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Leukemic B-Cell Lymphoma with Mott Cell Differentiation and Dual CLRA/LI in a Mongrel Dog

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ABSTRACT

Lymphoma represents a malignant disorder resulting from abnormal multiplication of lymphoid tumor cells. A 4-year-old female mixed-breed dog was brought in due to a single swollen lymph node. On physical examination, there was a marked enlargement of the right prescapular node together with visible abdominal distention. The complete blood profile indicated pronounced lymphocytosis, and the peripheral smear revealed numerous lymphoblasts as well as Mott cells. Fine-needle aspiration of the affected node demonstrated that the cell population consisted mainly of lymphoblasts and Mott cells. These cytologic and hematologic results supported the diagnosis of a leukemic-phase, multicentric B-cell lymphoma showing Mott cell differentiation. PCR for antigen receptor rearrangement and flow cytometric analyses confirmed the occurrence of cross-lineage rearrangement (CLRA) and lineage infidelity (LI), respectively. The animal was treated with a CHOP-based chemotherapy protocol; however, the neoplastic process advanced rapidly, and death occurred three months after initial presentation. B-cell lymphoma with Mott cell features (MCL) is scarcely mentioned in veterinary case reports and tends to follow an atypical course. To date, there are no previous descriptions of canine MCL presenting with both CLRA and LI. This paper outlines the clinical observations, diagnostic procedures, and therapeutic management of a case of MCL showing CLRA and LI.

Keywords: Cross-lineage rearrangement, Canine, Flow cytometry, Lineage infidelity, Lymphoma, Mott cell, PCR for antigen receptor rearrangement

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Introduction

Lymphoma (also termed lymphosarcoma, LSA) refers to the uncontrolled multiplication of neoplastic lymphoid cells, originating in lymphoid organs or occasionally in other tissues. It is among the most frequently observed malignant hematopoietic diseases in dogs, representing roughly 83% of such tumors [1]. There is no recognized sex predisposition, and although LSA may occur at any age, middle-aged and senior animals are more commonly affected. Epidemiological data indicate an incidence of 1.5 per 100,000 in dogs younger than one year, rising to 84 per 100,000 in ten-year-old dogs [2]. The underlying causes of LSA remain uncertain but are believed to involve a mix of hereditary, environmental, molecular, immunologic, and infectious influences [3].

LSA can be categorized by its anatomic pattern (multicentric, gastrointestinal, mediastinal, or cutaneous), histopathologic architecture, immunophenotype (B-cell or T-cell), and the World Health Organization (WHO) clinical staging scheme [3–5]. The primary diagnostic approach relies on cytologic or histologic findings from fine-needle aspirates or biopsies, with identification of more than 50% lymphoblasts often considered diagnostic [4]. Ancillary methods—immunohistochemistry (IHC), flow cytometry (FC), and PCR for antigen receptor rearrangement (PARR)—further refine diagnosis and classification.

Because lymphoma in dogs commonly exhibits systemic involvement, chemotherapy remains the preferred therapeutic option. Among available protocols, CHOP—cyclophosphamide (C), doxorubicin

(hydroxydaunorubicin), vincristine (oncovin), and prednisone or prednisolone (P)—is generally regarded as the most successful [2, 6]. Survival expectations differ according to numerous elements, including clinical stage, anatomical distribution, response to chemotherapy, immunophenotype, and neoplastic cell morphology [7, 8].

Mott cells, derived from plasma cells with impaired antibody secretion, contain spherical Russell bodies composed of retained immunoglobulin within the rough endoplasmic reticulum [9–11]. They appear in various pathologic conditions such as chronic inflammatory disorders, autoimmune diseases, plasma cell dyscrasias, multiple myeloma, and certain lymphomas [11]. As terminally differentiated B-cells, they may also occur in B-cell forms of lymphoma [12]. Up to the present, only nine canine cases of B-cell lymphoma with Mott cell change (MCL) have been documented [13–21]. Its etiology and clinical pattern remain uncertain; earlier cases were mostly euthanized shortly after diagnosis or after limited chemotherapy, providing minimal outcome data. MCL appears to behave atypically compared to ordinary B-cell lymphoma [13]. Understanding its chemotherapeutic response and prognosis, therefore, requires further investigation. Furthermore, MCL displaying either CLRA or LI has not previously been reported, and its biological behavior remains completely undefined. This report presents a case of canine MCL with both CLRA and LI, describing its clinical presentation, diagnostic findings, and treatment response.

