



## WEDNESDAY SLIDE CONFERENCE 2014-2015

# Conference 20

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**Guest Moderator:**

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**CASE I:** B1319791 (JPC 4048572).

**Signalment:** 9-year-old castrated male beagle dog, *Canis familiaris*.

**History:** The dog was referred to a veterinary surgeon for evaluation of a possible splenic mass. An abdominal ultrasound showed a 2 inch mass in the cranial aspect of the spleen, which was confirmed at surgery for a splenectomy. No other gross abnormalities were noted by the submitting veterinarian.

**Gross Pathology:** The surgeon reports a single splenic nodule and no other gross abnormalities.

**Laboratory Results:** Immunohistochemistry: The lymphocytes are strongly CD79a-positive and CD3-negative. PCR for antigen receptor rearrangement (performed by the Leukocyte Antigen Biology Laboratory at UC Davis): Molecular clonality analysis of IgH2, IgH3 and KDE (B cell) revealed polyclonal rearrangements.

**Histopathologic Description:** The splenic nodule consists of coalescing nodules of lymphocytes. The intervening tissue is congested with a mixture of plasma cells, myeloid and erythroid precursors, megakaryocytes and hemosiderophages. The coalescing lymphoid

tissue consists mainly of marginal zone cells which are intermediate in size (nuclei approximately 1.5 times the diameter of a red blood cell). The cells have a scant to moderate



1-1. Spleen, dog: Normal architecture is replaced by coalescing nodules of lymphocytes, separated by a mixed population of plasma cells and extramedullary hematopoiesis. (HE 4.5X)

amount of eosinophilic cytoplasm and round to oval nuclei with a single prominent central nucleolus. Admixed throughout this proliferation are smaller numbers of larger cells with oval open nuclei (interpreted as dendritic cells), remaining germinal center cells, and scattered lymphocytes with small hyperchromatic nuclei (measuring 1 times the size of a red blood cell). Mitoses within the marginal zone cell population range from 0-2 in a single high power field.

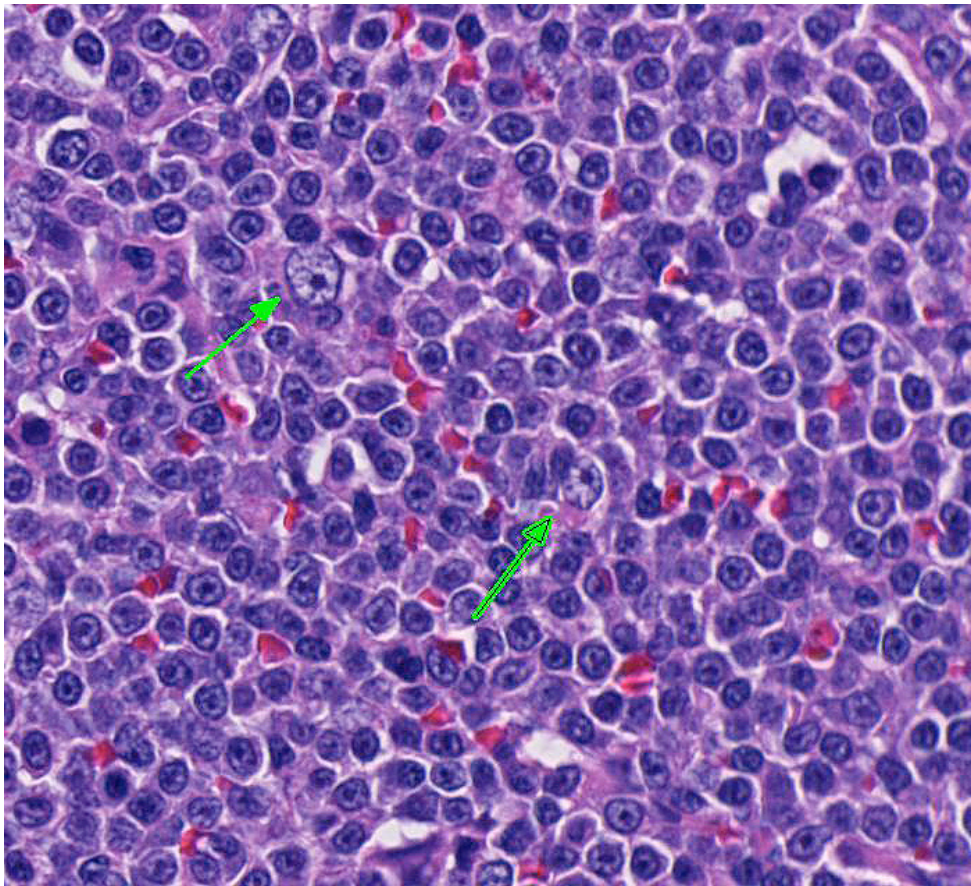
**Contributor's Morphologic Diagnosis:** Splenic Marginal zone lymphoma (probable).

