Cruz Biotechnology Inc., Dallas, TX, USA), anti-human smooth muscle actin mouse monoclonal antibody[1] (diluted 1:1000, clone: 1A4, Dako, Carpinteria, CA, USA), anti-chicken smoothelin mouse monoclonal antibody (diluted 1:100, clone: R4A, Acris Antibodies, San Diego, CA, USA), anti-human S-100 rabbit monoclonal antibody (diluted 1:500, clone: EP1576Y, Abcam, Cambridge, UK), anti-human Schwann cell mouse monoclonal antibody (diluted 1:2500, clone: Schwann/2E, CosmoBio, Tokyo, Japan), and anti-cow osteocalcin mouse monoclonal antibody (diluted 1:500, clone: OC4-30, Abcam).

On microscopic examination, growth of tumor cells

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was observed in hepatic tissue (Fig. 2). The tumor partly showed invasive growth into the hepatic parenchyma, and the adjacent hepatic tissue was atrophied. Neither intrahepatic nor pulmonary metastases were observed. In the central area of the tumor tissue including the macroscopically cystic area, multifocal necrosis and hemorrhage were observed. The mass consisted of two different mesenchymal components (Fig. 2). One component was spindle cells with oval to spindle nuclei and eosinophilic cytoplasm arranged in interlacing fascicles that were immunohistochemically positive for vimentin, smooth muscle actin (SMA) and smoothelin, and negative for S-100 and Schwann cells, indicating leiomyosarcomatous differentiation (Fig. 3). The other component was intricately observed in the leiomyosarcomatous area and mainly located in the macroscopically gritty area. Proliferative cells contained round nuclei and short spindle basophilic cytoplasm, which were often embedded in various amounts of eosinophilic osteoid-like and bone-like matrices, indicating differentiation to osteoblasts and bone tissue (Fig. 4). The tumor cells in this area were positive for vimentin and S-100, which could be consistent with osteosarcoma[2], and negative for SMA, smoothelin, and Schwann cells (Fig. 4). The osteoid-like and bone-like matrices were positive for osteocalcin (Fig. 4). Osteoclast-like multinucleated cells, which were immunohistochemically positive only for vimentin, were sporadically observed in this area. These histopathological and immunohistochemical characteristics were indicative of osteosarcomatous differentiation. In total, the area of leiomyosarcomatous lesion was more predominant than the osteosarcomatous area. Furthermore, apparent sequential histopathology was not observed between the two components. Mild anisokaryosis of tumor cells was observed in both proliferative components. Based on these findings, the mass was diagnosed as a hepatic leiomyosarcoma with osteosarcomatous differentiation (malignant mesenchymoma).

The term “malignant mesenchymoma” has been applied to sarcomas that exhibit two or more lines of differentiation[3, 4]; however, there is a clear difference between humans and animals in the World Health Organization

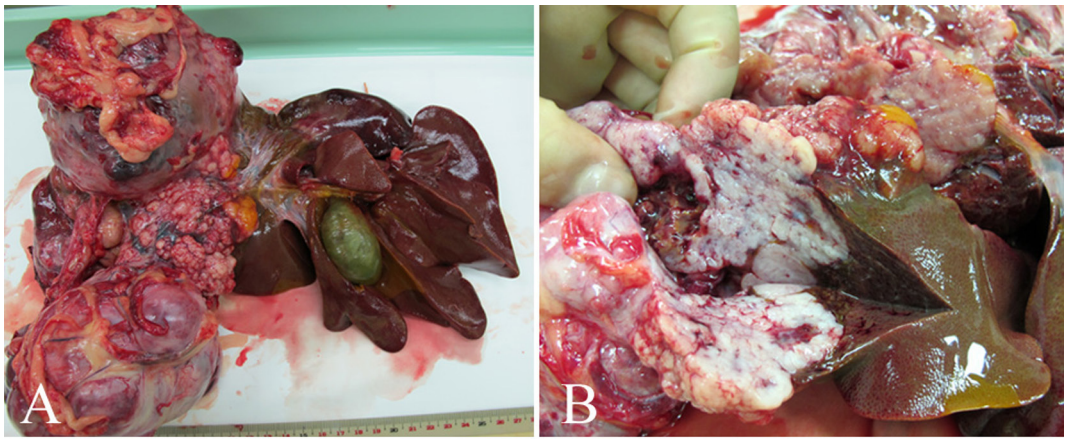

Fig. 1. Macroscopic findings. A large endoceliac mass (approximately 20 × 10 × 10 cm) originating from the left lateral hepatic lobe was observed. (A) Tumor origination from the left lateral lobe of liver. (B) On cross section, white to grayish solid tissue was observed.

