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NOTE

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Large granular lymphocyte lymphoma in the skin and urinary bladder of a dog

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ABSTRACT. A 10-year-old female Cavalier King Charles Spaniel presented with hematuria, pollakiuria and skin rash. Based on the histopathological and cytological examination of the skin and bladder mucosa, the dog was diagnosed with large granular lymphocytic (LGL) lymphoma of the bladder and skin. The dog responded well to the initial chemotherapy with nimustine for 3 months. Since recurrence of skin erosion and bladder wall thickening were observed, the dog was subsequently administered chemotherapy with other anticancer drugs, including chlorambucil, vincristine, doxorubicin, L-asparaginase, cytosine arabinoside, and cyclophosphamide. The dog survived for 11 months and died due to tumor-related disseminated intravascular coagulation. This is the first report of a canine case of LGL lymphoma in the skin and bladder.

KEY WORDS: azurophilic granule, cancer chemotherapy, canine (dog), large granular lymphocyte, nimustine

Large granular lymphocytic (LGL) lymphoma is a hematopoietic tumor originating from natural killer (NK) cells, cytotoxic T cells, or γδ T cells. Morphologically, granular lymphocytes are variably sized cells with azurophilic granules containing cytotoxic proteins [15]. In cats, LGL lymphoma tends to occur in older animals (>9 years) and most affected cats are negative for the feline leukemia virus [1, 9, 19]. These tumors are commonly seen in the intestinal tract and have a poor prognosis since they are highly aggressive and malignant [7, 19]. Few reports of canine LGL lymphoma have been reported, and these tumors are presumed to arise frequently from both the lymph nodes and the extranodal sites [3, 5, 6, 10, 17]. However, there have been no reports on canine LGL lymphoma concurrently located in the bladder and the skin. In this case study, we present an overview of the chemotherapy regimen, including nimustine for the treatment of canine LGL lymphoma co-occurring in the urinary bladder and the skin.

A 10-year-old spayed female Cavalier King Charles Spaniel, weighing 7.2 kg, was referred to the Animal Medical Center of Rakuno Gakuen University for evaluation, and had a 3-month history of hematuria and pollakiuria. These symptoms did not resolve after treatment with the antibiotics prescribed by the referring veterinarian. Although hematuria improved with the prednisolone (dosage of 1–2 mg/kg) administered by the referring veterinarian, there was no improvement in pollakiuria and occult blood on urinalysis. Additionally, the dog had rashes on the lower jaw, lower left eyelid, and skin of the left dorsal cervix, thorax, and lumbar region and inguinal region, and exhibited itching that was evident by scratching around the mouth for four months (one month before hematuria and pollakiuria began); however, these symptoms improved with prednisolone administration.

On presentation to our animal medical center, several nodular lesions were observed on the skin of the left flank, dorsal and inguinal region (Fig. 1A). The lesions were extensively crusted; erosion and hair loss were observed in these lesions as well as on the skin over the mandible (Fig. 1B). Additionally, an erosive lesion was observed in the right nostril (Fig. 1C).

A blood test revealed no abnormalities except for marked thrombocytopenia (10,000/μl), which was derived from breed-related congenital macrothrombocytopenia. Abdominal ultrasound imaging revealed severe thickening of the bladder wall around the circumference and irregular mucosal surface (Fig. 2A). No intra-abdominal lymphadenopathy or abnormal findings of the liver or spleen were observed. Urinalysis showed hematuria with bacterial infection, but neither crystals nor atypical cells were observed.

