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Case Report

The First Case Report of a Primary Mast Cell Tumor Originating from the Inguinal Lymph Node in a Nine-Year-Old Female Maltese Dog

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Simple Summary: Here, the authors report the first case of a primary mast cell tumor originating from the inguinal lymph node in a nine-year-old intact female Maltese dog that had undergone a left ureteral stent, ureterotomy and splenectomy, and left-side mastectomy, including inguinal lymph node removal and ovariohysterectomy. The patient is recovering well as of February 2025, following surgery and 16 weeks of chemotherapy with a combination of prednisolone and vinblastine. The authors also propose a hypothesis for the rarity of primary lymph node mast cell tumors and the correlation between mammary gland tumors and mast cell tumor growth based on a literature review.

Abstract: A splenic mass, ureterolithiasis, left third mammary gland tumor (MGT), and left inguinal lymph node enlargement were incidentally found during a routine examination of a nine-year-old intact female Maltese dog in South Korea in July 2024. The patient underwent comprehensive surgery, including the placement of a left ureteral stent, ureterotomy for the removal of ureterolithiasis, splenectomy for the splenic mass, and a left-side mastectomy that involved the left inguinal lymph node and left third MGT and ovariohysterectomy. The splenic mass, mammary gland mass, and inguinal lymph node underwent histopathological examination, resulting in the diagnosis of nodular hyperplasia, grade 1 mammary complex carcinoma, and metastatic mast cell tumor (MCT), respectively. The origin of the MCT from the inguinal lymph node was especially uncertain. Through a blood smear test, mast cell leukemia was ruled out, and a computed tomography (CT) scan was performed to determine the MCT's origin. After CT scanning by veterinary radiologists and a biopsy of all possible masses, it was concluded that the MCT primarily originated from lymph nodes, which is extremely rare in dogs. The patient underwent 16 weeks of chemotherapy with a combination of prednisolone and vinblastine considering C-kit PCR result of left inguinal lymph node result after the surgical removal of the MCT. The patient is recovering well as of February 2025, just 7 months after first diagnosis. This re-port is significant for two reasons: first, the rarity of MCTs originating from lymph nodes other than the skin and gastrointestinal organs; second, the correlation between MGT and MCT growth, which will be investigated in a literature review focusing on molecular mechanisms.

Keywords: mast cell tumor; lymph node; mammary gland tumor

Abbreviations: mast cell tumor (MCT); mammary gland tumor (MGT); tumor-associated macrophages (TAMs); vascular endothelial growth factor (VEGF).

1. Introduction

Mast cells are bone marrow-derived cells involved in allergic and hypersensitivity reactions and also secrete histamine, heparin, and proteases¹. Mast cell tumors (MCTs) account for 21% of common dog skin cancers², and Boxers (1.95%) and Golden Retrievers (1.39%) are commonly known to develop MCTs³. The metastasis of an MCT to another organ is approximately 4%⁴. In dogs, MCTs mostly occur on the skin⁵, but they can also occur in other organs, such as the gastrointestinal tract⁶, oral mucosa⁷, and lungs⁸. Primary mast cell tumors originating from lymph nodes are exceedingly rare, with only a few reports having documented cases in visceral lymph nodes such as the hepatopancreatic lymph node⁹ and the mesenteric lymph node^{10,11}. To date, there have been no documented cases of primary mast cell tumors originating from cutaneous lymph nodes in dogs. Here, the authors report the first canine case of a primary mast cell tumor originating from the inguinal lymph node. Additionally, in humans, mast cells are associated with various types of tumors, either contributing to their inhibition or promoting their growth¹². Mast cells are hypothesized to contribute to the development of canine mammary malignant tumors (MGTs) by promoting angiogenesis, similar to some tumors described in the human species¹³. The role of MCTs in promoting MGT progression is not fully elucidated, although evidence from human studies suggests that mast cells play a role in weakening stromal–epithelial interactions, and this process may contribute to MGT development and facilitate angiogenesis¹². The case in this study also supports this point, as the MCT primarily originated from the nearby inguinal lymph node and facilitated the concurrent growth of MGT. We investigated the molecular mechanism of correlation between MCT and MGT through a literature review and provided a plausible explanation of this case by focusing on vascular endothelial growth factor (VEGF)¹⁴ and tumor-associated macrophages (TAMs)¹⁵.

