

## Primary T-cell high-grade lymphoma of the feline uterus

Daigo AZAKAMI<sup>1)\*</sup>, Eri ONOZAWA<sup>1)</sup>, Masahiro MIYABE<sup>1)</sup>, Kazuhiko OCHIAI<sup>1)</sup>, Masaki MICHISHITA<sup>2)</sup>, Taichi HIRANO<sup>3)</sup>, Yutaka MOMOTA<sup>1)</sup>, Katsumi ISHIOKA<sup>1)</sup> and Toshinori SAKO<sup>1)</sup>

<sup>1)</sup>Department of Veterinary Nursing and Technology, Faculty of Veterinary Science, Nippon Veterinary and Life Science University, 1-7-1 Kyonan-cho, Musashino-shi, Tokyo 180-8602, Japan

<sup>2)</sup>Department of Veterinary Pathology, Faculty of Veterinary Science, Nippon Veterinary and Life Science University, 1-7-1 Kyonan-cho, Musashino-shi, Tokyo 180-8602, Japan

<sup>3)</sup>Hirano Animal Hospital, 4-1-8 Fuji-cho, Nishitokyo-shi, Tokyo 202-0014, Japan

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**ABSTRACT.** A 12-year-old female American shorthair cat presented with a one-month history of hematuria and general lethargy. Abdominal ultrasonography revealed complete thickening of the left uterine wall. At a diagnostic laparotomy, a large mass arising from the left uterine horn was discovered, and ovariohysterectomy was performed. Histological diagnosis revealed a T-cell high-grade lymphoma of the uterus. After the ovariohysterectomy, the patient achieved complete remission and was maintained by combination chemotherapy from 14 days after surgery. However, relapse occurred in the urinary bladder wall on day 287, and the patient died of postrenal acute renal failure on day 310. This is the first report of a feline case of primary uterine lymphoma that was treated with ovariohysterectomy followed by systemic chemotherapy.

**KEY WORDS:** chemotherapy, extranodal lymphoma, feline, T-cell origin, uterine

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Feline extranodal lymphomas mainly occur in the gastrointestinal (GI) tract, but other anatomical locations are also affected. Other non-GI feline extranodal lymphomas arising from the kidney, nasal cavity, central nervous system and skin have been reported [10, 12]. However, primary uterine lymphoma in cats has never been reported in the veterinary literature. Further, because of the rarity of this tumor, the pathological and/or clinical features of the primary uterine lymphoma have not been well described in cats. In this report, we describe a feline case of primary uterine T-cell high-grade lymphoma treated with ovariohysterectomy followed by systemic combination chemotherapy.

A 12-year-old null parous female American shorthair cat was presented to the veterinary medical teaching hospital of Nippon Veterinary and Life Science University with a one-month history of mild hematuria and general lethargy (day 0). Physical examination revealed a large abdominal mass occupying the mid-abdominal area. No superficial lymph nodes were palpable. Complete blood count and serum chemistry were all within the normal reference ranges, except for a mild increase in serum aspartate aminotransferase levels (59 U/l; reference range 16–53 U/l). Abnormal leukocytes were not detected in a blood smear. A moderate number of erythrocytes, leukocytes (mainly neutrophils) and

a few calcium oxalate crystals, and no atypical cells were observed in the urinary sediment. A blood ELISA assay against feline leukemia virus antigen and feline immunodeficiency virus antibody (SNAP<sup>®</sup> FeLV/FIV combo; IDEXX laboratories, Westbrook, ME, U.S.A.) were both negative.

Abdominal radiography showed a large, well-marginated mass (5.5 × 5.5 cm) occupying the left mid-abdominal area and many bladder calculi (Fig. 1A). Thoracic radiography did not reveal any signs indicative of metastatic disease. Abdominal ultrasonography revealed enlargement of left uterine horn with complete thickening of the uterine wall (Fig. 1B). Furthermore, the cranial urinary bladder wall, which was attached to the left uterine mass, was mildly thickened. No abnormalities were detected in the abdominal lymph nodes or other abdominal organs.

Given the clinical findings, we suspected uterine neoplasm. Consequently, a diagnostic laparotomy was performed on day 7. A large mass arising from the left uterine horn and adhering to the cranial bladder wall was discovered (Fig. 2). The right uterine horn was mildly dilated and thickened. No gross changes were seen in the ovaries or other abdominal organs. An ovariohysterectomy and excision biopsy of the thickened urinary bladder wall were performed, and the abdomen was closed using a routine method. Diagnostic cytology of an impression smear revealed massive proliferation of lymphoblasts in the left uterine mass (Fig. 3A). The neoplastic cells contained moderate basophilic cytoplasm and medium- to large-sized nuclei. Concurrently, a bone marrow biopsy was taken, which showed normocellular bone marrow and no tumor involvement. At day 14, all clinical signs were resolved, and the patient was discharged.