**Contributor's Comment:** Marginal zone lymphoma (MZL) is an indolent B-cell neoplasm derived from the cells of the marginal zone of lymphoid follicles. Three types of MZL with different clinical and molecular characteristics are recognized in humans: extranodal mucosa-associated lymphoid tissue (MALT) lymphoma, splenic MZL (SMZL) and nodal MZL (NMZL).

In humans, SMZL is rare (1-3% of lymphomas) and usually involves the spleen, bone marrow, and blood. The disease can present as an incidental finding or with symptoms of splenomegaly. Anemia, lymphocytosis, or thrombocytopenia are reported in about 25% of cases.<sup>7</sup> Currently, there is no known genetic abnormality specific for SMZL, but deletions of chromosome 7q are found in 30-50% of cases.<sup>5</sup> Therapy for SMZL in humans remains controversial with options including splenectomy, various chemotherapeutic agents, or rituximab alone.<sup>1,5,7</sup> Most disease-related deaths in SMZL are associated with transformation to diffuse large B cell lymphoma.<sup>5</sup>

Indolent lymphomas in dogs include follicular, mantle cell, marginal zone, and T-zone lymphomas. Valli et al examined 66 dogs with indolent lymphoma which included 33 dogs with nodal MZL and 13 cases of splenic MZL; however, only 3 of these cases had outcome data available.<sup>9</sup> Two recent studies describe SMZL in 5

and 34 dogs, respectively, and provide better insight into clinical characteristics and outcome of this disease.<sup>4,6</sup> In the larger study by O'Brien et al, the overall median survival time (MST) after splenectomy was 383 days and dogs that had MZL as an incidental finding had a longer MST (1,153 days) compared to dogs with clinical signs associated with MZL (309 days). Other factors such as lymph node involvement, hemoabdomen, adjuvant chemotherapy, and concurrent malignancies did not influence survival.<sup>4</sup>



1-2. Spleen, dog: The neoplasm consists mainly of marginal zone cells which are intermediate in size (nuclei approximately 1.5 times the diameter of a red blood cell), and have a high mitotic rate. Mitotic figures are rare. Scattered among these cells are fewer larger lymphocytes with a moderate amount of granular cytoplasm, and larger vesicular nuclei (centroblasts – green arrows). (HE 360X)

Assessment of tissue architecture is needed for a diagnosis of MZL, and therefore, histopathology is required. MZL has a distinct nodular pattern in which the lighter-staining neoplastic marginal zone cells form a dense cuff around small foci of darkly stained mantle cells (fading follicles). The neoplastic marginal zone lymphocytes are intermediate in size, with nuclei measuring approximately 1.5 times the diameter of a red blood cell, and have a single prominent central nucleolus. Benign marginal zone hyperplasia (MZH) has a similar architectural appearance, although the expanded marginal zone is heterogeneous, containing a mixture of small and intermediate sized lymphocytes.<sup>10</sup> Differentiating between MZH and MZL is challenging because MZL arises on the background of MZH. Therefore, immunophenotyping and molecular clonality are ultimately required for a definitive diagnosis.

This case highlights the difficulty in differentiating between MZL and MZH and this distinction is especially difficult in the spleen of dogs. Lymphoid nodular hyperplasia and complex nodular hyperplasia ('fibrohistiocytic nodules') are common in the canine spleen; it is possible that many cases of nodular hyperplasia contain areas of MZL. In this case, the architectural feature of homogenous coalescing marginal zone cells was more suggestive of MZL than MZH. The fields in which there were up to 2 mitotic figures further supported this diagnosis, and is likely indicative of later stages of disease development, as mitoses increase with disease progression.<sup>9,10</sup>