In July 2024, a 9-year-old intact female Maltese was diagnosed with kidney stones and a spleen tumor at a local hospital and was referred to Yeeun Animal Hospital. At Yeeun Animal Hospital, tumors in the 3rd and 5th mammary glands on the left were additionally confirmed via physical examination. Cytological examination was conducted on two palpable masses in the left mammary region.

2. Case Presentation

In March 16, 2024, splenic tumor and kidney stones were incidentally found in a 9-year-old intact female Maltese visiting a local hospital and were referred to Yeeun Ani-mal Hospital (Seoul, South Korea). After physical examination on Yeeun Animal hospital, mammary gland masses were additionally found through palpation which were located in the left 3rd and 5th mammary gland. In May 1, Fine needle aspiration (FNA) was done in the left 3rd and 5th mammary gland and after checking mast cell tumor in the left 5th mammary gland through FNA and benign tumor in the left 3rd mammary gland, efforts to find a clear primary mast cell tumor origin including additional physical examination, radiography, and abdominal ultrasonography were performed in May 4.

After the examination and procedures, hydronephrosis arose due to a ureteral stone descending from the left kidney. Therefore, emergency surgery was performed in May 8 with comprehensive surgical procedure including ureterotomy for ureteral stent and stone removal and left partial mastectomy with inguinal lymph node, Splenectomy and ovariohysterectomy. Also, histopathological examination was performed by Antech (Seongnam, South Korea) after the comprehensive surgery and the results were nodular lymphoid hyperplasia (spleen), grade 1 mammary complex carcinoma (left third mammary tumor), and metastatic mast cell tumor (left inguinal lymph node), respectively, in May 23 as shown in Table 1. Additional C-kit mutation PCR test was done by the Michigan State University Veterinary Diagnostic Laboratory (MI, USA) in June 2024. At the pet owner's request, IHC (immuno-histochemical staining) staining was not performed. Mast cell leukemia was ruled out via a peripheral blood smear and finally CT scans to find mast cell tumor origin were performed in June 21, 2024 at Shine Animal Hospital (Seoul, South Korea). After CT scan, additional biopsy of the mast cell tumor origin candidates was performed by Antech and

three inguinal nodules were diagnosed as mild lymphoid follicular hyperplasia, and the other three masses found in the hind body were diagnosed as nodular sebaceous hyperplasia, lipoma, and normal-haired skin respectively, in June 27, 2024 (table 1).

Based on all imaging tests and biopsies that were performed on this dog, the tumor was diagnosed as a primary mast cell tumor, which originated from the left inguinal lymph node. Even though the findings of histopathological examinations, such as those shown in Figure 1D, are generally seen in metastatic mast cell tumors, they may also be seen in primary mast cell tumors. There were no other findings of primary mast cell tumors in other organs (supplementary figure, figure 2), such as those shown in Table 1, as confirmed through consecutive biopsy and CT scans.

After finding the origin of the tumor, the patient received vinblastine and prednisolone-based chemotherapy 16 for 16 weeks as C-kit PCR 8 and 11 was negative (Table 2) which can be interpreted as less likely to respond to tyrosine kinase inhibitors. The chemotherapy protocol was started on July 20, vinblastine was administered intravenously at a dose of 2 mg/m² biweekly for a total of eight treatments (16 weeks). Prednisolone (2 mg/kg) was orally administered daily and was gradually tapered before discontinuation. As of October 2024, no metastases, recurrences, or new tumors were observed in follow-up ex-aminations. As of February 2025, the patient is recovering well with no clinical signs or tumor recurrence to date and as well in April 2025.

Table 1. Primary tumor candidates for the mast cell tumor.