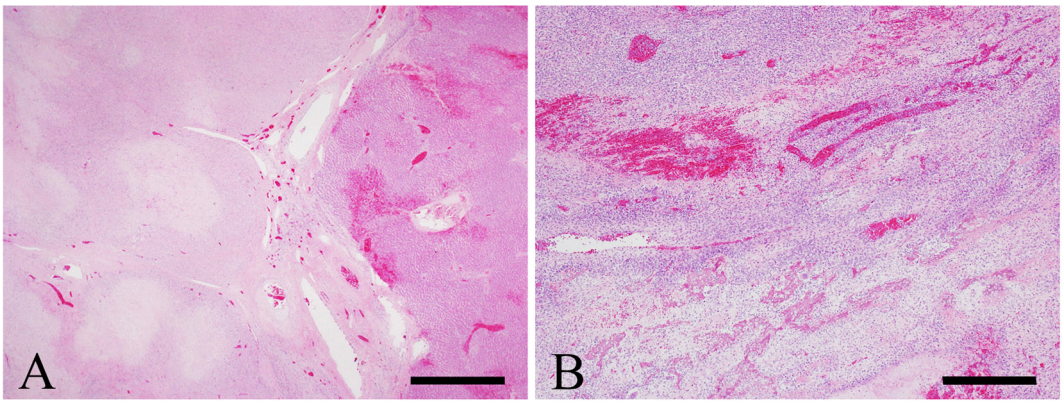

Fig. 2. Histological features of tumors in the liver at low magnification. (A) Growth of mesenchymal solid tumor cells was observed adjacent to hepatic tissue. In this area, tumor cells showed leiomyosarcomatous differentiation as shown in Fig. 3. (B) In macroscopically gritty area, proliferative cells showed osteosarcomatous differentiation as shown in Fig. 4. Bar=1.6 mm (A) and 0.5 mm (B).

Classification of Tumors. In humans, descriptive diagnosis such as leiomyosarcoma with osteosarcomatous differentiation[5] is preferred instead of the usage of malignant mesenchymoma[2, 6]. On the contrary, malignant mesenchymoma is the terminology currently used for the classification of animal tumors[4]. Based on these criteria, this case can be categorized as malignant mesenchymoma, but descriptive terminology modification such as leiomyosarcomatous and osteosarcomatous would be ideal as a diagnosis.

Canine malignant mesenchymomas are rare. Several cases were reported in various organs such as the heart[7], spleen[8], abdominal cavity[9], bone[10], and submandibular tissue[11]. In the liver, only one case has been reported[12], which showed rhabdomyosarcomatous and hemangiosarcomatous phenotypes. In addition, primary hepatic bone or smooth muscle tumors are rare [13]. Therefore, the present case was the second hepatic malignant mesenchymoma reported in dogs with relatively rare histological phenotypes such as leiomyosarcomatous and osteosarcomatous differentiation.

The malignant mesenchymomas might be derived from undifferentiated cells which have pluripotent property such as mesenchymal stem cells (MSCs) mentioned in other cases of mesenchymomas in dogs[8, 11]. Moreover, MSCs and MSC-like cells have been found to harbor in various organs[14], which supports the hypothesis that mesenchymomas are derived from MSCs.