Case presentation

A 4-year-old female mixed-breed dog was presented with an isolated, enlarged lymph node. There was no history indicating toxin contact or infection. On examination, the right prescapular lymph node measured approximately 3.9 × 3.5 cm² and was markedly enlarged, and the abdomen appeared distended. A complete blood count (CBC, ADVIA® 2120, Siemens Healthcare Diagnostics, Deerfield, IL, USA) revealed severe lymphocytic leukocytosis—lymphocytes: 16,390 cells/µL (reference 1300–4100 cells/µL); leukocytes: 28,850 cells/µL (reference 5200–13,900 cells/µL)—together with mild anemia (hematocrit 30.9%; reference 37.1–57.0%) **(Table 1).** Microscopic examination of the blood smear showed abundant lymphoid cells and numerous Mott cells **(Figure 1).**

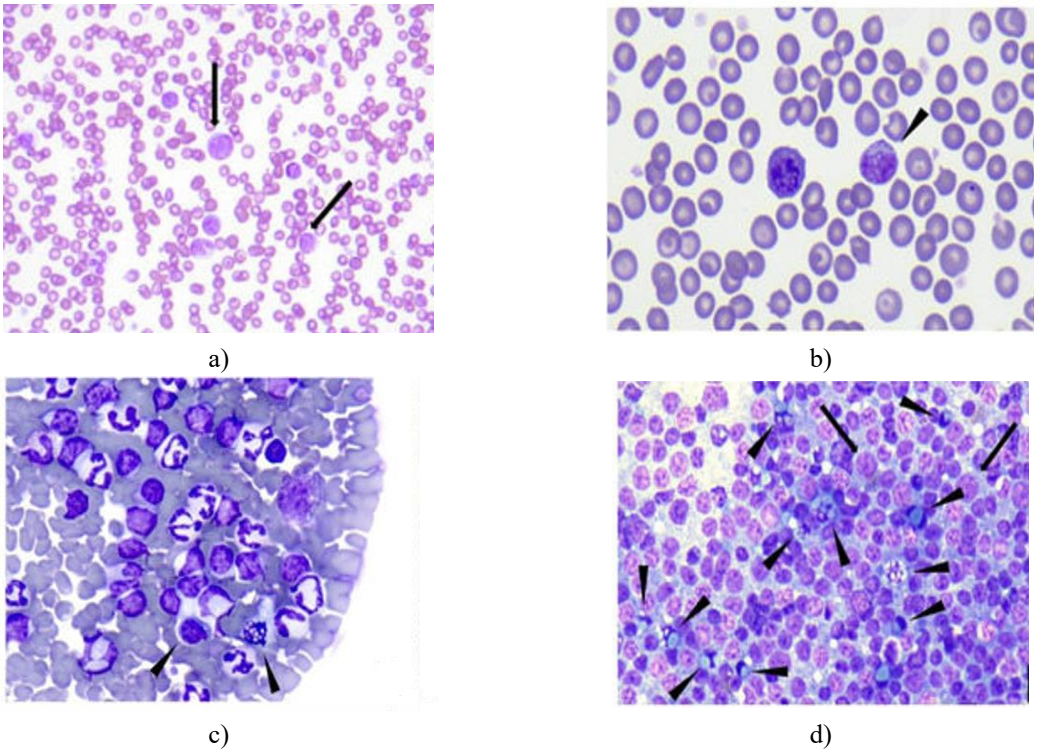


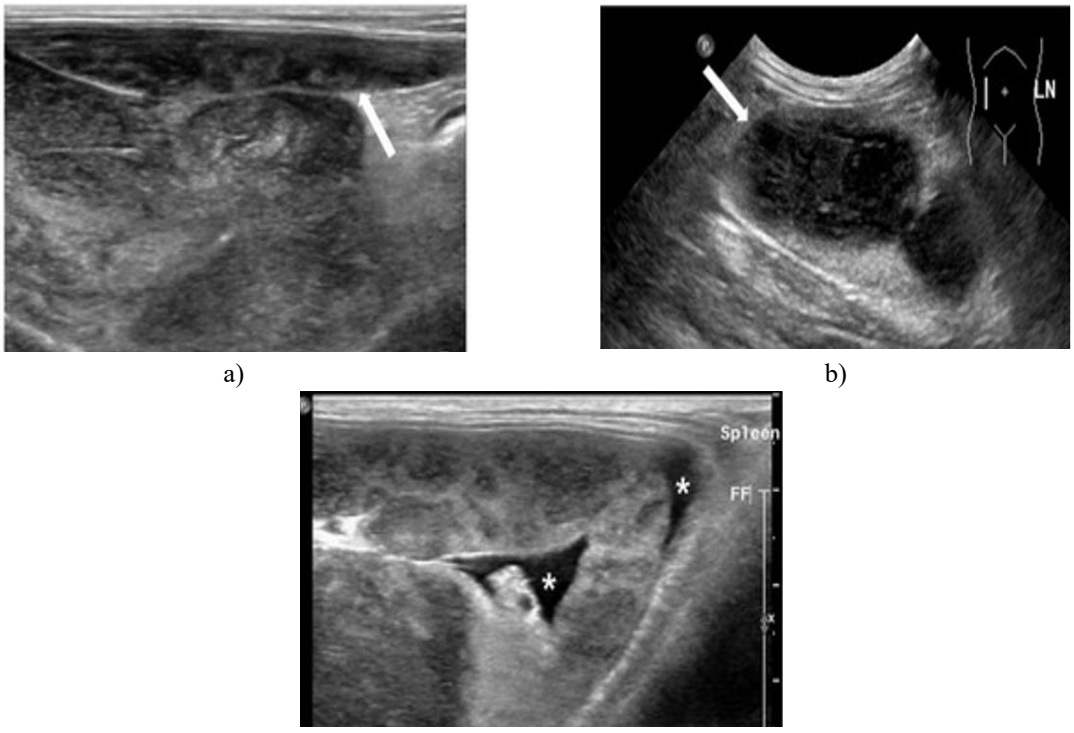
Figure 1. Microscopic view (Modified Wright's stain, ×40 objective). (a) Peripheral smear showing lymphoblasts (arrows). (b) Peripheral smear with a Mott cell (arrowhead). (c) Peripheral smear highlighting multiple Mott cells (arrowheads). (d) FNAC sample from the right prescapular lymph node showing Mott cells (arrowheads) and lymphoblasts (arrows). Note that lymphoblasts dominate the population and are visibly larger than small lymphocytes.