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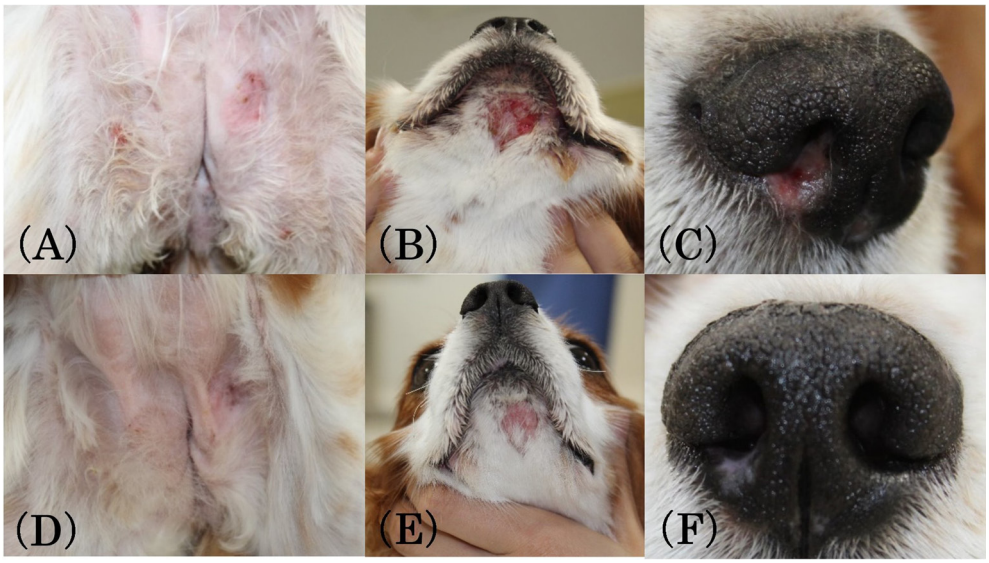

Fig. 1. Appearance of the skin at initial presentation and after chemotherapy. **A**. Several nodular lesions are observed on the skin of the inguinal region; **B**. Similar lesions are found in the mandibular region; **C**. An erosive lesion is also found in the right nostril; **D**. Skin of the inguinal region after chemotherapy showing improvement of crusty skin and erosions on day 34; **E**. Improvement in erosion in the mandibular region; **F**. Erosion of the right nostril improved and completely disappeared.

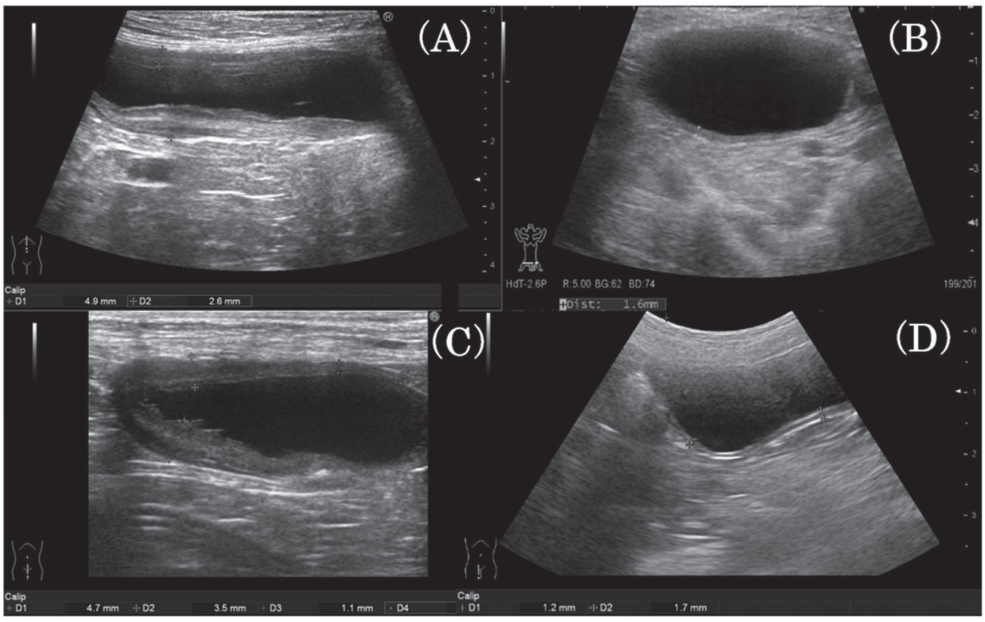

Fig. 2. Abdominal ultrasonographic images of the bladder. **A**. The bladder wall appeared severely thickened around the circumference, and mucosal surface irregularity is noted at initial presentation; **B**. Hematuria and thickening of the bladder wall showing improvement after initiating chemotherapy with nimustine on day 20; **C**. Recurrence of bladder wall thickening can be observed on day 125; **D**. Thickening of the bladder wall cannot be observed on day 328.

As part of bacterial cystitis treatment, prednisolone was stopped and treatment with fosfomycin (Fosmicin®, Meiji Seika Pharma Co., Ltd., Tokyo, Japan, 17 mg/kg ter in die) was initiated based on the results of the urine culture and antibiotic sensitivity testing; consequently, hematuria recurred after 7 days, and the number of nodular lesions of the skin and erosions in the mandibular region increased. Therefore, biopsies of the bladder mucosa and skin were performed under anesthesia.