As expected, the cells were CD79a positive and CD3 negative, indicating a B cell phenotype. Tissues were sent to the Leukocyte Antigen Biology Laboratory at UC Davis. Molecular clonality analysis of IgH2, IgH3, and KDE (B cell) revealed polyclonal rearrangements, which suggested a reactive process rather than a neoplasm. However, upon review of the histopathological and immunohistochemical findings, the reviewing pathologists at UC Davis were also highly suspicious of MZL and that the PARR testing might be a false negative result. The O'Brien paper also found a subset of cases (27%) that did not demonstrate a clonal population (pseudoclonal and polyclonal rearrangements)<sup>3</sup>, which is consistent with the published sensitivity of this PCR-based test.<sup>2,8</sup> In that study, the

polyclonal rearrangements were attributed to a mutation in V or J segments of Ig. Similarly, the most likely reasons for false negative results in this case are mutation of gene segments that are not covered by the primer sets or mutation of primer sites during somatic hypermutation. In support of this suspicion is the fact that the IgH3 locus did not show a robust polyclonal curve as would be expected in a hyperplastic lesion, but instead had non-reproducible peaks of variable height within a weak polyclonal background.

**JPC Diagnosis:** vSpleen: Lymphoma, intermediate size, low grade, consistent with marginal zone lymphoma.

**Conference Comment:** The contributor provides an exceptional overview to splenic marginal zone lymphoma and discusses its diagnostic challenges, specifically in distinguishing from hyperplastic nodules. Splenic nodular hyperplasia is a common finding in dogs and presents with variable histologic appearance depending on its cellular constituents. The simple or lymphoid form of hyperplasia is composed of discrete lymphocytes often forming follicles with germinal centers. The complex form of nodular hyperplasia additionally contains a proliferative stroma. Some variations of these lesions were previously diagnosed as fibrohistiocytic nodules, and recent advances in immunohistochemistry has led to their reclassification into a diverse group of diseases to include the above hyperplastic nodules, histiocytic sarcoma, and various subtypes of lymphoma.<sup>3</sup>

Using the grading criteria based on mitotic figures per single 400x field (indolent = 0-1, low = 2-5, intermediate = 5-10, high >10) and cell size determined by comparison to red blood cells (small = 1xRBC, intermediate = 1.5xRBC, large  $\geq$  2xRBC), we identified this neoplasm as intermediate size and low grade, with definitive classification of MZL requiring immunophenotyping and molecular clonality testing.<sup>8</sup>

**Contributing Institution:** University of Pennsylvania School of Veterinary Medicine  
<http://www.vet.upenn.edu/research/academic-departments/pathobiology>

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**CASE II: 09-12665 (JPC 3164837).**

**Signalment:** 1.5-year-old spayed female Bassett hound, *Canis familiaris*.

**History:** The dog was presented to the veterinary teaching hospital with inappetence, severe hepatomegaly and icterus. Bloodwork showed circulating lymphoblasts that were fragile and therefore often misshapen. Within one day, the dog developed thrombocytopenia, melena and shock, and died. Unsuccessful therapy included 10,000 IU of L-asparaginase and 1mg/kg of dexamethasone the day prior to death.

**Gross Pathologic Findings:** The mucus membranes and internal organs were moderately icteric. The abdominal cavity contained 1L of watery red effusion. The liver and spleen were both markedly enlarged (2 and 3 times normal weight, respectively). The liver had a prominent reticular pattern. The stomach contained a large blood clot and several gastric ulcers were identified. Digested blood was present throughout the intestinal track. Cranial mesenteric lymph nodes were also enlarged.

**Laboratory Results:** The total WBC on this slide was 85,600/microliter with lymphocytes composing 83,032/microliter of the total, neutrophils were at 2568/microliter. The HCT was decreased at 32% (38-56) and the platelets

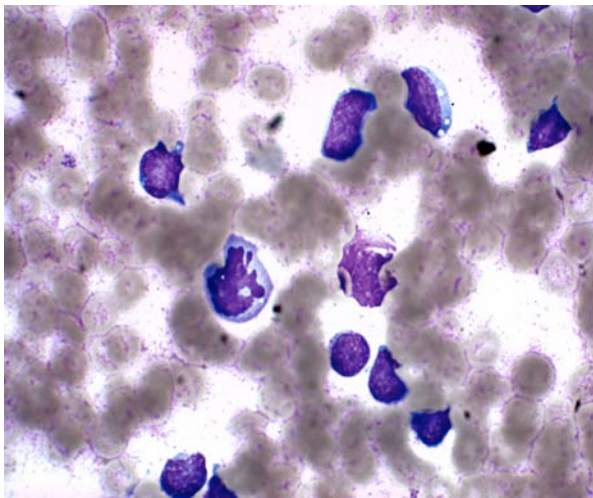
were decreased, 58,000/microliter (150,000-500,000).

