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Clinicopathologic features and clinical outcome in a cat with nodal T-zone lymphoma

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Abstract

Case summary An 11-year-old male castrated domestic shorthair cat presented with increased respiratory effort, pleural effusion, lymphadenopathy, lethargy and decreased appetite with weight loss. A diagnosis of T-zone lymphoma was made from histopathology of an extirpated popliteal lymph node that had a marked paracortical expansion of small lymphocytes and prominent high endothelial venule proliferation. T-cell receptor gamma (TRG) molecular clonality PCR yielded a clonal rearrangement and immunohistochemistry demonstrated that the neoplastic lymphocytes expressed CD3 and did not express CD20. The cat was initially treated with two doses of intravenous vincristine and oral prednisolone followed by oral chlorambucil. The pleural effusion, lymphadenopathy, lymphocytosis, abdominal organomegaly and lethargy resolved, and the cat's appetite and body weight returned to normal. At the time of manuscript submission, the cat continued to do well, more than 24 months after presentation.

Relevance and novel information T-zone lymphoma is a common indolent lymphoma in dogs, but it has only been histopathologically described in one cat before this report. This is the first report to describe the clinical presentation, clinicopathologic findings and outcome for a cat with T-zone lymphoma.

Keywords: Feline lymphoma; indolent; T-cell; lymphoproliferative disorder; clonality

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Introduction

Lymphoma is a common neoplasm of dogs and cats with considerable variability in morphology, biological behavior and prognosis. The incidence is estimated to be 200 in 100,000 cats[1,2] with indolent lymphomas comprising 36%.[3]

T-zone lymphoma (TZL) is a common indolent lymphoma in dogs, comprising 16–62% of canine indolent lymphoma cases.[4,5] The majority of dogs with TZL present with lymphadenopathy (100%) and lymphocytosis (53–64%).[6–8] TZL has characteristic histopathology consisting of small to occasionally intermediate-sized lymphocytes with clumped chromatin, mostly inapparent nucleoli and moderate volumes of clear cytoplasm that expand the paracortex and often compress the residual lymphoid follicles against the capsule.[8,9] Concurrent proliferation of paracortical high endothelial venules is common. The immunophenotype of TZL in dogs has been reported as CD3 positive (100%), CD20 negative (100%) and CD45 negative (92–100%).[6,9,10] In dogs, there are a wide variety of reported clinical approaches for TZL, including monitoring without treatment, glucocorticoids alone or chemotherapy, with the majority experiencing survival times years beyond diagnosis regardless of approach.[5–8,11]

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Table 1 Serial select complete blood count data of an 11-year-old male castrated cat with T-zone lymphoma

	Hematocrit (%)	Leukocytes (K/µl)	Lymphocytes (K/µl)	Neutrophils (K/µl)	Platelets (K/µl)
Reference interval	30.3–52.3	2.87–17.02	0.92–6.88	2.30–10.29	151–600
Day 0	35.0	10.90	5.66	3.92	**124*** (with clumping)
Day 5	47.6	7.40	2.77	3.96	184
Day 43	38.30	15.42	**10.42**	4.14	220
Day 48	34.8	17.68	**10.53**	6.22	264
Day 54	**26.10**	4.72	2.02	**2.19**	235
Day 60	**25.20**	6.17	3.45	2.36	180
Day 76	**23.6**	6.12	3.38	2.37	**120**
Day 89	**26.7**	5.50	2.73	2.52	**150**
Day 125	**27.2**	7.42	3.70	3.39	**114**
Day 153	**29.4**	11.50	1.87	9.26	**4*** (with clumping)
Day 161	**28.0**	9.35	2.45	6.44	**138**
Day 196	**28.6**	9.56	2.70	6.25	**149**
Day 238	**26.6**	8.78	1.68	6.61	**130**
Day 287	**28.7**	8.88	1.88	6.36	190
Day 343	**27.4**	8.96	1.57	6.90	189
Day 427	33.0	6.76	1.43	4.68	183
Day 634	36.1	7.95	1.62	5.53	183

Bold denotes findings outside the reference interval.
*Significant platelet clumping was identified on a follow-up blood smear.