Histological examination revealed a transmural proliferation of medium- to large-sized lymphoblasts in the left uter-

\*CORRESPONDENCE TO: AZAKAMI, D., Department of Veterinary Nursing, Faculty of Veterinary Science, Nippon Veterinary and Life Science University, 1-7-1 Kyonan-cho, Musashino-shi, Tokyo 180-8602, Japan. e-mail: azakami@nvl.ac.jp

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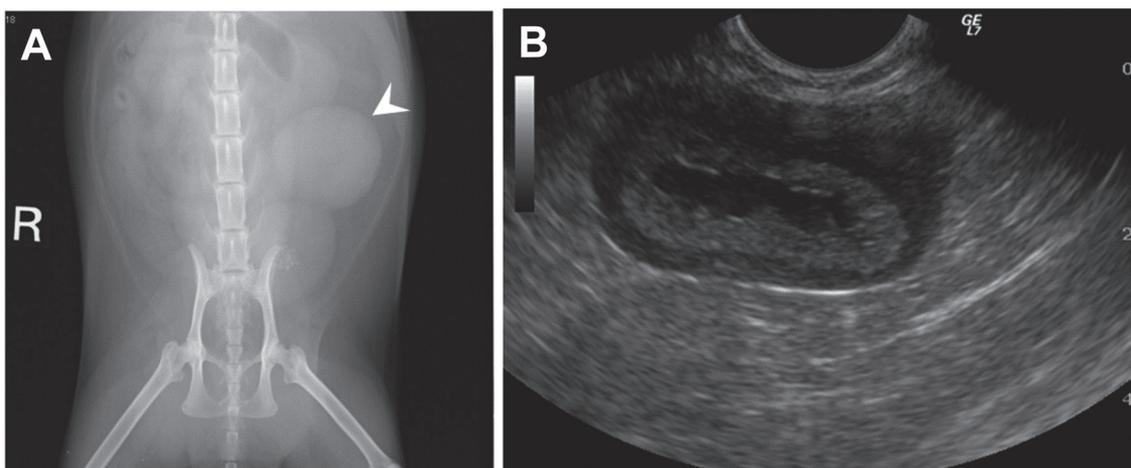


Fig. 1. Abdominal radiography and ultrasonography of a cat with uterine lymphoma. (A) Abdominal radiography (dorsoventral view). Note a large, well-margined mass in the left mid-abdominal area (arrowhead). (B) Abdominal ultrasonography. A part of the left uterine horn was palpated, and both mucosal and muscle layers were thickened. Uterine lumen was dilated.

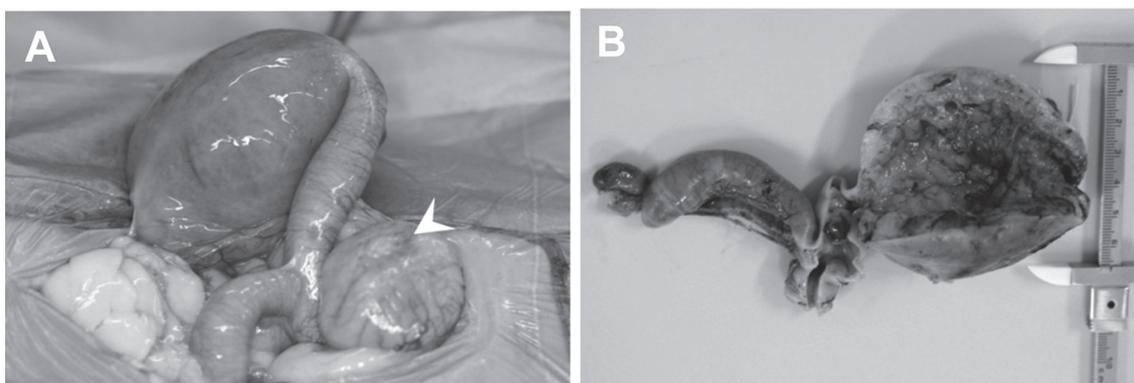


Fig. 2. Gross findings of uterine lymphoma. (A) Intraoperative photograph. The arrowhead points to the adhesion site of the urinary bladder with the uterus. (B) Surgically removed uterus and ovaries. Note the thickened uterine wall.

ine horn (Fig. 3B). The mucosal lamina propria was almost effaced, and few neoplastic cells showed epitheliotropism. In the right uterine horn, mild to moderate endometrial cystic hyperplasia was observed, but infiltration of neoplastic cells was not apparent. In the urinary bladder, the subserous musculature was heavily infiltrated by neoplastic lymphoblasts, which extended to the mucosal layer. Immunohistochemical staining with anti-CD3 polyclonal antibody (catalog #A0452, DAKO, Glostrup, Denmark) and anti-BLA. 36 monoclonal antibody (clone A27-42, BioGenex, Fremont, CA, U.S.A.), revealed massive proliferation of CD3-positive and BLA. 36-negative lymphoblasts in the left uterine horn (Fig. 3C-D). A PCR-based molecular clonality assessment of the T cell receptor-gamma (*TCRG*) and immunoglobulin heavy chain (*IgH*) genes against DNA extracted from the uterine tumor tissue revealed a clonal rearrangement of both the *TCRG* and *IgH* genes. A definitive diagnosis of primary uterine T-cell high-grade lymphoma was made based on the clinical, pathological, immunohistochemical and molecular

findings.