Organ Method	Mammary gland	Spleen	Left inguinal lymph node	Mast cell leukemia	Others (including inguinal and hind body regions)
Full CT scan	Not applicable	Not applicable	Not applicable	Not applicable	Three inguinal nodules and three masses were found
Biopsy (or histopathology) results	Mammary complex carcinoma, grade 1	Nodular lymphoid hyperplasia	Mast cell tumor	Not applicable	Mild lymphoid follicular hyperplasia, nodular sebaceous hyperplasia, lipoma, and normal-haired skin
Blood smear	Not applicable	Not applicable	Not applicable	Ruled out	Not applicable

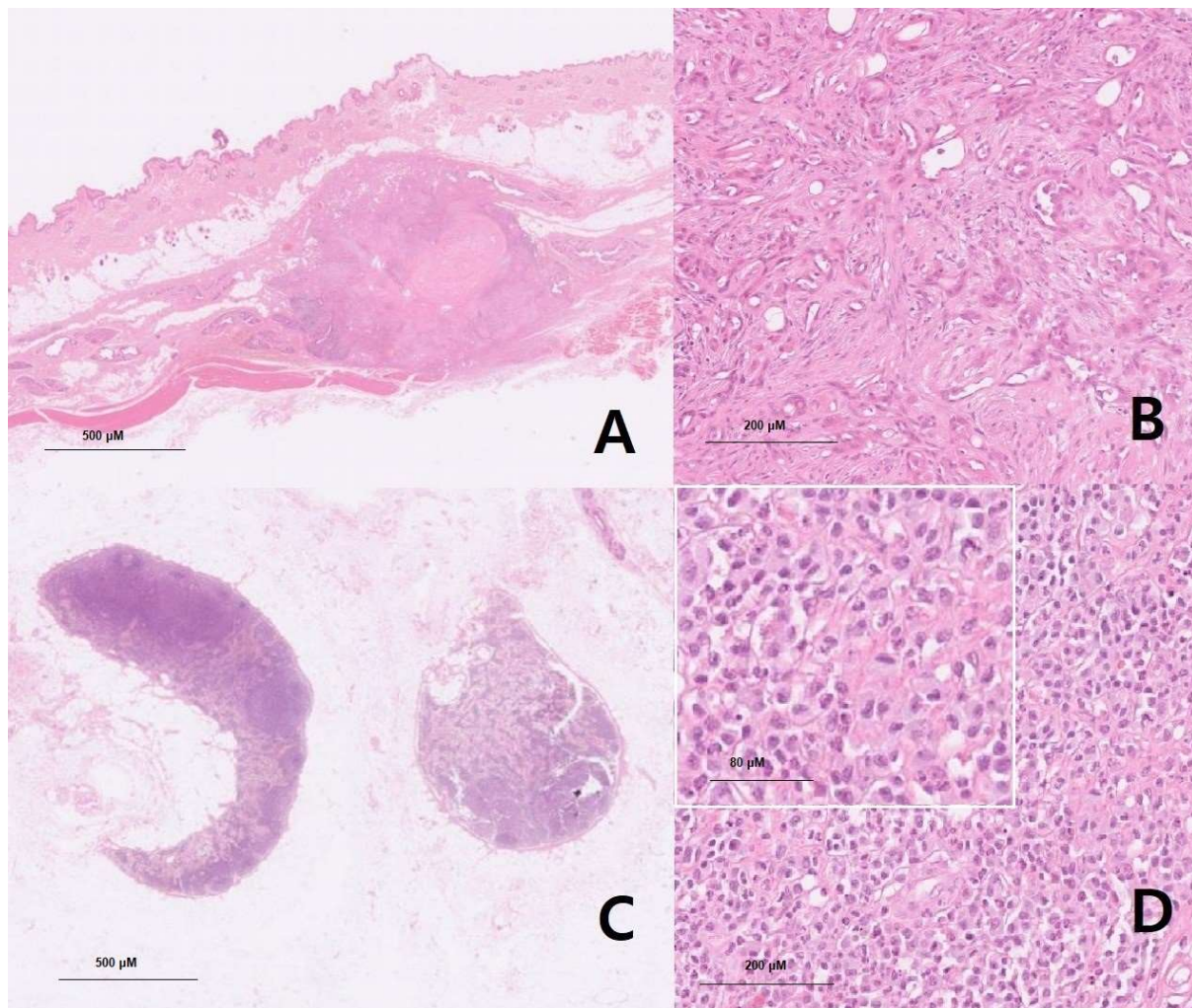


Figure 1. (A, B, C, and D): Histopathologic examination of the masses (mammary gland and inguinal lymph node).