TZL is poorly understood in cats. A case of TZL has been reported in a cat; however, details including case presentation, treatment and outcome were not described.[12] To the authors' knowledge, there are no other reports of feline TZL. The aim of this case report was to describe the clinicopathological features and outcome in a cat with TZL.

Case description

An 11-year-old male castrated domestic shorthair cat weighing 4.6 kg presented (day 0) with a 2-week history of hiding and 2 months of intermittent soft stool with mild hematochezia. The cat had historical diagnoses of hypertrophic cardiomyopathy and feline asthma, which was well-controlled with a fluticasone propionate aerosol. A complete blood count (CBC) (Table 1), chemistry profile and urinalysis were unremarkable. Five days later, the cat was presented to its primary veterinarian with increased respiratory rate and effort, and relevant abnormalities from whole-body radiographs included moderate bilateral pleural effusion, multilobar pulmonary consolidation or an alveolar pattern, mild hepatomegaly and splenomegaly. A repeated CBC was unremarkable. The cat was referred for continued care.

Upon presentation to the referral hospital on day 5, a grade III/VI systolic heart murmur was detected along with bilateral dull lung sounds on auscultation. A thoracic focused assessment with ultrasonography for tracking (TFAST) scan revealed marked pleural effusion and thoracocentesis under sedation removed 155 ml of fluid. Thoracic radiographs after thoracocentesis did not identify a mass or cardiomegaly to suggest a cause for pleural effusion. The recovered fluid was turbid and pale red, with a protein concentration of 3.6 g/dl, fewer than 100,000 red blood cells/µl and 18,850 white blood cells/µl with a predominance (93%) of small lymphocytes (lymphocytic effusion). The effusion triglyceride and cholesterol concentrations were 73 mg/dl and 63 mg/dl, respectively, which is atypical for chylous effusion, although serum triglyceride concentration was not measured. Thoracic and abdominal CT revealed moderate pleural effusion, multiple enlarged lymph nodes measuring up to 2.7 cm, splenomegaly with an irregular margin and large intestinal wall thickening with ill-defined layering. The spleen was further evaluated using ultrasound and was 1.2 cm thick with a mottled echotexture. Cytology of the spleen showed numerous heterogeneous small lymphocytes and a mild increase in intermediate and large lymphocytes, consistent with lymphoid hyperplasia.

On day 10, the cat continued to have soft stools and was coughing and wheezing. An examination revealed an enlarged left popliteal lymph node, and fine-needle aspiration cytology confirmed lymphoid hyperplasia. Thoracic radiographs and TFAST revealed mild pleural effusion.

On day 17, the cat's left popliteal lymph node was measured at 1.2 cm. Decreased ventral lung sounds were ausculted and thoracic radiographs revealed marked bilateral pleural effusion with static multilobar consolidation or alveolar patterns. Thoracocentesis removed 175 ml of pleural effusion.