Table 1. Complete blood count values obtained from the patient.

Hematologic Parameter	Reference Interval	Patient Results
RBC (×10¹²/L)	5.7–8.8	4.4
Hct (%)	37.1–57.0	30.9
Hgb (g/dL)	12.9–18.4	9.79
WBC (×10⁹/L)	5.20–13.90	28.85
Neutrophils (×10⁹/L)	3.90–8.00	9.42
Lymphocytes (×10⁹/L)	1.30–4.10	16.39
Monocytes (×10⁹/L)	0.20–1.10	2.59
Eosinophils (×10⁹/L)	0.00–0.60	0.08
Platelets (×10⁹/L)	143–400	370

Hct**:** hematocrit; Hgb**:** hemoglobin; RBC**:** red blood cells; WBC**:** white blood cells.

Serum biochemistry analysis (BS-200 Chemistry Analyzer; MINDRAY™, Shenzhen, China) revealed no remarkable deviations from normal values. Ultrasonographic examination of the abdomen demonstrated notable enlargement of intra-abdominal lymph nodes, the presence of ascitic fluid, and a splenic lesion displaying a honeycomb-like internal pattern **(Figure 2)**. Cytological evaluation of a fine-needle aspirate from the right prescapular lymph node showed a predominance of lymphoblasts with scattered Mott cells **(Figure 1).**

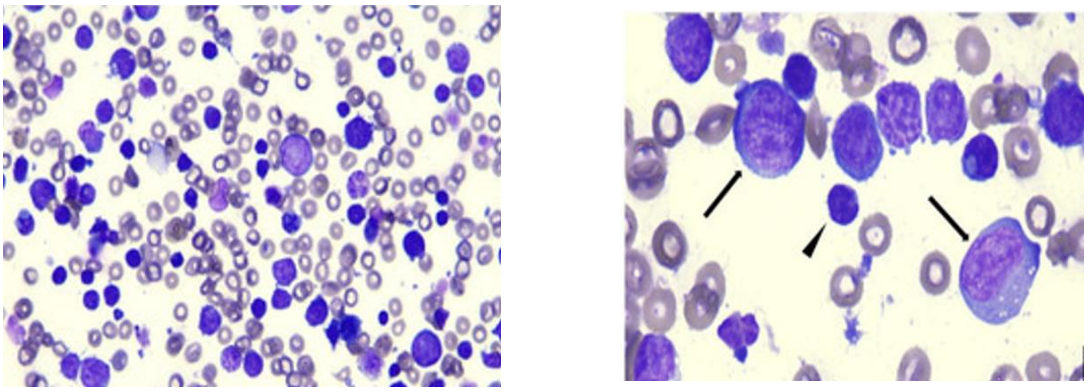


a) b)

c)

Figure 2. Abdominal ultrasound findings: (a) honeycomb-patterned area within the splenic tissue (arrow = spleen); (b) mesenteric lymph node hypertrophy (arrows = enlarged nodes); (c) ascitic fluid accumulation surrounding the spleen (asterisks = ascites).

Analysis of the serosanguineous abdominal fluid classified it as an exudate, with a total nucleated cell concentration of 148,300 cells/µL and a total protein level of 4.1 g/dL, as determined by CBC and refractometer readings. Cytology showed that lymphoid cells predominated, compatible with neoplastic effusion **(Figure 3)**.



a) b)

Figure 3. Microscopic views of ascitic fluid stained with modified Wright's stain. (a) Abundant lymphoid cells in high-power view (×40). (b) Arrows mark lymphoblasts, and the arrowhead denotes small, normal lymphocytes (×100). The lymphoblasts were notably larger than the small lymphocytes.