Several medium-to-large round cells with fine azurophilic granules were observed in the impression smears of the skin on the left flank, dorsal and inguinal regions (Fig. 3A). The nuclear chromatin was irregular, and the nucleolus could be clearly recognized in these cells. The nucleocytoplasmic ratio was low-to-moderate, and a rare mitotic figure was observed. Several round cells exhibiting azurophilic granules were observed in the impression smear of the right nostril, lower jaw, and lower left eyelid, similar to those seen in other sites. Histopathological examination of the skin from the left flank, dorsal and inguinal regions showed medium-sized atypical lymphocytes with moderately clear cytoplasms and round nuclei infiltrating the epidermis and follicular epithelium (Fig. 4). These cells showed moderate size variability, and a rare mitotic figure was observed. Cystoscopy revealed bleeding throughout the bladder mucosa. Since the amount of bladder tissue obtained was small, no obvious tumor cell infiltration was observed in the histopathological examination. However, several medium-to-large round cells with fine azurophilic granules were observed in the impression smears of the bladder mucosa (Fig. 3B). Polymerase chain reaction for antigen receptor rearrangement (PARR) revealed that the skin tissue had clonal rearrangement of the TCR gene (Fig. 5). However, in the present case, the sample volume was small and flow cytometry could not be performed. Based on these findings, the patient was diagnosed with LGL lymphoma of the bladder and skin.

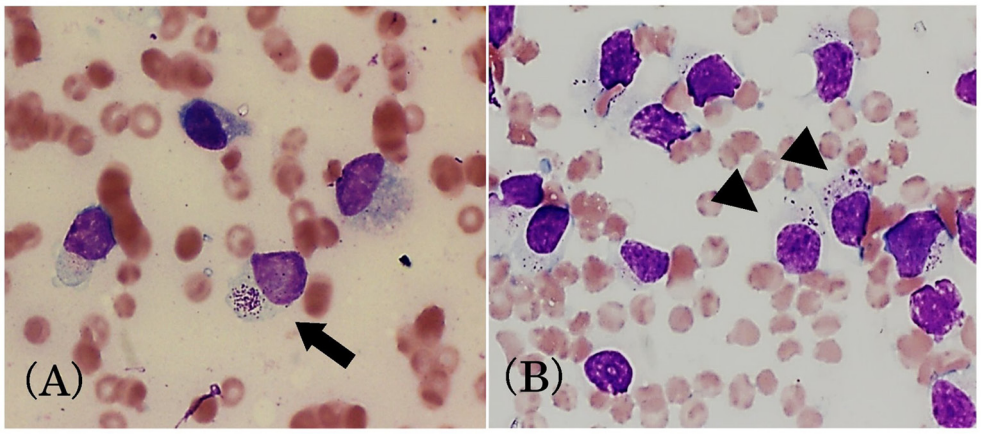

Fig. 3. Impression smears of the skin from the dorsal region and the bladder mucosa stained with Wright–Giemsa stain. **A**. A smear of the skin from the dorsal region shows several medium-to-large round cells with fine azurophilic granules (black arrow); **B**. Smear of the bladder mucosa also shows several round cells with azurophilic granules (black arrowheads).