Specimens A and B: Left third mammary gland mass, 0.8 cm x 0.6 cm (4.4 cm x 3.2 cm including skin), firm and solid with no hemorrhage, and solitary.

MICROSCOPIC DESCRIPTION: (A) At X40 magnification, neoplastic epithelial cells were surrounded by myoepithelial cells and were well demarcated and nodular. Anisocytosis and anisokaryosis were moderate in the neoplastic cells in the mammary mass specimen, with no mitotic figures observed. (B) At X100 magnification, myoepithelial cells appeared spindle-shaped to stellate with indistinct cell borders, with moderate amounts of amphophilic to eosinophilic to basophilic vacuolated to fibrillary to homogeneous cytoplasm and ovoid to elongate open nuclei with variable amounts of coarse chromatin and either indistinct or 1-2 small nucleoli. Neoplastic cells were polygonal to cuboidal and had variable distinct cell borders. Necrosis was seen in the central area, while numerous plasma cells and lymphocytes were present in the periphery. Grade 1 mammary complex carcinoma was confirmed comprehensively. Scale bars = 500 µM, and 200 µM (inset).

Specimens C and D: Left inguinal lymph node, 1.1 cm x 1.0 cm, firm and solid with no hemorrhage, and solitary.

MICROSCOPIC DESCRIPTION: (C) At X40 magnification, moderate follicular and paracortical hyperplasia were observed in the lymph node specimen, accompanied by moderate sinus histiocytosis. Anisocytosis and anisokaryosis were moderate, and mitotic figures were frequently observed. (D) At X100 magnification, the neoplastic mast cells featured distinct cell borders and exhibited a round morphology with moderate amounts of cytoplasm containing basophilic granules. Finely stippled chromatin was centrally located in an oval nucleus. A small

number of eosinophils were mixed among neoplastic mast cells. These effacements of normal nodal structure, along with an overt number of mast cells, are generally seen in metastatic mast cell tumors (HN3, scale HN0-HN3). Scale bars = 500 μ M, 200 μ M and 80 μ M (inset).

Table 2. C-kit PCR result of tissue (left inguinal lymph node).

Procedure	Result		
C-kit PCR specimen	Formalin-Fixed	Paraffin-Embedded	Tissue, positive
C-kit PCR 8 K9 Only	Negative		
C-kit PCR 11 K9 Only	Negative		