Polymerase chain reaction for antigen receptor rearrangement (PARR; IDEXX Laboratories, Westbrook, ME, USA) on the right prescapular lymph node revealed monoclonal rearrangements of both immunoglobulin and T-cell receptor genes, confirming concurrent lineage rearrangement (CLRA).

Flow cytometric immunophenotyping was performed on aspirates from the right prescapular lymph node (LN) and peripheral blood. Lymphoid cells were initially separated based on forward (FSC) and side scatter (SSC) characteristics, followed by exclusion of doublets to isolate singlets **(Figure 4)**. These singlet lymphoid populations were evaluated using antibodies against CD3, CD5, CD21, and CD34. The lymphoid cells from LN and blood exhibited roughly 90% uniformity, characterized as CD3+/CD5−/CD21+/CD34− and CD3−/CD5−/CD21+/CD34−, respectively **(Table 2, Figure 4)**. As CD3 marks T lymphocytes and CD21 marks B lymphocytes, these findings suggested lineage infidelity (LI) in the right prescapular LN.

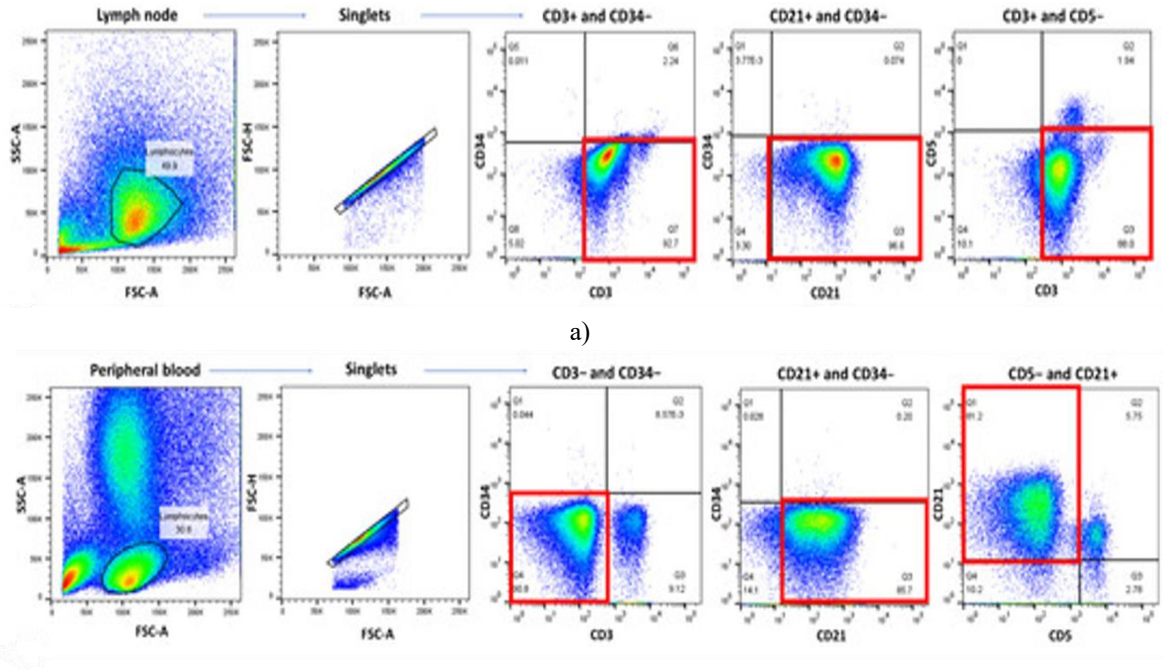


Figure 4. Flow cytometric profiles of right prescapular LN and peripheral blood (PB). FSC vs. SSC plots indicate lymphoid gating in both samples. Two-parameter density plots display singlet lymphoid populations post-doublet exclusion. (a) Right prescapular LN: around 90% of lymphoid cells co-express CD3 and CD21 (red squares). (b) PB: Approximately 90% of lymphoid cells express CD21 only (red squares).

