

**NOTE Pathology****Diffuse Bilateral Hemangiosarcoma of the Uterus in a Dog**Yuichi MURAKAMI<sup>1)</sup>, Kazuyuki UCHIDA<sup>1)</sup>, Ryoji YAMAGUCHI<sup>1)</sup> and Susumu TATEYAMA<sup>1)\*</sup><sup>1)</sup>Department of Veterinary Pathology, Faculty of Agriculture, Miyazaki University, Nishi 1-1, Gakuen Kibana Dai, Miyazaki 889-2192, Japan

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**ABSTRACT.** A 15-year-old female mongrel dog showed abdominal swelling, marked hemorrhagic ascites and vulvar discharge, and ovariohysterectomy was performed. Grossly, the uterus was enlarged bilaterally without apparent mass formation. Histologically, the uterine muscular wall was composed of proliferated sinusoidal vessels. In some areas, irregular and small vessels proliferated markedly, while in others, pleomorphic and atypical tumor cells forming irregular vascular structures were predominant. From these findings, the case was diagnosed as diffuse bilateral hemangiosarcoma of the uterus that invaded to the ovary and broad ligament. The relationship between the tumor and angiomatosis was discussed.

**KEY WORDS:** canine, hemangiosarcoma, uterus.

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Hemangiosarcoma is a common malignant neoplasm of endothelial cells. In dogs, it is frequently observed in the spleen, liver, heart and skin. Histologically, hemangiosarcoma consists of hyperchromatic, pleomorphic spindle cells that form cleft-like channels reminiscent of blood vessels. The tumor is highly infiltrative and readily recur is following local excision. In humans, there are several reports of primary uterine hemangiosarcomas, but the occurrence is rare [6, 7, 10, 11, 14]. To our knowledge, uterine hemangiosarcoma is extremely rare in dogs. We report here one of such rare cases. We describe the morphological features of the tumor, discuss its pathogenesis, and compare the case with human uterine hemangiosarcoma.

A female mongrel dog, 15 years old, was brought to us because of abdominal swelling, marked hemorrhagic ascites and vulvar discharge. When ovariohysterectomy was performed, numerous hemorrhagic spots were seen on the peritoneum. Two days after the surgery, the dog developed chylous ascites.

For routine histopathological and immunohistochemical studies, the ovaries and uterus were fixed in 10% buffered formalin. The samples were embedded in paraffin, sectioned at 4  $\mu$ m, and stained with hematoxylin and eosin (HE). Selected sections were also stained using Watanabe's silver impregnation method. Immunohistochemical staining was performed with Envision-Polymer reagent (Dako, Kyoto, Japan). The primary antibodies used were rabbit polyclonal antibody against factor VIII-related antigen (Dako, Japan) and mouse monoclonal antibody against alpha-smooth muscle actin ( $\alpha$ -SMA, Dako, Japan). The chromogenic reaction was performed with diaminobenzidine (Sigma, St. Louis, U.S.A.), and the sections were counterstained with Mayer's hematoxylin.

Grossly, the uterus and ovaries were massively enlarged, and the broad ligament adjacent to the uterus was heavily

thickened and had rough surface (Fig. 1). The tumor bilaterally involved the uterus, ovaries and broad ligament without apparent mass formation. The cut surface was hard and varied from gray to yellow in color, having partly reddish-black hemorrhagic foci with necrosis.

Histopathologically, neoplastic lesions were located bilaterally in the uterus, which was almost totally replaced by proliferated neoplastic cells. The cells spreaded diffusely throughout the subendometrial and muscular layers (Fig. 2). In some areas, sinusoidal vessels extended between individual muscle fibers (Fig. 3). The vessels were lined by a single layer of well-differentiated, flattened endothelium and contained variable amounts of blood. The morphology of the endothelium was almost normal, but papillary proliferation was occasionally seen. In other areas, there was proliferation of small capillaries of irregular shape (Fig. 4). Neoplastic cells in these areas had minimal cytoplasm and hyperchromatic nuclei that protruded into the vascular lumina. Mitotic figures were rare. There were also areas with high cellularity consisting of proliferating pleomorphic tumor cells. The cells in such areas were arranged in solid sheets, often showing vessel-like formation of various sizes (Fig. 5) and invaded markedly into the surrounding tissues. Most of these cells were large and pleomorphic with abundant cytoplasm and atypical round nuclei containing distinct nucleoli. Mitotic figures were numerous. Reticular fibers surrounding the packs of the neoplastic cells were prominent with Watanabe's silver staining. By immunostaining for factor VIII-related antigen, the inner surface of the sinusoidal vessels and small capillaries reacted strongly, and the cytoplasm of the pleomorphic cells reacted slightly to moderately (Fig. 6). The various types of lesions described above often merged with each other without a distinct border. An additional finding in the uterus was cystic hyperplasia of the uterine glands, which was frequently observed in the endometrium.