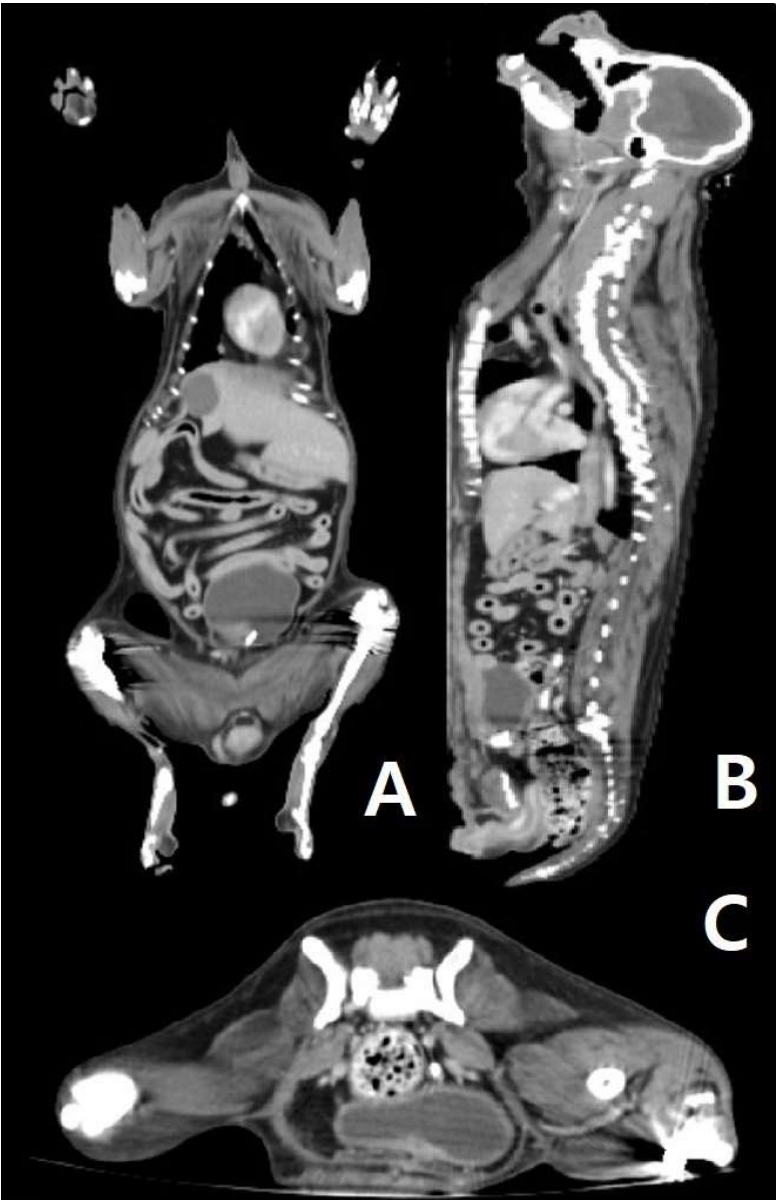


Figure 2. (A, B, and C): CT scan of the patient’s body. (A) In the dorsal view of the CT scan, there is no sign of a primary tumor in the abdominal organ and thorax. (B) In the sagittal view of the CT scan, there is no sign of a primary tumor in the abdominal organ and thorax. (C) In the transverse view of the CT scan (posterior abdomen), there is no sign of a primary tumor in the abdominal organ and thorax.

3. Discussion

Canine MCTs primarily occur in the skin, as previously described, with numerous cases reported of cutaneous MCT metastasizing to other organs, such as the heart¹⁷, bone marrow¹⁸, urinary bladder, spleen, liver, and kidney¹⁹. The involvement of lymph nodes is common, and identifying the primary organ of MCTs is essential for prognosis and treatment.¹⁹

During the process of finding the origin of the MCT, mast cell leukemia, which is rare in dogs²⁰, was first considered due to the infiltration of the mast cells in the lymph nodes. However, this was excluded since there was no increase in the number of mast cells in a peripheral blood smear. During the first surgery, the large tumor on the left mammary gland and the spleen were removed, and these organs were found to not be a primary MCT. After surgery to identify the primary organ of MCT, even the small nodules found through CT were biopsied, but no suspected mast cell tumors other than the lymph nodes were found. Therefore, the final diagnosis for the patient in this case was a primary MCT of the lymph node and it is significant as being first case to utilize ultrasound, CT scan and biopsy to scrutinize the origin.

In general, canine lymph node primary MCT is uncommon, and to the authors' knowledge, there have been no case reports since 2009¹¹. Previous reports of primary MCT in lymph nodes are rare and include cases in the hepatopancreatic lymph node⁹, cranial mesenteric lymph node¹⁰, and mesenteric lymph node¹¹. This is the first reported case of MCT primarily occurring in cutaneous lymph nodes, notable for its academic significance in employing advanced imaging techniques for the identification of primary cutaneous MCT and performing biopsies on all suspicious lesions. Cutaneous lymph nodes have the advantage of being easily palpated during physical examination and accessible for cytological evaluation. If mast cell infiltration is observed in lymph nodes with concurrent MCT in a nearby skin mass, which can be confirmed by cytological examination, it is generally considered lymph node metastasis from proximal skin tumors. However, as shown in this case, if a primary mass is not identified near the lymph nodes via physical examination or imaging, the possibility of primary MCT in the lymph nodes should be considered. This study represents an essential trial to challenge existing assumptions and expand the diagnostic perspective in small-animal cancer.