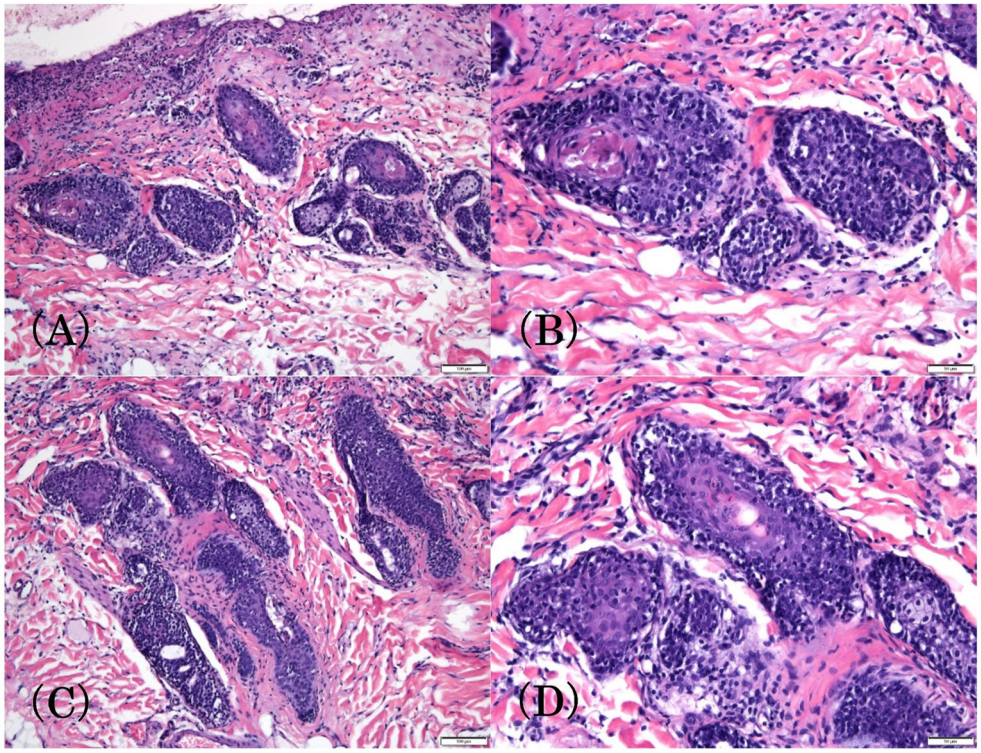

Fig. 4. Photomicrographs of histopathological sections of the skin stained with hematoxylin and eosin. **A**. Skin from the left flank region demonstrates medium-sized, atypical lymphocytes with moderately clear cytoplasm and round nuclei infiltrated the epidermis and follicular epithelium. Scale bar=100 µm; **B**. Lymphocytes show moderate size variability, and a rare mitotic figure can be observed. Scale bar=50 µm; **C**. Skin from the dorsal region. Scale bar=100 µm; **D**. Similar to the skin from the left flank region, the tissue in the dorsal region also shows medium-sized, atypical lymphocytes infiltrated into the epidermis and follicular epithelium. Scale bar=50 µm.

Chemotherapy with nimustine (Nidran®, Daiichi Sankyo Co., Ltd., Tokyo, Japan, 25 mg/m^2, on day 13 and day 34; 20 mg/m^2, on day 62 and day 90) and prednisolone (Prednisolone®, Sanwa Kagaku Kenkyusho Co., Ltd., Nagoya, Japan, 2 mg/kg) was started (Table 1), and improvements were seen in hematuria and thickening of the bladder wall after 7 days (Fig. 2B). Nodular lesions of the skin and erosion of the mandibular skin and right nostril regressed on day 34 (Fig. 1D–F). Lenograstim was administered on observation of chemotherapy-induced neutropenia, (days 41, 55, 70 and 118). Although improvements in hematuria, thickening of the bladder wall, and skin lesions were maintained for 3 months, recurrence of the erosion on the mandibular skin and thickening of the bladder wall were observed (Fig. 2C). Therefore, chemotherapy with chlorambucil (Leukeran®, Aspen Pharmacare Holdings Ltd., Durban, South Africa, 2.5 mg/m^2 once a day) was initiated on day 125, and the skin erosion and bladder wall thickening persisted for 1 month without any aggravation. To treat the recurrence, chemotherapy with vincristine (Oncovin®, Nippon Kayaku Co., Ltd., Tokyo, Japan, 0.7 mg/m^2, on day 167 and day 195) and doxorubicin (Adriacin®, Aspen Japan Co., Tokyo, Japan, 30 mg/m^2, on day 181 and day 209), and L-asparaginase (Leunase®, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan, 400 U/kg, on day 223) and nimustine (20 mg/m^2, on day 223 and day 251) treatment were initiated. Both regimens maintained partial remission for 2 months each; however, the skin lesion subsequently recurred.