K+	6.1 (4-5.4)
Phosph	12.4 (2.2-6.4)
Creatinine	2.1 (0.7-1.6)
BUN	109 (9-26)

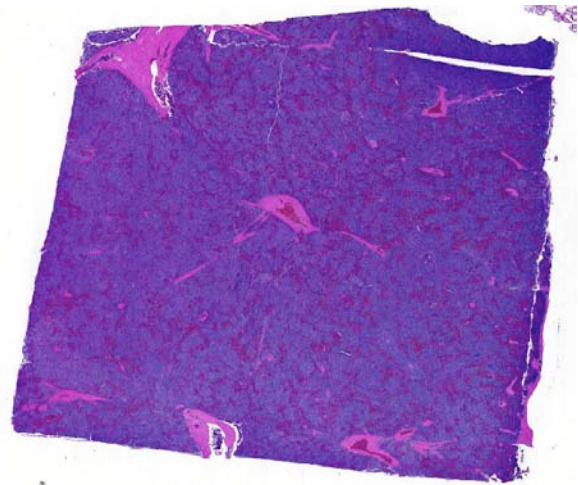
**Histopathologic Description:** Spleen: In several sections of the spleen, the white and red pulps were completely replaced by a highly cellular mass. The mass was composed of round lymphoid cells arranged in sheets and supported by a delicate fibrovascular stroma. The neoplastic cells had distinct margins with scant to moderate amounts of eosinophilic cytoplasm. Nuclei were round to pleomorphic, had a finely clumped chromatin pattern, and 1 to 2 nucleoli. The nuclear diameter of the neoplastic cells was equal to the diameter of two regional erythrocytes. Mitotic figures ranged from 5 to 12 in ten 400x random fields. The tumor was not immunophenotyped.

Lungs: Within the lumen of some of the small-size pulmonary arteries, there were clusters of neoplastic lymphoid cells and karyorrhectic debris. Fibrin thrombi were present in many pulmonary vessels.

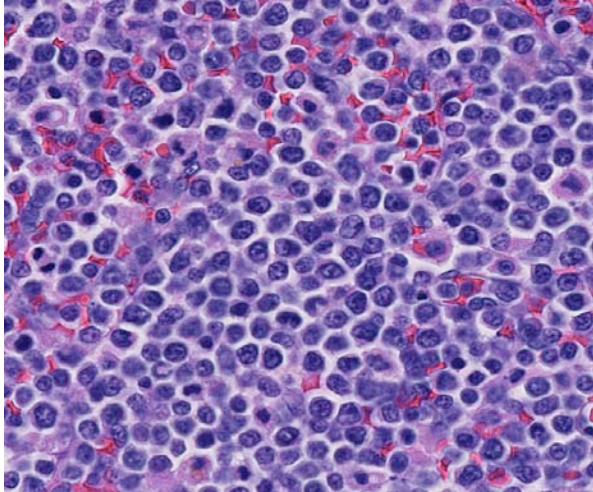
Neoplastic infiltrates were also present in the bone marrow, liver, heart and multiple visceral lymph nodes (not shown).



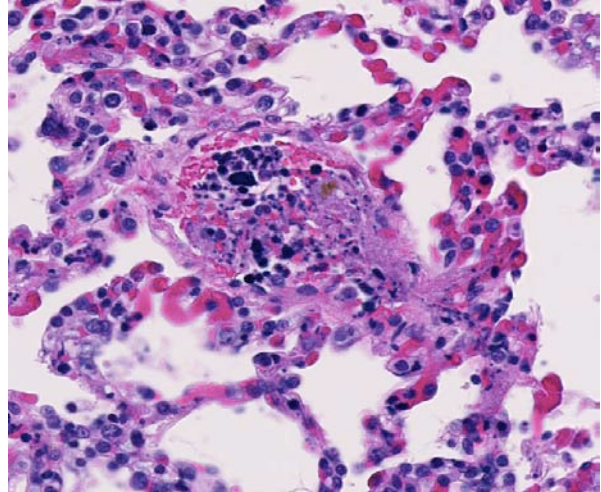
2-1. Peripheral blood, dog: A blood smear showed circulating lymphoblasts that were fragile and therefore often misshapen. (Wright-Romanovsky, 1000X) (Photo courtesy of: Department of Veterinary Microbiology and Pathology, College of Veterinary Medicine, Washington State University, Pullman, WA 99164-7040, www.vetmed.wsu.edu)