The patient did not have clinically detectable lymphoma after ovariectomy. Wisconsin–Madison combination chemotherapy was started from 14 days after the ovariectomy (day 21) with series of L-asparaginase, cyclophosphamide, vincristine, doxorubicin, methotrexate and prednisone [4, 6]. The patient maintained complete remission until day 280, but a relapse occurred in the urinary bladder wall at day 287. At the time of relapse, urinary bladder wall was thickened, and many neoplastic cells were seen in fine needle aspiration of bladder wall. Thoracic radiography and abdominal ultrasonography did not reveal any other relapse lesions except in the urinary bladder wall. Rescue chemotherapy involving CCNU was not successful, and the patient died from postrenal acute renal failure presumably caused by bilateral neoplastic ureteral obstruction on day 310. A necropsy was not performed.

Feline uterine tumors are uncommon and comprise only 0.29% of all neoplasms [5]. Further, it has been reported

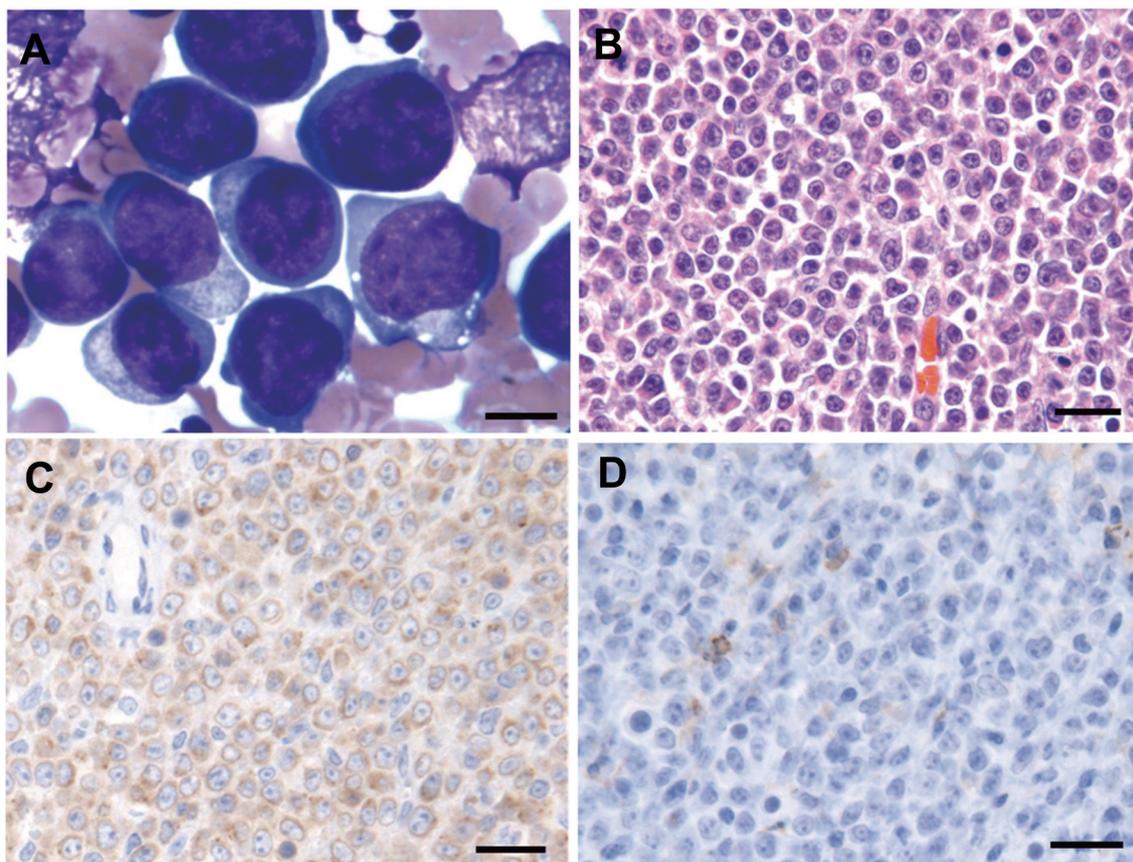


Fig. 3. Cytology and histology of uterine lymphoma. (A) Impression smears of the uterine mass. Neoplastic lymphoblasts had deeply basophilic cytoplasm without any granules and medium to large nuclei with finely granular chromatin. Prominent nucleoli can be seen. Wright and Giemsa stain, bar=10  $\mu$ m. (B) Histologic section of the uterine mass. The neoplastic cells are proliferating transmurally in the left uterine horn. H&E, bar=50  $\mu$ m. (C) The neoplastic lymphoblasts have positive immunoreactivity for CD3 and (D) negative for BLA. 36. 3,3'-diaminobenzidine tetrahydrochloride chromogen and Mayer's hematoxylin counterstain, bar=50  $\mu$ m.