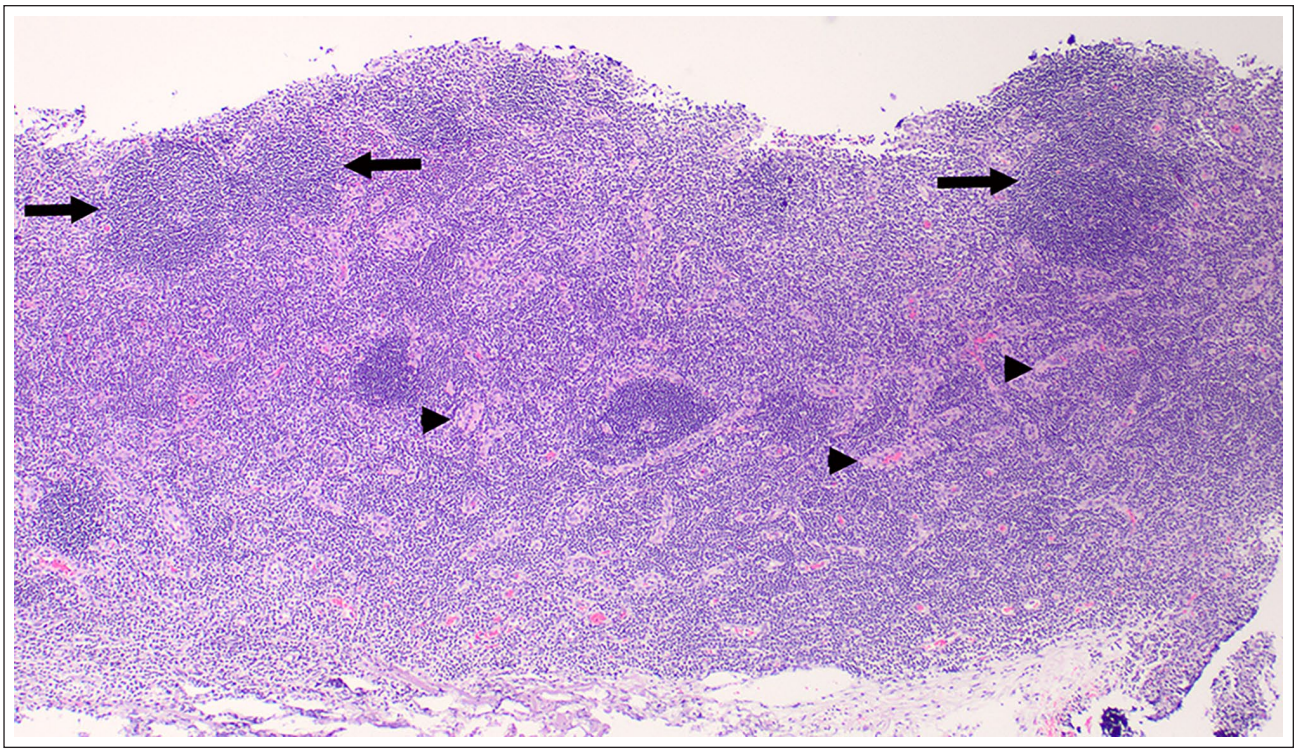

Figure 1 Photomicrograph of a popliteal lymph node of an 11-year-old cat with T-zone lymphoma. There is marked paracortical expansion with residual follicles pushed to the periphery (arrows), and prominent proliferation of high endothelial venules (arrowheads) throughout the expanded paracortex. Hematoxylin and eosin; ×4 objective

On day 19, the cat's examination findings revealed enlarged bilateral popliteal and mandibular lymph nodes with decreased ventral lung sounds. An ultrasound-guided liver aspirate, extirpation of the left popliteal lymph node and thoracocentesis were performed under general anesthesia, where 224 ml of pleural effusion was removed. Liver cytology showed mild vacuolar change with moderate to marked lymphocytic and mild neutrophilic and plasmacytic infiltrates. Blood was submitted for infectious disease PCR (*Anaplasma*, *Bartonella*, *Cryptococcus*, *Cytauxzoon*, *Ehrlichia*, *Mycoplasma*, *Salmonella* and *Toxoplasma* species, and calicivirus, coronavirus, panleukopenia, feline leukemia virus and feline immunodeficiency virus) and was negative.

The cat presented with dull mentation and increased respiratory rate and effort 43 days after initial presentation. A CBC revealed lymphocytosis (10.42 K/µl; reference interval [RI] 0.92–6.88). Thoracic and abdominal radiographs revealed marked pleural effusion and progressive hepatomegaly compared with imaging on day 5. Thoracocentesis removed 380 ml of effusion. Radiographs after thoracocentesis showed a static multilobar consolidation or an alveolar pattern. Given the suspicion for neoplasia, prednisolone therapy was initiated (1.1 mg/kg PO q24h).