2-2. Spleen, dog: Normal architecture is replaced by coalescing nodules of lymphocytes. (HE 4.5X)



2-3. Spleen, dog: Neoplastic lymphocytes are 1.5-2x the size of an erythrocyte, with large irregularly round, often indented nuclei. Mitotic figures range up to 10 per high power field. (HE 328X)



2-4. Lung, dog: Neoplastic lymphocytes are present within moderate numbers with pulmonary capillaries. Within larger vessels, there are multifocal fibrin thrombi which contain neoplastic cells, cellular debris, and variably-sized globules of basophilic aggregated protein. (HE 284X)

**Contributor's Morphologic Diagnosis:** 1) Multicentric lymphoblastic lymphosarcoma.  
2) Intravascular chromatin emboli compatible with tumor lysis syndrome.

**Contributor's Comment:** Acute tumor lysis syndrome (ATLS) is a life-threatening metabolic derangement associated with rapid cell death in high volume tumors, most often leukemias and lymphomas. Although it can occur spontaneously in untreated individuals, the most common presentation is at some period after the institution of chemotherapy or radiation therapy.<sup>2</sup> Risk factors in human patients include tumors of high growth fraction, large tumor bulk and the form of therapy. It is most commonly induced by treatment with a variety of chemotherapeutic agents, including L-asparaginase, but has also been seen after treatment with ionizing radiation, biological response modifiers, hormone therapy and glucocorticoid therapy.<sup>2</sup>

Clinical signs, which can include vomiting, lethargy, respiratory distress and cardiac arrest, are related to the massive release of intracellular purines, phosphorus, uric acid, potassium and lactate.<sup>1</sup> Common clinicopathologic abnormalities include hyperphosphatemia, hyperkalemia and acidosis. Individuals with renal insufficiency may be at greater risk for ATLS (due to reduced ability to clear metabolites from the blood) and ATLS patients are also at risk for developing renal failure if realkalinization of blood leads to

calcium and phosphorus precipitation in the kidney.<sup>2</sup>

ATLS has been reported in dogs<sup>5</sup>, a cat<sup>1</sup> and in mice with experimentally induced lymphoid malignancies.<sup>6</sup> The histologic lesion of ATLS, large chromatin emboli in blood vessels, especially in the lung, was recently described in a 129/SvEv mouse with experimentally induced acute myeloid leukemia that had been treated with valproic acid, a histone deacetylase inhibitor known to produce tumor lysis.<sup>6</sup>

In dogs, ATLS has been associated with dramatic reduction in tumor mass.<sup>5</sup> In this case, the dog had severe clinical signs and may have been manifesting ATLS, DIC or both at the time of presentation. However, both chemotherapeutic agents the dog received have been associated with ATLS. Although no dramatic reduction in tumor size was noted clinically or pathologically, there was necrosis of tumor cells in the spleen, and the characteristic histologic lesions in the lung indicate that ATLS was most likely at least partly responsible for the dog's demise.

**JPC Diagnosis:** 1. Lung, Spleen: Lymphoma, intermediate to large cell, high grade. 2. Lung, septal capillaries: Neoplastic thrombi with necrosis.

**Conference Comment:** The tumor lysis syndrome occurs when neoplastic cells release more of their contents in the bloodstream than can

be handled by the body's normal homeostatic mechanisms, and is defined clinically as two or more of the following metabolic abnormalities appearing simultaneously: hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. Hyperkalemia can cause fatal dysrhythmias. Hyperphosphatemia can precipitate as calcium phosphate crystals in multiple organs and also exacerbate hypocalcemia. Hypocalcemia itself leads to tetany, dysrhythmias and seizures. Uric acid accumulation can cause acute renal injury due to vasoconstriction, impaired autoregulation, decreased renal blood flow, oxidation, and inflammation. Additionally, the lysis of neoplastic cells induces the release of cytokines.<sup>3</sup> This combination of metabolic derangements often proves lethal due to multiple organ failure.