To treat further recurrence, chemotherapy with cytosine arabinoside (Cylocide®, Nippon Shinyaku Co., Ltd., Kyoto, Japan, 286 mg/m^2, on day 279), cyclophosphamide (Endoxan®, Shionogi & Co., Ltd., Osaka, Japan, 200 mg/m^2, on day 286), and L-asparaginase (400 U/kg, on day 286) was administered; however, the patient was unresponsive to these treatments. Therefore, nimustine (25 mg/m^2,

on day 300) was administered; however, the dog experienced hematochezia and diarrhea, white blood cell count (WBC: 3,910/µl) and hematocrit (Ht: 12.3%) decreased, and almost no platelets were observed on the blood smear although the skin lesion showed partial response on day 328. No hematuria or thickening of the bladder wall was observed at that time (Fig. 2D). Treatment with transfusion and antibiotics was performed for potential gastrointestinal toxicity or colitis resulting from myelosuppression. However, the symptoms did not improve; myelosuppression (WBC: 900/µl, Ht: 16.6%, almost no platelets were observed on the blood smear), left shift and toxic change of neutrophils were observed on day 338. Treatment with transfusion, antibiotics and lenograstim, and chemotherapy with L-asparaginase (400 U/kg on day 338) were performed for progression of LGL lymphoma. However, the dog lost her appetite and developed astasia. Hypothermia (37.7°C), myelosuppression (WBC: 700/µl, Ht: 15.7%, platelet count: 48,000/µl), left shift and toxic change of neutrophils, and subcutaneous bleeding were observed on day 342. The dog consequently died on day 356 due to presumptive sepsis and disseminated intravascular coagulation (DIC). Necropsy was subsequently performed. As observed during the physical examination in the initial presentation, several nodular lesions were found on the skin of the flank, dorsal and inguinal regions. Medium-sized atypical lymphocytes infiltrated the epidermis and follicular epithelium in this region. These cells exhibited epithelial tropism and stained for granzyme B, which is a protease stored in the secretory granules of cytotoxic T lymphocytes and NK cells. However, there were no obvious abnormalities in the kidney, ureter, bladder, urethra, liver, spleen, or bone marrow (Fig. 6).

This case is interesting because there are no previous reports of canine LGL lymphoma presenting concurrently in both the bladder and the skin. In our case, no obvious abnormalities in the kidney, ureter, bladder, urethra, or bone marrow were observed in the necropsy. The dog appeared to have died due to myelosuppression and gastrointestinal toxicity, which are side effects of anticancer drugs, rather than tumor progression.

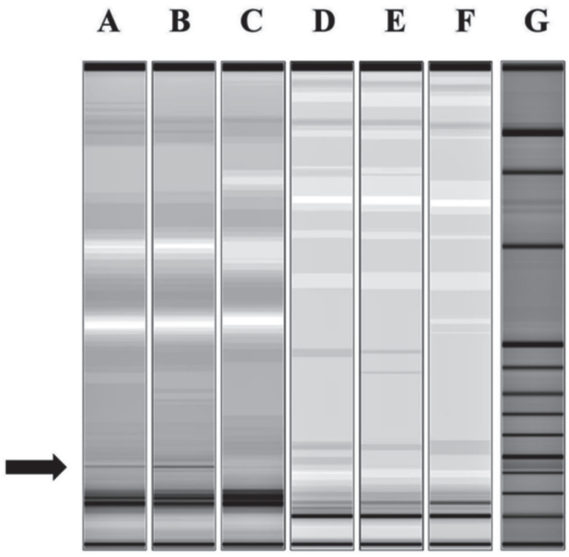

Fig. 5. Polymerase chain reaction for antigen receptor rearrangement of the skin tissue. **A**, **B**. TCR-Yagihara (Vgb)/Keller (J): Duplicate 70–100 bp. A weak monoclonal peak of 82 bp was observed (arrow). **C**. TCR-Yagihara (Vgb)/Keller (J): Negative control. **D**, **E**. B-major (CB1/CB2) Duplicate 120 bp. **F**. B-major: Negative control. **G**. TAKARA 20 bp DNA Ladder.