Histopathology of the popliteal lymph node revealed marked paracortical expansion (Figure 1) of small to intermediate-size lymphocytes with mostly round nuclei measuring approximately 1.25–1.5 red blood cells (RBCs) in diameter. Some nuclei had sharp, shallow indentations. Chromatin was clumped with inapparent nucleoli and mitotic figures were extremely rare (Figure 2). Cells had moderate volumes of clear cytoplasm that resulted in distinctive separation of the small nuclei with prominent proliferation of high endothelial venules (Figure 1). Immunohistochemistry was undertaken on formalin-fixed, paraffin-embedded sections using antibodies vs CD3 (clone CD3-12; Serotec) and CD20 (RB-9013; LabVision), as described previously.[13] Neoplastic lymphocytes were CD3 positive and CD20 negative (Figure 3), indicating a T-cell origin of the marked paracortical expansion. Both B-cell and T-cell PCR for antigen receptor rearrangement (PARR) was also performed as described previously.[14,15] T-cell receptor gamma primers resulted in a reproducible clonal rearrangement whereas IgH FR2, IgH FR3 and kappa-deleting element (B-cell) primers showed polyclonal rearrangements.[13,16] TZL was diagnosed based on histomorphology, immunohistochemistry and PARR.

On day 48, the cat had decreased lung sounds ventrally and sedated thoracocentesis removed 322 ml of pleural effusion. A CBC revealed static lymphocytosis and was otherwise unremarkable. Vincristine (0.5 mg/m^2 IV) was administered.

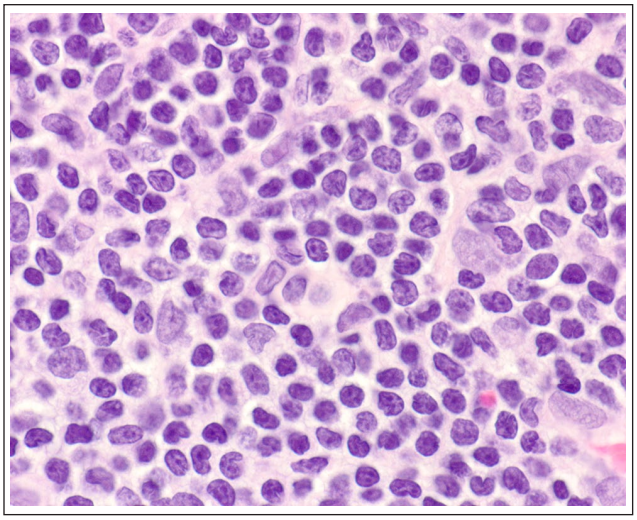

Figure 2 Photomicrograph of a popliteal lymph node of an 11-year-old cat with T-zone lymphoma. Neoplastic lymphocytes are small to intermediate in size, with nuclei approximately 1.25 to occasionally 1.50 red blood cells in diameter. Nuclei are round, sometimes with sharp, shallow indentations or clefts. Chromatin is clumped with inapparent nucleoli and mitotic figures are extremely rare. Cells have moderate volumes of clear cytoplasm that result in distinctive separation of the small nuclei. Hematoxylin and eosin; × 100 objective

On day 54, the cat had mildly decreased ventral lung sounds, the right popliteal lymph node was subjectively smaller per the attending clinician, and its appetite and energy level had improved. The cat's soft stool resolved with metronidazole (9.6 mg/kg PO q12h), but recurred each time metronidazole was discontinued. A TFAST scan revealed scant pleural effusion. The cat's lymphocytosis resolved and a Veterinary Cooperative Oncology Group grade 1 afebrile neutropenia (2.19 K/µl; RI 2.30–10.29) and grade 1 anemia (26.10%; RI 30.3–52.3) were detected.[17] A second dose of vincristine (0.5 mg/m^2 IV) was administered.