Lymphoblastic lymphoma (LBL) is a diffuse lymphoma characterized by a dispersed chromatin pattern which obscures nuclear detail, and thus has indistinct nucleoli. Of note, the term "lymphoblast" has been commonly misused in veterinary medicine. By definition, the lymphoblasts of LBL are *intermediate-sized cells* and not the large lymphocytes seen in cases of diffuse large B cell lymphoma or peripheral T cell lymphoma. LBL can look very similar to hepatosplenic lymphoma (HS-TCL) and both are comprised of T-cells. HS-TCL is centered on the liver and spleen; however, it occurs without significant lymph node involvement which was identified in this case.<sup>4</sup> Additionally, another distinct entity in the liver has been proposed called hepatocytotropic lymphoma (HC-TCL) for those subtypes that are not confined to the sinusoids but rather invade hepatic cords.<sup>4</sup> All three discussed subtypes, (LBL, HS-TCL, HC-TCL) are associated with a poor prognosis in dogs.<sup>4,7</sup>

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**References:**

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**CASE III:** B1316893 (JPC 4048571).

**Signalment:** 10-year-old castrated male golden retriever, *Canis familiaris*.

**History:** The dog was previously diagnosed with T-cell lymphoma based on PARR only. A CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone)-based chemotherapy protocol commenced for 6 months with minimal response. One month after cessation of chemotherapy treatment, the lymph nodes enlarged further. A fine needle aspirate and biopsy was performed on the left mandibular lymph node at a referring practice and in-house cytology revealed a small to intermediate cell lymphoma with low mitotic index. The biopsy sample was submitted for histopathology and immunohistochemistry.

**Gross Pathology:** N/A

**Laboratory Results:** N/A

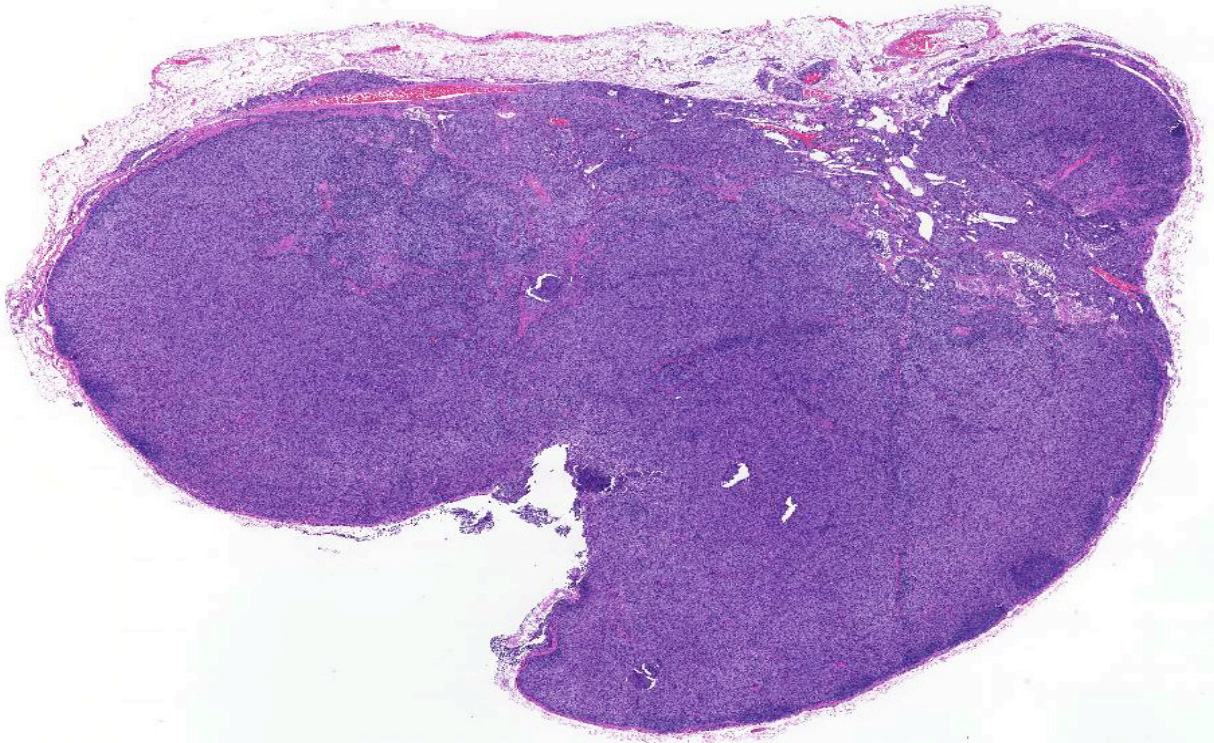
**Histopathologic Description:** Two sections of the lymph node are evaluated. The nodal

architecture is almost completely obliterated by a somewhat nodular infiltrate. The fading follicles are compressed and pushed against the nodal trabeculae. The neoplastic cells are arranged in broad sheets and consist of intermediate sized round cells with nuclei approximately 1-1.5 times the diameter of a red blood cell. The cells have a small amount of lightly eosinophilic cytoplasm and the nuclei are round to oval with sharp shallow nuclear indentations. Mitoses are rare.