In addition, this patient did not show any lymph node changes upon physical examination as of December 2024, after the first diagnosis of primary MCT of lymph nodes in March 2024, and other skin masses are not palpable. Also, X-ray U/S phase metastasis has not been confirmed. It is also believed to enhance the academic value of the paper by providing prognostic information for primary surface lymph node metastatic cancer (MCT) treatment involving surgical removal and adjuvant chemotherapy through continuous follow-up monitoring. Since there was no c-kit mutation in the specimen, as confirmed by PCR test, chemotherapy was performed as opposed to targeted therapy according to the standard protocol^{21 22}.

3.1. Correlation Between MCT and MGT Growth

Although it is uncertain whether MGT is positively correlated with primary MCT, and in some case reports, MCT and MGT arise concurrently²³, MGT is common in senior intact female dogs; therefore, the occurrence of MCT and MGT in the patient may be an independent event. Additionally, BRCA-1 gene mutation, which is crucial in breast cancer, affects the regulation of VEGF, which leads to dysregulation of the gene and increases angiogenesis in humans²⁴. Also, mast cells release VEGF and promote tumor angiogenesis in humans²⁵, and a similar phenomenon was detected in canines²⁶, but the detailed mechanism has not been well documented in canines compared to humans. On the other hand, there are subclasses of macrophages: M0²⁷, M1, M2, and M2-like TAM²⁸. MGT and TAM are positively correlated in canines²⁹, and TAM also releases cytokines such as VEGF, TNF- α . TAM and mast cells work together in the tumor environment, inhibiting or facilitating the progression of the tumor depending on the stage³⁰. It has also been reported that tumor-associated mast cells are less frequently observed in malignant mammary gland tumors than in mammary gland

hyperplasia³¹. Considering these factors together, it is not clear whether the growth of MCT and MGT is positively correlated because it is multifactorial.

3.2. Hypothesis of Rare Primary Lymph Node MCT

Mast cells release VEGF³², and the overexpression of VEGF in the skin leads to the growth of tumors³³. Therefore, by putting these facts together, it is plausible to determine that cutaneous MCT is more common than in other organs. On the other hand, lymphatic vessel endothelium is more permeable than blood vessel endothelium³⁴, which makes it more difficult to attach to the blood vessel, contributing to the tumor microenvironment³⁵. However, mast cells lead to chemotaxis to laminin³⁶ and is essential in the metastasis of primary tumors, as mediated by macrophages³⁷. Nevertheless, it is theoretically possible that MCT primarily originates from the lymph node, as previously reported in the visceral lymph node⁹, and this study is the first to report MCT originating from the cutaneous lymph node.

4. Conclusions

This case report is significant because it is the first to report MCTs primarily originating from the inguinal lymph node utilizing ultrasound, CT scan and biopsy. We also provide possible explanation for rarity of MCT originated from lymph node which can be investigated in future follow up research. Additionally, since there have been very few cases of primary MCT in lymph nodes, no histopathological criteria currently exist for assessing prognosis. This case study also suggests that if numerous cases of lymph node primary MCT are reported, pathological criteria for prognosis evaluation can be examined in a follow-up study.