At 60 days after presentation, the cat's appetite and stool quality had improved. A TFAST scan revealed mild pleural effusion bilaterally. On CBC, the lymphocyte concentrations remained normal, neutropenia resolved and anemia remained relatively static. The cat was started on compounded chlorambucil (6.4 mg/m^2 PO q48h; Wedgewood Pharmacy).

Between days 76 and 161, the cat was presented for five rechecks and was doing well at home, with a normal appetite and was gaining weight. Examination showed a progressively decrease in the size of the right popliteal and left mandibular lymph nodes, with a persistent mild decrease in ventral lung sounds. Serial CBCs revealed progressive improvement in anemia and

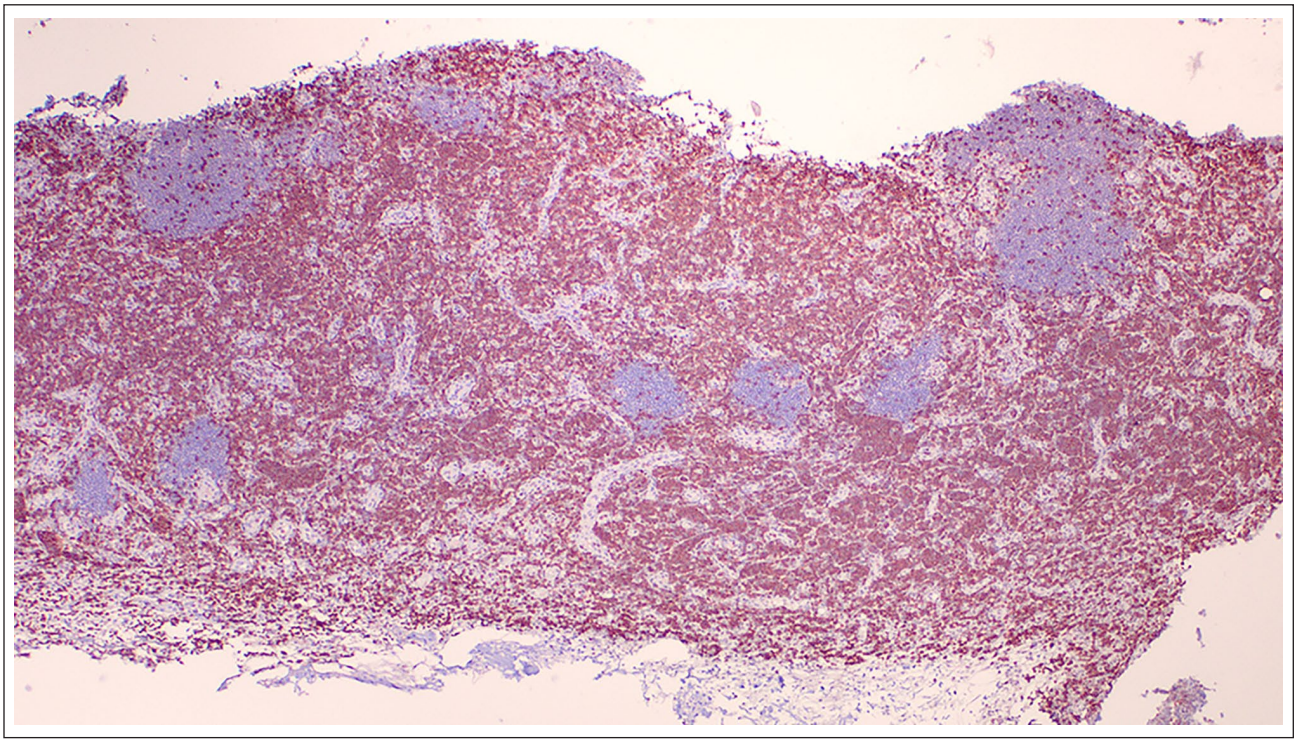

Figure 3 Photomicrograph of a popliteal lymph node of an 11-year-old cat with T-zone lymphoma. The marked paracortical expansion consists of neoplastic lymphocytes that are strongly CD3 positive, in contrast with the residual circular follicles and proliferative high endothelial venues. CD3 immunoperoxidase stain: Vector red substrate, hematoxylin counterstain; × 4 objective

a new thrombocytopenia (120 K/µl on day 76; RI 151–600). The pleural effusion remained static on TFAST scans. The prednisolone dose was reduced on day 161 (0.45 mg/kg PO q24h) and chlorambucil was continued at the previous dosing.