Immunohistochemical stains CD3, CD20 and CD79a were performed. The neoplastic cells have strong positive CD3 immunoreactivity. The peripheralized fading follicles have positive CD20 and CD79a immunoreactivity. This staining pattern confirms the diagnosis of a T-zone lymphoma.

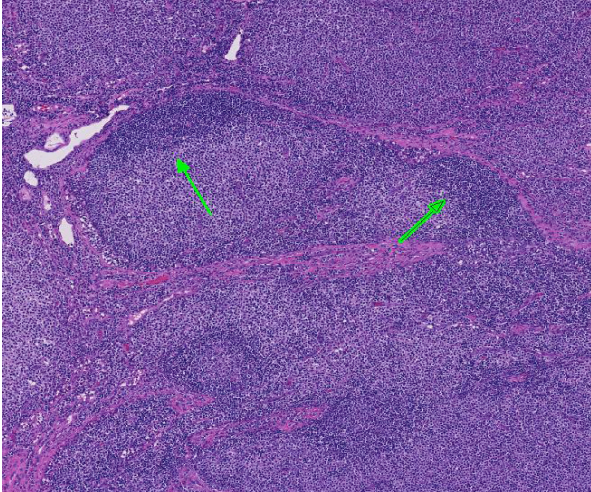
**Contributor's Morphologic Diagnosis:** Left mandibular lymph node: T-zone lymphoma, intermediate cell.

**Contributor's Comment:** T-zone lymphoma (TZL), which is of T-cell lineage, is classified as

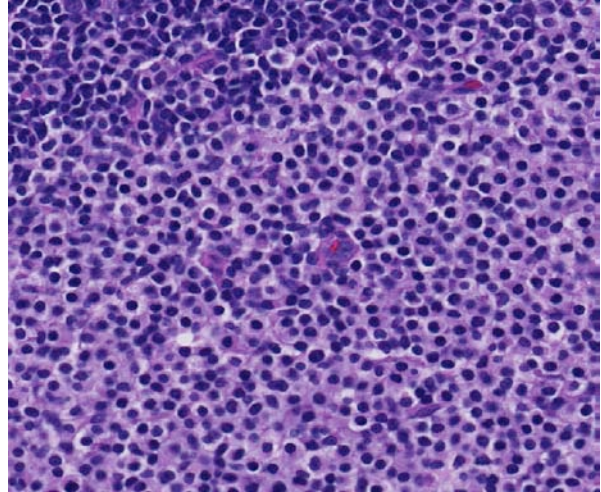


3-1. Lymph node, dog: The lymph node architecture is largely replaced by a lymphoid neoplasm composed of expanding nodules of neoplastic cells. (HE 6X)





3-2. Lymph node, dog: Expanding nodules neoplastic lymphocytes compress pre-existent follicular lymphocytes to the periphery (arrows) ("fading follicles"). (HE 75X)



3-3. Lymph node, dog: Neoplastic cells are small, with a moderate amount of cytoplasm and small round hyperchromatic nuclei. Mitotic figures are rare. (HE 380X)

one of the subtypes of canine indolent lymphomas. Canine indolent lymphomas are a heterogeneous group of lymphoma subtypes that are similar to specific subtypes of non-Hodgkin's lymphomas in humans.<sup>2</sup> Other subtypes include, nodal and splenic marginal zone lymphoma, follicular lymphoma and mantle cell lymphoma, which are all of B-cell lineage, T-cell rich B-cell lymphoma, small lymphocytic lymphoma of B- and T-cell, and lymphoplasmacytic lymphoma.<sup>2,7</sup> These subtypes have a low mitotic index and slow clinical progression.<sup>8</sup> Dogs usually retain a normal appetite and physical activity, even in advanced stages of disease.<sup>7</sup>