Cats with LGL lymphoma typically present with gastrointestinal tract and abdominal lymph node involvement, and sometimes have more widespread dissemination (to the mesentery, liver, and peripheral blood) [4, 7, 9, 18, 20]. The response rate in cats treated with combination chemotherapy with COP (vincristine, prednisolone, and cyclophosphamide) and CHOP (COP plus doxorubicin) was 30% (5%, complete remission; 25%, partial remission) [7]. In canine spinal, mediastinal, splenic and hepatosplenic LGL lymphoma, several chemotherapy protocols combining lomustine, vincristine, procarbazine, and prednisolone, lomustine and cytarabine, or lomustine and cyclosporine A have been reported [10, 13, 16]. In a dog with LGL lymphoma of the skin and intestine, combination chemotherapy with CHOP has been performed [5]. In contrast, treatment of cutaneous epitheliotropic lymphoma with lomustine, a nitrosourea-based agent, was found to be effective in 78–83% of cases [11, 21]. Therefore, we selected chemotherapy with nimustine, a nitrosourea-based agent, for the treatment of the current case of LGL lymphoma complicated by bladder and skin involvement, based on the clinical presentation as well as the ease of dosage adjustment. The initial dose was calculated based on the data from a previous report [14]. Nimustine and other chemotherapeutic drugs were added over time; however, the dog died of presumptive sepsis and DIC caused by the myelosuppression and gastrointestinal toxicity of the anticancer drugs, suggesting the necessity for dose reduction of anticancer drugs such as nimustine and fine-tuning the chemotherapy protocol.

In the present case, nimustine chemotherapy was initiated followed by combination therapy with vincristine and doxorubicin, and a relatively long survival of 356 days was observed. In dogs,

Table 1. Chemotherapy in large granular lymphocyte lymphoma of the bladder and skin

Day	13	34	62	90	125	139	167	181	195	209	223	251	279	286	300	338
Nimustine (mg/m$^{2)}$	25	25	20	20							20	20			25	
Prednisolone (mg/kg SID)	2.0–1.4	0.7	0.2	0.2	0.2	0.2	1.5–1.0	0.5	0.2	0.2	0.2	0.2	0.2	0.2	1.5–1.0	2
Chlorambucil 2.5 mg/m^2 SID					●	●										
Vincristine 0.7 mg/m^2							●		●							
Doxorubicin 30 mg/m^2								●		●						
L-asparaginase 400 U/kg											●			●		●
Cytosine arabinoside 286 mg/m^2													●			
Cyclophosphamide 200 mg/m^2														●		
Treatment response	PR	PR	PR	PR	SD	PD	PR	PR	PD	PD	PR	SD	SD	PD	PR	PD

PR: skin lesions partially improved; SD: skin lesions did not change; PD: skin lesions got worse; SID: semel in die.