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Institutional Review Board Statement: Informed consent was waived (or exempted) from the IRB (SNUIRB-2025-NH-005) due to the retrospective nature of this case study. Prior to collecting samples, all pet owners signed informed consent.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A (Supplementary Figures)

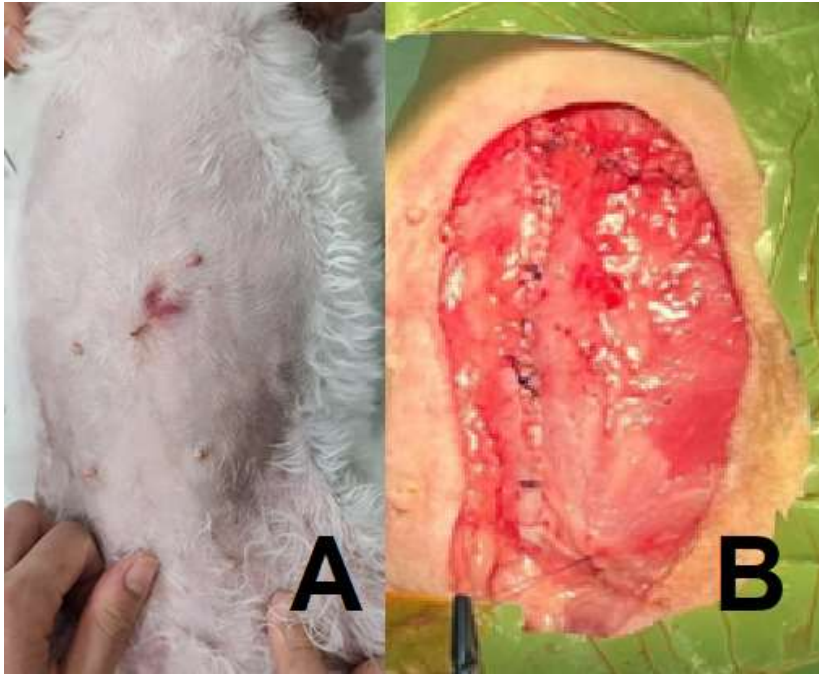


Figure 1. (A, B). (A) Macroscopic lesion of the left inguinal lymph node mass. (B) Surgical removal of the left 3rd, 4th, and 5th mammary gland tumors.

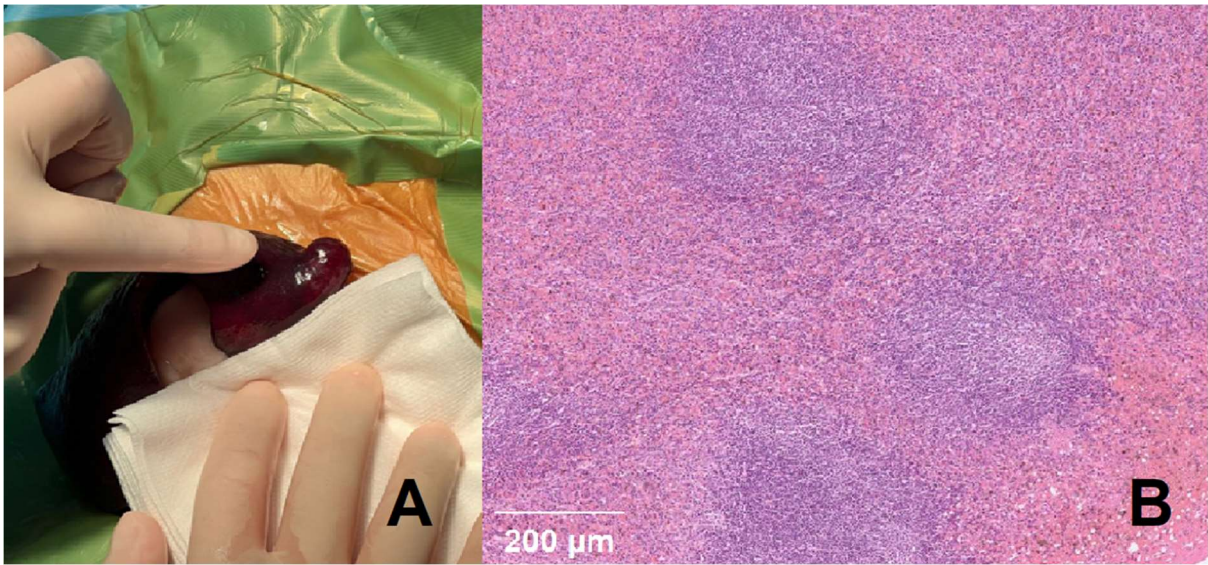


Figure 2. (A, B). (A) Macroscopic lesion of the splenic mass. (B) Nodular lymphoid hyperplasia of spleen, Sections of the spleen contained a large nodular mass that was characterized by proliferation of multiple hyperplastic lymphoid follicles surrounded by red blood cells ad-mixed with hematopoietic precursor cells and megakaryocytes. Lymphoid follicles had retained polarity and prominent mantle zones. There was no evidence of neoplastic dis-ease within the sections examined histologically. (Scale bars = 200 μM, inset.).