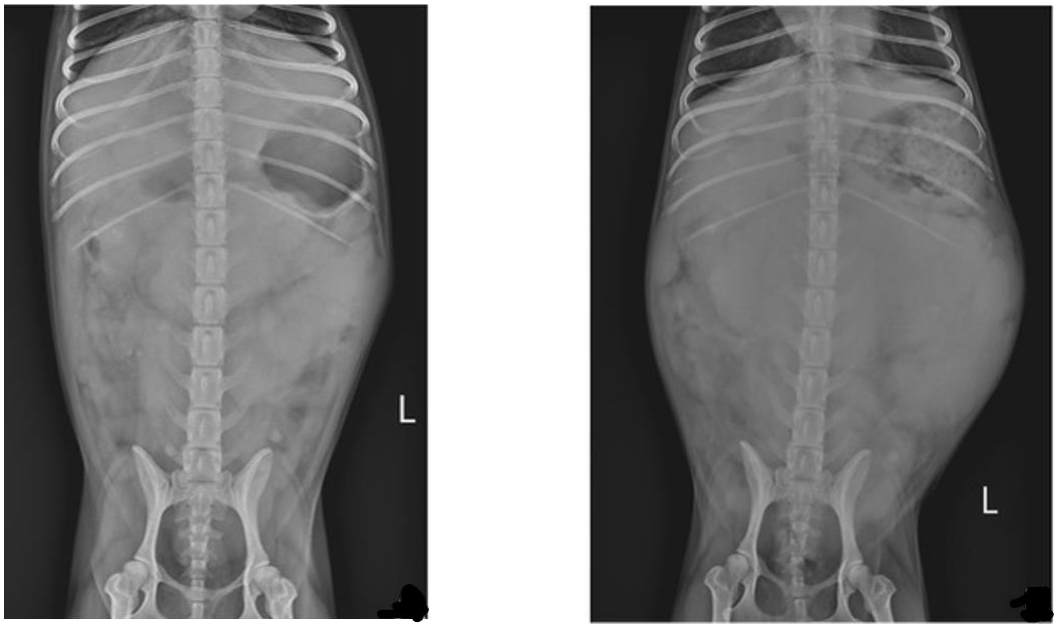
Table 2. Antibodies employed for flow cytometric analysis.

Antibody	Target Cells	Clone	Fluorochrome	Supplier
CD3	T lymphocytes	CA17.2A12	FITC	Bio-Rad
CD5	T lymphocytes	YKIX322.3	APC-eFluor780	Thermo Fisher Scientific
CD21	Mature B lymphocytes	CA2.1D6	PE	Bio-Rad
CD34	Hematopoietic progenitor cells	1H6	Alexa Fluor 405	R&D Systems

Manufacturers: Bio-Rad (Hercules, CA, USA), Thermo Fisher Scientific (Waltham, MA, USA), and R&D Systems (Minneapolis, MN, USA). FITC = fluorescein isothiocyanate; APC = allophycocyanin; PE = phycoerythrin.

Integrating the cytological (FNAC), molecular (PARR), and immunophenotypic (FC) data, along with the presence of Mott cells, the patient was diagnosed with stage Va (leukemic phase) multicentric B-cell lymphoma (LSA) featuring Mott cell differentiation, CLRA, and LI. A CHOP-based chemotherapy regimen was initiated, including cyclophosphamide (250 mg/m² IV), vincristine (0.7 mg/m² IV), doxorubicin (1 mg/kg IV), and prednisolone (2.0 mg/kg PO once daily for seven days, tapered gradually). The animal was reassessed weekly, with abdominal ultrasonography performed after every cycle.

The initial chemotherapy cycle yielded a positive response, with lymph node and abdominal mass sizes reduced by about 40% and normalization of lymphocytosis (4.05 × 10⁹ cells/L). Nevertheless, full remission (CR) was not attained; partial remission (PR) persisted for roughly four weeks. At week 6 (start of the second cycle), the recurrence of lymph node and splenic enlargement indicated progressive disease (PD). L-asparaginase (400 U/kg SC) was added to the CHOP protocol, yet therapeutic response remained poor during the subsequent four weeks. Upon the owner's request, treatment shifted to palliative care using chlorambucil (6 mg/m² PO q24h) and prednisolone (1.0 mg/kg PO q24h). Despite this, lymph node and spleen sizes continued to increase **(Figure 5)**. Approximately three months after presentation, the patient developed anorexia and lethargy and died 81 days following the start of treatment.



a) b)

Figure 5. Ventrodorsal abdominal radiographs at the first and last visits (74 days apart). (a) Initial examination. (b) Final examination. Marked splenic enlargement accounts for the increased abdominal volume in panel B.

At the six-month evaluation, the dog had regained full functional ability and displayed no signs of recurrence or clinical abnormalities.

This report outlines the diagnostic process and therapeutic management of a canine case presenting with multicentric B-cell lymphoma (LSA) characterized by Mott cell differentiation, concurrent lineage rearrangement (CLRA), and lineage infidelity (LI). Although histopathological confirmation through immunohistochemistry

(IHC) was unavailable due to the owner's decision, the final diagnosis of Mott cell lymphoma (MCL) was established based on cytological evidence from FNAC—demonstrating lymphoblast proliferation and Mott cell features—and flow cytometric (FC) immunophenotyping of peripheral blood showing CD3−/CD5−/CD21+/CD34− expression.

Mott cells originate from mature plasma cell–stage B lymphocytes, and when such differentiation accompanies neoplastic lymphoid proliferation, it signifies a B-cell–type LSA [12]. The findings in this patient, therefore, support a diagnosis of multicentric B-cell LSA with Mott cell differentiation, CLRA, and LI. Moreover, both lymphoblasts and Mott cells were observed in peripheral smears. Circulating lymphoblasts commonly appear in leukemic variants of lymphoma or in leukemia itself, but differentiating between the two solely by this feature is challenging. Distinction is typically made using clinical context—such as widespread lymph node enlargement—and flow cytometric assessment of CD34.