Neoplastic tissues partly invaded both ovaries, and heavy proliferation of neoplastic cells was observed in some parts

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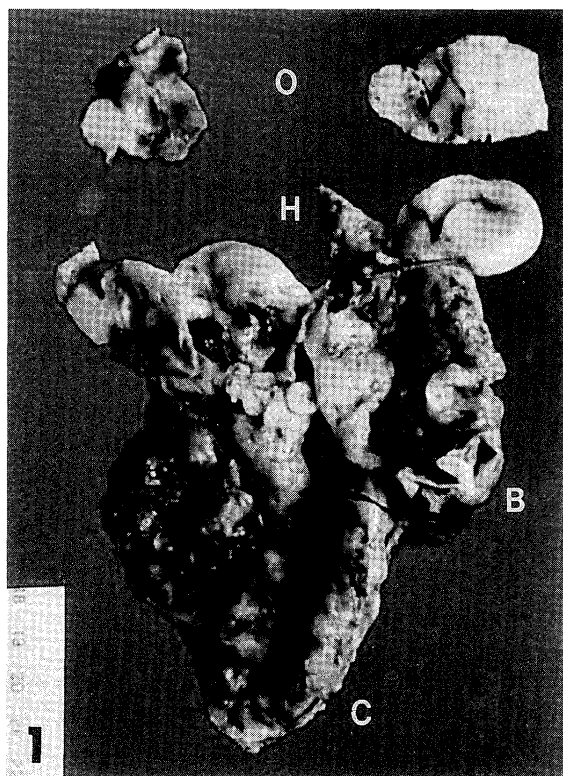


Fig. 1. Massively enlarged uterus and ovaries. The tumor involves the uterus, the ovaries and the broad ligament without apparent mass formation. O: ovary, H: horn of uterus, B: body of uterus, C: cervix of uterus.

of the stroma.

Tumor cells also infiltrated the whole area of the broad ligament adjacent to the uterus, forming multiple foci (Fig. 7).

Malignant nature of this tumor was supported by the high frequency of mitosis, presence of necrosis and significant cellular atypia of tumor cells. In addition, vascular formation and immunopositive reaction for factor VIII-related antigen by neoplastic cells confirmed the endothelial origin of the tumor. Based on these findings, the tumor was diagnosed as hemangiosarcoma of the uterus.

The major characteristic in this case was the lack of mass formation, or the diffuse proliferation of neoplastic tissues. Hemangiosarcoma is usually recognized as a hemorrhagic mass [9, 13, 16]. Human uterine hemangiosarcoma has also been reported to manifest as a mass [6, 7, 10, 11, 14]. The growth pattern of the present case was, therefore, different from that of typical hemangiosarcomas. A plausible explanation is that the hemangiosarcoma here arose in preexisting angiomas. In humans, angiomas is a well documented clinicopathologic entity, and there are several reports of uterine angiomas [1, 3, 12]. The lesions are usually diffuse and extensive, and contain proliferative blood vessels of varying sizes. Similar vascular anomalies have not yet been reported in dogs. However, lesions resembling human angiomas were present in our case. They consisted of diffusely proliferative structurally normal

blood vessels: there was infiltration of blood vessels into tissues, but the morphology of the endothelium was almost normal. Such lesions may be regarded as preexisting angiomas. In humans, there are several reports of hemangiosarcoma arising in angiomas [1, 8], although malignant conversion from a preexisting benign vascular tumor is unusual. In the present case, diffuse development of angiomas over a period of several years might have led to the progression of the lesion to diffuse hemangiosarcoma.

Interestingly, the neoplastic lesions in the present case markedly affected not only the uterus but also the broad ligament. This may suggest that the tumor originated in the broad ligament rather than the uterus. In humans, hemangiosarcoma of the serous membrane is recognized as a diffuse vascular tumor [2, 4, 5, 15]. Thus, it is possible that, in our case, the diffuse hemangiosarcoma arose in the broad ligament and extended bilaterally to the uterus.

In conclusion, this paper has described the morphological features of diffuse bilateral hemangiosarcoma of the uterus in a dog. The tumor exhibited various morphological features, which led to intriguing speculation on its pathogenesis. We suggest that the tumor may have arisen in preexisting angiomas of the uterus.