that endometrial adenocarcinoma or leiomyoma is the most common uterine tumors in cats [5]. In humans, most cases of uterine lymphomas include secondary involvement of the disease and account for less than 1% of the primary malignant lymphomas that occur in the female genital tract [8]. Domestic animals appear to be similar to humans, in that most cases entail secondary uterine involvement. Primary uterine lymphoma in domestic animals has been previously described in a dog [3] and a cow [11], but accurate incidence rates in domestic animals remain unclear. Although lymphoma may develop everywhere in the body, the uterus is a rare site for the occurrence of primary tumor in both humans and domestic animals.

In the current case, the lesion in the left uterine horn was the largest, and no other significant lesions were observed in other organs. Additionally, leukemia was excluded following bone marrow examination, and thus, we diagnosed the cat as having primary uterine lymphoma. Although neoplastic cells were also seen in the urinary bladder wall, we hypothesized that it was the result of a direct invasion from the uterus,

because the bladder lesion was attached to the left uterine horn, and the most severe bladder wall lesion was located in the subserous musculature.

T-cell derived uterine lymphoma is quite rare in humans, as the majority of primary uterine lymphomas represent diffuse large B-cell lymphoma [2, 8]. The immunophenotype of a primary uterine lymphoma in a dog was previously reported as B-cell origin [3], whereas those in bovines were reported as T-cell origin [11]. In the present case, immunohistochemical analysis revealed that the tumor cells were T-cell origin. It has been reported that CD4+ T-cell and CD8+ T-cells mainly distribute in the feline normal uterus [1], and thus, these normal resident T-cells in the uterine horn may possess the potential for malignant transformation.

PCR-based molecular clonality assessment of uterine tumor tissue indicated clonal rearrangement of both the *TCRG* and *IgH* genes, although immunohistochemistry strongly suggested T-cell proliferations. A prior report indicated that three of the 12 cases of feline T-cell lymphomas determined by immunohistochemistry had *IgH* gene clonal rearrange-

ment [9]. The author suggested that neoplastic T-cells might have cross-lineage rearrangements [9], but this phenomenon could also be due to pseudoclonality. The PCR-based molecular clonality assay strongly amplifies the target DNA sequence, and thus, a small number of residual normal B lymphocyte scattered in neoplastic tissue could be detected as a clonal population. In this case, we could not determine whether neoplastic cells had cross-lineage rearrangement or pseudoclonality. Accordingly, immunohistochemistry should remain the primary detection method for cell lineage determination, and the PCR-based molecular clonality assay should be used as an adjunctive tool.

The major anatomical form of feline lymphoma is the GI type, and its median survival time (MST) is reported as only 47 days [10]. The MST of feline non-GI extranodal lymphomas including nasal, renal, laryngeal and central nervous system lymphomas is reported as 140, 91, 112 and 70 days, respectively [12]. Even though the prognosis of feline uterine lymphoma has been unknown, the current case achieved a longer survival time compared to other reported cases of extranodal lymphoma. Generally, lymphomas arising from extranodal tissues are difficult to remove all affected areas; this is one possible reason why the presented case had a longer survival. It is easy to perform a complete resection of the uterus compared to other organs. Ovariohysterectomy reduced tumor cells considerably, which might contribute to improve the effect of combination chemotherapy. Hence, complete excision of the primary lesion could result in longer survival periods in this case.

Unfortunately, the owner did not consent to a postmortem examination, and thus, it was impossible to determine if the patient had localized involvement in the urinary bladder at the time of relapse. In humans, bilateral ureteral obstruction is a frequent complication of uterine lymphoma, but can usually be treated with chemotherapy at the first-onset of disease [7]. However, bilateral ureteral obstruction is lethal, if the tumor cells are resistant to chemotherapy, similar to the current patient. To obtain longer survival time in this patient, urinary bladder radiation therapy might be considered.

We reported a case of feline primary uterine T-cell high-grade lymphoma that was treated with ovariohysterectomy followed by systemic chemotherapy. We are hopeful this report will provide useful information for the further investigation of the pathological and clinical features of feline uterine lymphomas.

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