CD34, a transmembrane phosphoglycoprotein found in several species, including dogs and humans [22], is normally expressed by hematopoietic progenitors in bone marrow and umbilical cord blood [23]. Owing to this distribution, CD34 is frequently applied to differentiate leukemic-stage LSA from acute lymphoblastic leukemia (ALL), and to distinguish ALL from chronic lymphocytic leukemia (CLL) [4]. However, exceptions exist: both CD34+ lymphoma and CD34− leukemia have been documented in dogs, making this marker alone insufficient for definitive classification. Given this patient's generalized lymphadenopathy and the predominance of CD34−lymphoid cells, a leukemic-phase lymphoma was considered the most probable diagnosis.

CLRA and LI were identified through PARR and FC testing, respectively. PARR is widely used to determine clonality in both B- and T-cell LSAs [24]. Typically, immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangements correspond to B- and T-lineages, respectively. CLRA disrupts this principle, representing simultaneous rearrangement or expression of lineage-specific genes (e.g., both Ig and TCR in one clone) [25–29]. Previous research has recorded this rare finding in about 21% of canine marginal zone lymphomas and 5% of T-cell LSAs [27, 30]. Although the biological mechanism underlying CLRA is unclear, and its prognostic or therapeutic relevance remains uncertain, additional studies are necessary to clarify its clinical significance.

Flow cytometry is a valuable diagnostic technique for classifying LSA immunophenotypes because it enables multiparametric marker analysis beyond the scope of IHC or ICC [4]. It exhibits approximately 94% agreement with IHC and greater diagnostic sensitivity compared with PARR [31]. In this case, FC analysis of the right prescapular lymph node revealed that most lymphocytes displayed a CD3+/CD5−/CD21+/CD34− pattern. CD3 functions as a T-cell co-receptor expressed at all stages of T-cell development and serves as a reliable indicator of T-cell origin [32]. Conversely, CD21 is expressed on B lymphocytes and is used to confirm B-cell identity [33]. Co-expression of CD3 and CD21 within the same population made lineage assignment difficult and indicated LI, a phenomenon reported to confer chemoresistance and poor prognosis in human lymphoma and leukemia cases [29, 34–38]. Although the underlying cause is unclear, such resistance may relate to increased drug efflux activity or chromosomal instability [36–39]. While aberrant CD marker expression has been well documented in human hematologic malignancies, limited information exists on its relevance in dogs.

A previous FC-based investigation of 59 dogs with LSA identified LI in 13 individuals, with leukemic phases observed across B-, T-, and LI-phenotypes, the latter being most frequent [28]. Consistent with those findings, our patient exhibited a leukemic state, suggesting a potential link between LI and leukemic transformation. Since FC provides valuable information for both diagnosis and prognosis of LSA, it should be regarded as a front-line diagnostic tool. Expanded studies are needed to clarify the prognostic value of LI in canine lymphoma.

Although cure is uncommon, most lymphomas initially respond to chemotherapy, and therapeutic responsiveness is associated with improved survival [7, 8, 40]. Previous reports indicate that many dogs diagnosed with MCL were euthanized soon after diagnosis, though some underwent chemotherapy using protocols such as COP, CHOP, or corticosteroid monotherapy [14–21]. Only two earlier cases involved CHOP therapy [16, 17]. In one case, an early improvement was achieved, but the patient's condition declined by week 10, leading to euthanasia three months after diagnosis [16]. In the second case, remission was reached initially, but relapse occurred 2.5 months after induction; multiple rescue treatments, including dacarbazine, yielded only transient benefit, and the dog was euthanized nine months post-diagnosis due to severe seizures [17].

Similarly, in the current study, the patient was treated with CHOP supplemented by L-asparaginase, but the therapeutic response was brief and poor. Death occurred approximately three months after presentation, notably shorter than the mean survival time (MST) of 10–14 months reported for multicentric B-cell LSA [41]. Extensive nodal and extranodal involvement is typical of MCL [13]; correspondingly, this dog exhibited widespread lesions

in superficial and abdominal lymph nodes, the spleen, and bone marrow at presentation. Although splenectomy, marrow aspiration, and necropsy were declined, cytologic findings of lymphoblast-rich ascitic fluid and circulating lymphoblasts indicated probable infiltration of the spleen and marrow.

Due to the rarity of published MCL cases, predicting prognosis remains difficult, but evidence suggests that MCL represents a negative prognostic variant of canine lymphoma. Furthermore, the presence of CLRA and LI may also influence outcomes, and their interactions warrant further study. Future large-scale analyses are necessary to better characterize this subtype and to guide individualized therapeutic approaches for canine LSA exhibiting Mott cell differentiation, CLRA, or LI.