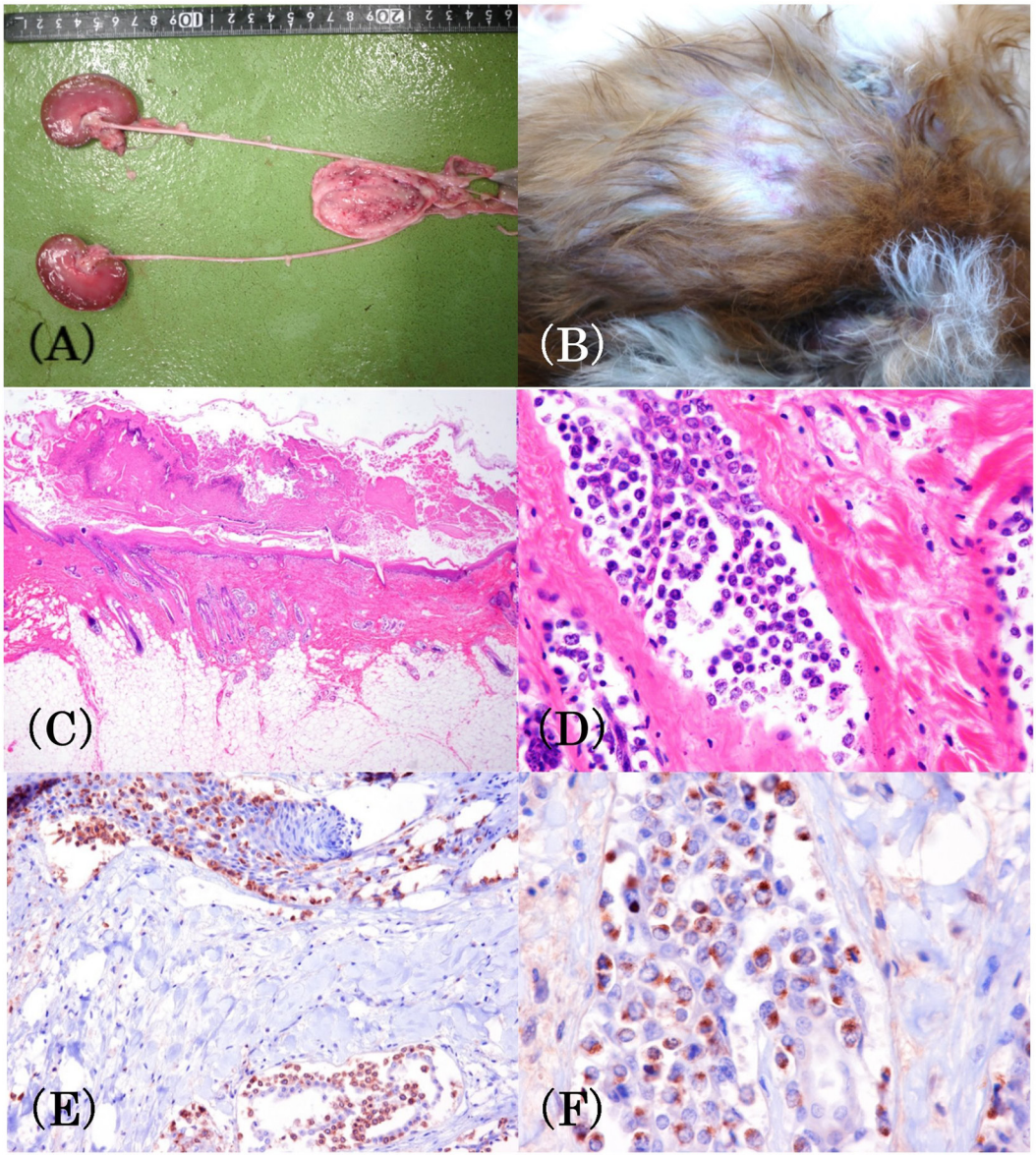

Fig. 6. **A**. Appearance of kidney, ureter, bladder, and urethra during necropsy. There are no obvious abnormalities; **B**. Several nodular lesions are found on the skin from the flank, dorsal and inguinal regions; **C**. Nodular skin lesion stained with hematoxylin and eosin (H&E), 10× objective; **D**. Nodular skin lesion stained with H&E, 40× objective. Medium-sized, atypical lymphocytes are seen infiltrating the epidermis and follicular epithelium. These cells exhibit epithelial tropism; **E**. Nodular skin lesion stained with granzyme B, 10× objective; **F**. Nodular skin lesion stained with granzyme B, 40× objective. These lymphocytes stained positive for granzyme B, which is a protease stored in the secretory granules of natural killer cells and cytotoxic T lymphocytes.

the survival times of patients with intraperitoneal, mediastinal, pleural, pericardial, gastrointestinal, pituitary, and adrenal LGL lymphomas were less than 30 days despite undergoing treatments such as chemotherapy and surgery [2, 3, 10, 12]. In contrast, relatively long survival times of 18 weeks and 195 days have been reported in cutaneous and spinal LGL lymphomas treated with CHOP-based protocol, respectively [6, 16]. In canine LGL lymphoma of the skin and intestine treated with chemotherapy with CHOP and surgery (the intestinal lymphoma in this report was localized and may have been completely removed by surgery), relatively long survival times of 508 days have also been reported [5]. Especially, dogs with spinal or cutaneous/intestinal LGL lymphoma were positive for clonal rearrangement of T-cell receptor in PARR analysis, as observed in the present case, and each of them experienced relatively long survival [5, 16]. In contrast, other cases of T-cell LGL lymphomas, anatomically classified as splenic, hepatosplenic, or ocular, had short survival durations (6–68 days); all of these cases showed lymphoma-associated hemophagocytic syndrome [13], which was not detected in the present case. In dogs with cutaneous epitheliotropic T-cell lymphoma, lomustine therapy resulted in a relatively long median survival time of 6 months [8]. We believe that in our patient, the same long-term prognosis could have been obtained with a treatment similar to those administered in cases with previous cutaneous T cell lymphomas. Therefore, it can be inferred that canine LGL lymphoma exhibits pathological conditions and prognoses based on the site of occurrence. However, studies on larger number of cases are warranted to further substantiate this.

CONFLICT OF INTEREST. Authors declare no conflicts of interest.

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