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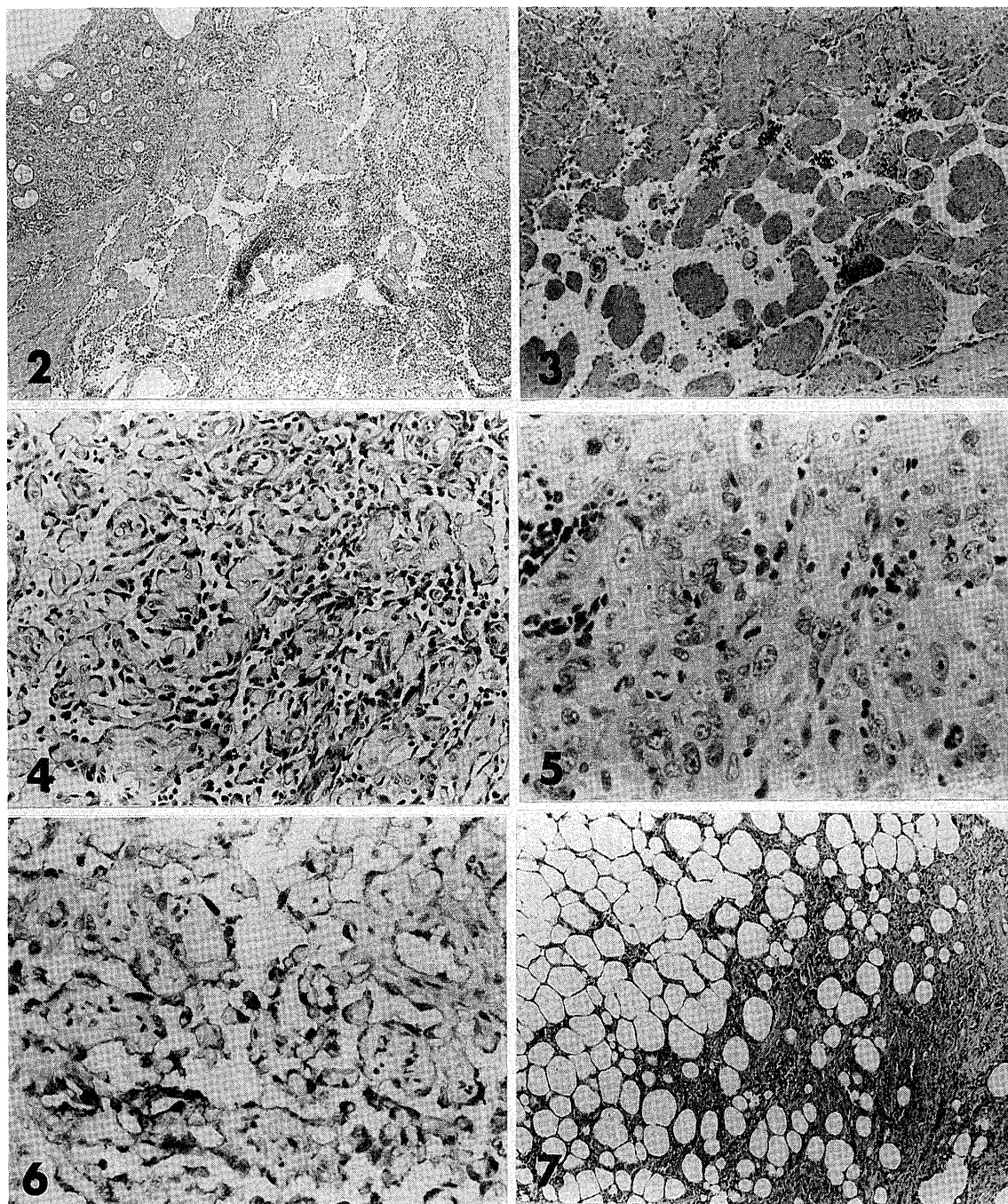


Fig. 2. Neoplastic cells proliferating diffusely throughout the subendometrial and muscular layers. HE stain.  $\times 50$ .

Fig. 3. Sinusoidal vessels extending between individual muscle fibers. HE stain.  $\times 150$ .

Fig. 4. Proliferation of small capillaries with irregular shape. HE stain.  $\times 300$ .

Fig. 5. Pleomorphic cells proliferating in solid sheets with vessel-like formation. HE stain.  $\times 600$ .

Fig. 6. Neoplastic cells showing positive reaction for factor VIII-related antigen. Immunostain.  $\times 400$ .

Fig. 7. Neoplastic cells infiltrating the broad ligament with formation of multiple foci. HE stain.  $\times 100$ .

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