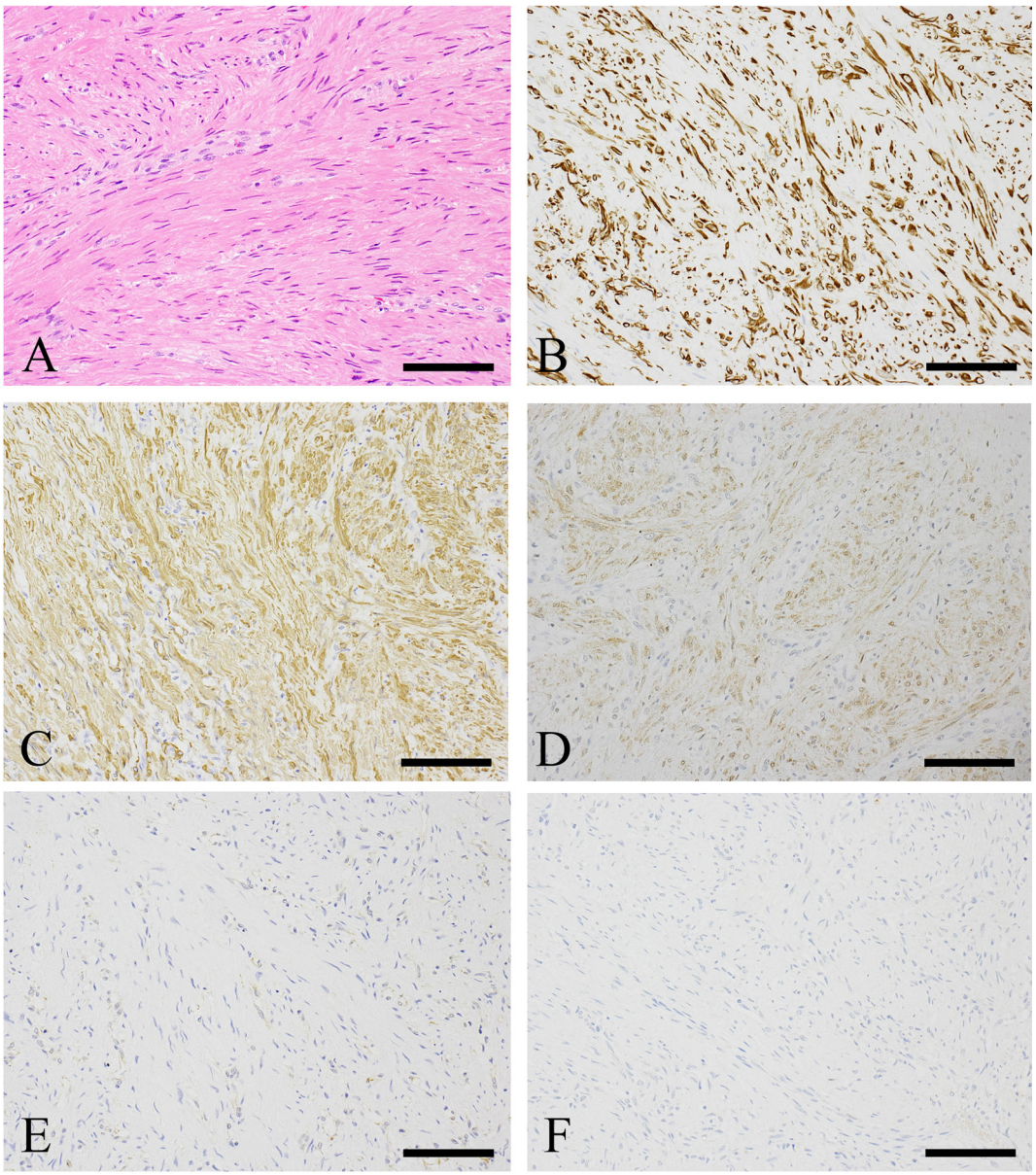

Fig. 3. Histopathological features of leiomyosarcomatous area. Proliferation of spindle cells arranged in interlacing fascicles was observed in hematoxylin and eosin (H&E) section (A). Cytoplasm of tumor cells were immunohistochemically positive for vimentin (B), smooth muscle actin (SMA) (C) and smoothelin (D), and negative for S-100 (E) and Schwann cell (F). Bar=100 µm.