Conclusion

To the best of our knowledge, this report represents the first documented case of Mott cell lymphoma exhibiting both concurrent lineage rearrangement (CLRA) and lineage infidelity (LI). Despite aggressive CHOP-based chemotherapy, clinical improvement was minimal, and the outcome remained poor. Collectively, these findings indicate that MCL may serve as an adverse prognostic factor and display an atypical clinical course within canine B-cell LSA. Comprehensive characterization through additional case reports and broader studies is necessary to elucidate the clinical and biological roles of CLRA and LI in this disease.

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Ethics Statement: None

References

1. Vail DM, Pinkerton M, Young KM. Hematopoietic Tumors. In: Vail DM, Thamm DH, Liptak JM, editors. Withrow & MacEwen's Small Animal Clinical Oncology. 6th ed. St. Louis, MO: W.B. Saunders; 2019. p. 688–772.
2. Marconato L, Gelain ME, Comazzi S. The dog as a possible animal model for human non-Hodgkin lymphoma: A review. Hematol Oncol. 2013;31(1):1–9.
3. Vail DM. Hematopoietic tumours. In: Ettinger SJ, Feldman E, Cote E, editors. Textbook of Veterinary Internal Medicine. 8th ed. Elsevier Health Sciences; 2017. p. 2065–77.
4. Burkhard MJ, Bienzle D. Making sense of lymphoma diagnostics in small animal patients. Clin Lab Med. 2015;35(3):591–607.
5. Valli VE, San Myint MS, Barthel A, Bienzle D, Caswell J, Colbatzky F, et al. Classification of canine malignant lymphomas according to the World Health Organization criteria. Vet Pathol. 2011;48(1):198–211.
6. Chun R. Lymphoma: Which chemotherapy protocol and why? Top Companion Anim Med. 2009;24(3):157–62.
7. Jagielski D, Lechowski R, Hoffmann-Jagielska M, Winiarczyk S. A retrospective study of the incidence and prognostic factors of multicentric lymphoma in dogs (1998–2000). J Vet Med A Physiol Pathol Clin Med. 2002;49(7):419–24.
8. Kiupel M, Teske E, Bostock D. Prognostic factors for treated canine malignant lymphoma. Vet Pathol. 1999;36(3):292–300.
9. Alanen A, Pira U, Colman A, Franklin RM. Mott cells: A model to study immunoglobulin secretion. Eur J Immunol. 1987;17(10):1573–7.
10. Bain BJ. Russell bodies and Mott cells. Am J Hematol. 2009;84(7):516.
11. Bavle RM. Bizarre plasma cell — Mott cell. J Oral Maxillofac Pathol. 2013;17(1):2–3.
12. Montes-Moreno S, Gonzalez-Medina A-R, Rodriguez-Pinilla S-M, Maestre L, Sanchez-Verde L, Roncador G, et al. Aggressive large B-cell lymphoma with plasma cell differentiation: IHC characterization of