The cat was rechecked five times between days 196 and 427, showing no clinical signs and a stable physical examination. The peripheral lymph nodes decreased in size to 0.5 cm and the scant pleural effusion resolved on TFAST scan. The thrombocytopenia resolved on day 287 and the non-regenerative anemia resolved on day 427. On day 427, the chlorambucil dosing was decreased (6.4 mg/m^2 PO q72h) to reduce the number of treatments administered by the owner.

By day 634, the cat had gained 1.46 kg since presentation and was experiencing no clinical signs, with normal-sized peripheral lymph nodes and normal lung sounds. The abdominal ultrasound was unremarkable, with resolution of splenomegaly, hepatomegaly, lymphadenopathy and the thickened intestinal tract. The CBC was unremarkable. At the time of manuscript preparation, the cat continued treatment with chlorambucil, prednisolone (0.45 mg/kg PO q48h) and metronidazole.

Discussion

This report describes the clinical presentation, clinicopathologic findings and outcome of a cat with TZL. While TZL has been well-described in dogs, clinical information on the diagnosis and outcome in cats is lacking. This case shared similar physical examination and diagnostic findings commonly reported in dogs with TZL, including lymphadenopathy and lymphocytosis.[6–8] However, the cat had pleural effusion with concurrent respiratory signs at diagnosis which, to the authors' knowledge, has not been reported in dogs with TZL. The anemia and thrombocytopenia that developed may have been secondary to chemotherapy administration or could be anemia of chronic disease. These changes resolved without intervention and no bone marrow examination was performed. The cat developed soft stool 2 months before presentation, which resolved with consistent metronidazole administration. It is unclear whether this was related to TZL or an unrelated comorbidity. Intestinal biopsies would have been helpful in making this differentiation; however, they were not performed.

The diagnosis of TZL in this cat was made by correlating histopathologic findings with immunohistochemistry and PARR. The cat's histopathology and immunophenotype aligned with what is commonly described in dogs with TZL.[6,9,10] Since immunohistochemical assessment of CD45 has not been validated in cats, it was not utilized. Future studies are needed to validate CD45 immunophenotyping in cats and to evaluate it in cases of feline lymphoma and TZL. PARR performed on genomic DNA extracted from the cat's popliteal node identified a clonal TRG gene rearrangement, confirming lymphoma and supporting a T-cell origin.

Treatment protocols for canine TZL vary, but most dogs have prolonged survival times of 21–33.5 months, with improvements in lymphadenopathy and resolution of lymphocytosis observed in those receiving chlorambucil and prednisolone.[5–8,18] In cats, chlorambucil with prednisolone is a treatment option for low-grade intestinal T-cell lymphoma with few side effects.[14,15] Similar symptomatic improvements and tolerance were observed in the present cat, which remained alive more than 24 months after initial presentation, with resolution of clinical signs, pleural effusion, lymphocytosis, abdominal organomegaly, and both peripheral and abdominal lymphadenopathy.

Conclusions

The cat in this report was diagnosed with TZL based on a combination of histopathology, immunophenotype and PARR. Treatment with vincristine, chlorambucil and prednisolone effectively resolved the cat's clinical signs, and it remained in clinical remission more than 24 months after initial presentation. Further studies are needed to better define both the immunophenotype and efficacy of this treatment modality and assess the long-term outcomes for cats with TZL.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for the procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved.

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