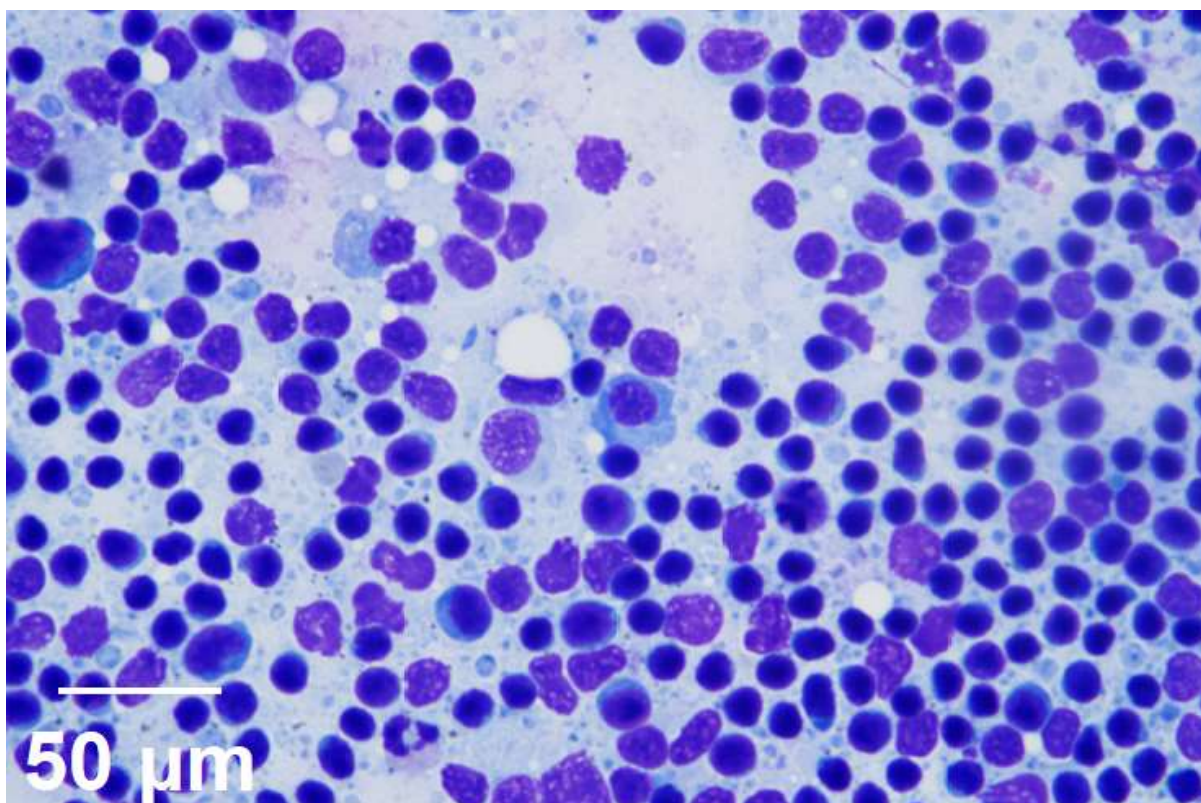


Figure 3. Reactive lymphoid hyperplasia (right inguinal lymph node), Moderate cellularity, mild erythrocytes infiltration, most of lymphocyte are small with small number of large lymphocyte and neutrophil, macrophage and plasma cell are shown. There is no evidence of infectious agent. (Scale bars = 50 μ M, inset).

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