plasmablastic lymphoma and DLBCL with partial plasmablastic phenotype. Haematologica. 2010;95(8):1342–49.
13. Snyman HN, Fromstein JM, Vince AR, Rare A. A rare variant of multicentric large B-cell lymphoma with plasmacytoid and Mott cell differentiation in a dog. J Comp Pathol. 2013;148(3):329–34.
14. Seelig DM, Perry JA, Zaks K, Avery AC, Avery PR. Monoclonal immunoglobulin protein production in two dogs with secretory B-cell lymphoma with Mott cell differentiation. J Am Vet Med Assoc. 2011;239(10):1477–82.
15. Kodama A, Sakai H, Kobayashi K, Mori T, Maruo K, Kudo T, et al. B-cell intestinal lymphoma with Mott cell differentiation in a 1-year-old miniature Dachshund. Vet Clin Pathol. 2008;37(4):409–15.
16. Stacy NI, Nabity MB, Hackendahl N, Buote M, Ward J, Ginn PE, et al. B-cell lymphoma with Mott cell differentiation in two young adult dogs. Vet Clin Pathol. 2009;38(1):113–20.
17. Kol A, Christopher MM, Skorupski KA, Tokarz D, Vernau W. B-cell lymphoma with plasmacytoid differentiation, atypical cytoplasmic inclusions, and secondary leukemia in a dog. Vet Clin Pathol. 2013;42(1):40–6.
18. De Zan G, Zappulli V, Cavicchioli L, Martino LD, Ros E, Conforto G, et al. Gastric B-cell lymphoma with Mott cell differentiation in a dog. J Vet Diagn Investig. 2009;21(5):715–9.
19. Yang Y, Jung JH, Hwang SH, Kim Y. Canine multicentric large B cell lymphoma with increased Mott cells diagnosed by flow cytometry. J Vet Clin. 2021;38(1):36–40.
20. Tamizharasan S, Vairamuthu S, Pazhanivel N, Savitha S, Chandrasekar M, Tirumurugaan KG, et al. Clinicopathological study of diffuse large B cell lymphoma in a Labrador dog: A case report. Pharma Innov J. 2022;11(4):509–14.
21. Rimpo K, Hirabayashi M, Tanaka A. Lymphoma in Miniature Dachshunds: A retrospective multicenter study of 108 cases (2006–2018) in Japan. J Vet Intern Med. 2022;36(3):1390–7.
22. Vernau W, Moore PF. An immunophenotypic study of canine leukemias and preliminary assessment of clonality by PCR. Vet Immunol Immunopathol. 1999;69(2–4):145–64.
23. Satterthwaite AB, Burn TC, Le Beau MM, Tenen DG. Structure of the gene encoding CD34, a human hematopoietic stem cell antigen. Genomics. 1992;12(4):788–94.
24. Lana SE, Jackson TL, Burnett RC, Morley PS, Avery AC. Utility of PCR for antigen receptor rearrangement in staging and prognosis in dogs with lymphoma. J Vet Intern Med. 2006;20(2):329–34.
25. Krejci O, Prouzova Z, Horvath O, Trka J, Hrusak O. TCR δ gene is frequently rearranged in adult B lymphocytes. J Immunol. 2003;171(1):524–7.
26. Moore PF, Woo JC, Vernau W, Kosten S, Graham PS. Characterization of feline T cell receptor gamma (TCRG) variable region genes for molecular diagnosis of feline intestinal T cell lymphoma. Vet Immunol Immunopathol. 2005;106(2):167–78.
27. Burnett RC, Vernau W, Modiano JF, Olver CS, Moore PF, Avery AC. Diagnosis of canine lymphoid neoplasia using clonal antigen receptor rearrangements. Vet Pathol. 2003;40(1):32–41.
28. Wilkerson MJ, Dolce K, Koopman T, Shuman W, Chun R, Garrett L, et al. Lineage differentiation of canine lymphomas/leukemias and aberrant expression of CD molecules. Vet Immunol Immunopathol. 2005;106(2):179–96.
29. Gelain ME, Mazzilli M, Riondato F, Marconato L, Comazzi S. Aberrant phenotypes and quantitative antigen expression in subtypes of canine lymphoma by flow cytometry. Vet Immunol Immunopathol. 2008;121(3–4):179–88.
30. Valli VE, Vernau W, de Lorimier LP, Graham PS, Moore PF. Canine indolent nodular lymphoma. Vet Pathol. 2006;43(2):241–56.
31. Thalheim L, Williams LE, Borst LB, Fogle JE, Suter SE. Lymphoma immunophenotype of dogs determined by IHC, flow cytometry, PCR for antigen receptor rearrangements. J Vet Intern Med. 2013;27(6):1509–16.
32. Chetty R, Gatter K. CD3: Structure, function, and role of immunostaining in clinical practice. J Pathol. 1994;173(4):303–7.
33. Hartley G, Elmslie R, Dow S, Guth A. Checkpoint molecule expression by B and T cell lymphomas in dogs. Vet Comp Oncol. 2018;16(3):352–60.
34. Wolach O, Stone RM, How I. How I treat mixed-phenotype acute leukemia. Blood. 2015;125(16):2477–85.
35. Liu J, Tan X, Ma YY, Liu Y, Gao L, Gao L, et al. Prognostic value of aberrant antigen in acute B lymphocytic leukemia. Clin Lymphoma Myeloma Leuk. 2019;19(6):e349–58.

36. Legrand O, Perrot JY, Simonin G, Baudard M, Cadiou M, Blanc C, et al. Adult biphenotypic acute leukaemia: An entity with poor prognosis related to cytogenetics & P-glycoprotein. Br J Haematol. 1998;100(1):147–55.
37. Nakagawa Y, Hasegawa M, Kurata M, Yamamoto K, Abe S, Inoue M, et al. Expression of IAP-family proteins in adult acute mixed lineage leukemia (AMLL). Am J Hematol. 2005;78(3):173–80.
38. Tiribelli M, Damiani D, Masolini P, Candoni A, Calistri E, Fanin R. Biological and clinical features of T-biphenotypic acute leukaemia: single centre report. Br J Haematol. 2004;125(6):814–5.
39. Manola KN. Cytogenetic abnormalities in acute leukaemia of ambiguous lineage: overview. Br J Haematol. 2013;163(1):24–39.
40. Baskin CR, Couto CG, Wittum TE. Factors influencing first remission and survival in 145 dogs with lymphoma: retrospective study. J Am Anim Hosp Assoc. 2000;36(5):404–9.
41. Richards KL, Suter SE. Man's best friend: What can pet dogs teach us about non-Hodgkin's lymphoma? Immunol Rev. 2015;263(1):173–91.