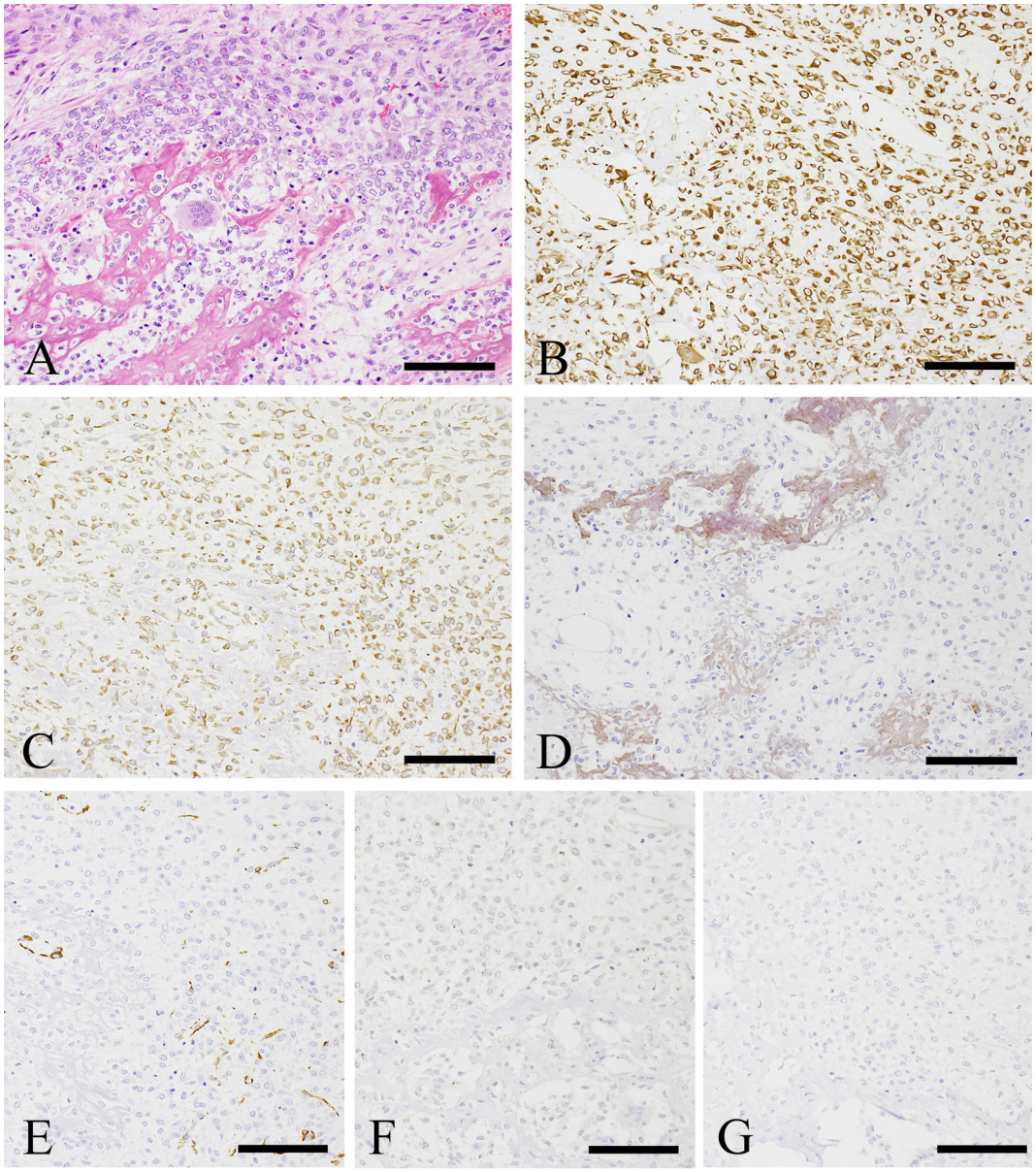

Fig. 4. Histopathological features of osteosarcomatous area. Proliferative cells were intricately observed in the leiomyosarcomatous area and contained polygonal cytoplasms, around which various amounts of eosinophilic osteoid-like and bone-like matrices were observed in hematoxylin and eosin (H&E) section (A). Cytoplasm of tumor cells were immunohistochemically positive for vimentin (B) and S-100 (C), and osteoid-like and bone-like matrices around the tumor cells were positive for osteocalcin (D). On the other hand, the cytoplasm of tumor cells is negative for smooth muscle actin (SMA) (E), smoothelin (F), and Schwann cells (G). Bar=100 µm.

Especially in the hepatic mesenchymomas, hepatic stellate cell (HSC) progenitor cells could be the origin as we suspect in the present case. HSC progenitor cells are derived from mesothelial and submesothelial cells during liver development, or from bone marrow cells of adult animals[15]. The HSC progenitor cells have the capacity to differentiate into osteoblast- and adipocyte-like cells, providing evidence of their multipotent nature[16, 17]. In addition, fibroblasts derived from bone marrow, which could contribute to liver fibrosis[18], also have pluripotency[19]. It has also been reported that there are MSCs in pericytes, which can differentiate into bone, cartilage, and adipose tissue[20]. Therefore, the origin of the tumor cells of the present case might be the cells possessing the phenotype of MSCs such as HSC progenitor cells, fibroblasts or pericytes.

Disclosure of Potential Conflicts of Interest: The authors declare that there are no conflicts of interest associated with this manuscript.

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