T-zone lymphoma first appeared in the Kiel classification with a description of a nodal lymphoma that occurs rarely in humans.<sup>7,8</sup> In 2008, a description was added to the human WHO (World Health Organization) classification as a morphologic variant of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), and is characterized by a clonal expansion of T-zone lymphocytes that exhibit a unique architectural and cytomorphologic pattern.<sup>2,5</sup> Human TZL comprise only 1.5% of all cases of PTCL-NOS.<sup>5</sup> Although the true incidence of canine TZL is unknown, two recent publications indicate that they are relatively common, comprising between 15.5 and 62% of all canine indolent lymphomas, which themselves are reported to have an incidence rate of 29% of all canine lymphomas.<sup>2,5,8</sup> Almost all cases of TZL occur in peripheral lymph nodes with a predilection for the mandibular node, and usually

have a history of a single enlarged lymph node for as long as a year.<sup>7</sup> A higher incidence rate is observed in the golden retriever and shih tzu breeds, and in the majority of cases, a lymphocytosis is frequently reported at the time of diagnosis.<sup>2, 5</sup>

The WHO system of classification of canine lymphomas defines TZL as a nodal T-cell lymphoma, in which neoplastic cells expand the paracortex and medullary cords without effacement of the nodal architecture.<sup>7</sup> The architecture of TZL has a signature pattern that results from the expanding population of neoplastic T-cells which peripheralizes fading atrophied germinal centers in the outer cortex and medulla. The capsule is usually focally thinned, the peripheral sinuses are compressed, and postcapillary venules are prominent. The intervening areas of paracortex are expanded by a uniform population of small or intermediate sized lymphocytes. There is no extension of the neoplasm into the peripheral sinuses or perinodal tissue. Areas of empty sinus ectasia are observed in the later stages. Two subtypes are categorized based on the nuclear size of the neoplastic T-cells compared to the diameter of a red blood cell (RBC). TZL of small cells have nuclei that are 1-1.25 x RBC, and TZL of intermediate-sized cells are 1.5 x RBC. Neoplastic cells have distinct cell borders with abundant cytoplasm. The nuclei have frequent sharp shallow indentations, are hyperchromatic with little internal detail, and inconspicuous nucleoli. The mitotic index is low, usually 0-1 on most 40x fields.

TZL must be differentiated from small lymphocytic lymphoma of T or B-cell type and benign small lymphocytes that are diagnosed via fine-needle aspirates.<sup>7</sup> B-cell proliferations symmetrically surround germinal centers. Small lymphocytic lymphomas are not associated with fading germinal centers or sinus ectasia, and the nuclei do not have consistent nuclear indentations.

Immunohistochemistry and flow cytometry are powerful tools when differentiating TZL from benign nodules of hyperplasia and other nodal lymphomas. TZL cells have a solid CD3 positive immunoreactivity and are negative for CD79a and CD20.<sup>5,7</sup> A recent study demonstrated CD45 immunophenotyping using flow cytometry on peripheral blood and lymph node aspirates.<sup>5</sup> CD45 is a tyrosine phosphatase that has a complex role in the regulation of signaling through the T-cell receptor, and in the regulation of cytokine receptor activation. Neoplastic T-cells do not express CD45. To date, there is no normal CD45 negative T-cell counterpart described in mice or people, and no evidence of CD45 negative T-cells in the blood or lymph nodes in normal or reactive canine lymph nodes. The loss of CD45 expression appears to be correlated with malignant transformation of T-cells; however, the mechanisms involved are not known.

**JPC Diagnosis:** Lymph node: T-zone lymphoma.

**Conference Comment:** The contributor presents an excellent case of T-zone lymphoma and adeptly outlines its histologic and cellular characteristics, which will aid in diagnosis of this common small to intermediate cell variant of nodal indolent lymphoma. This case illustrates the challenges of establishing a firm diagnosis to guide the treatment protocol. The initial diagnosis based on PARR led to the initiation of a treatment regimen that is largely ineffective with T-zone lymphomas due to their indolent nature because of their low mitotic rate. PARR is a PCR-based assay used for determining clonality. It can be useful in differentiating hyperplastic from neoplastic lesions and in monitoring response to treatment; however, it should be used in conjunction with other assessments including histopathology and immunohistochemistry in determining treatment strategy.<sup>1</sup>

Lymphoma can be readily diagnosed on fine needle aspirate; however, it is not yet possible to

subclassify it by cytology alone. Aspirates of T-cell lymphomas do sometimes have a “hand mirror” morphology when smeared onto a slide which may allow the examiner to favor this classification.<sup>3,6</sup> These cells are mentioned in other sources as reactive lymphocytes with plasmacytoid features, thus their presence should be interpreted with caution.<sup>4</sup>

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**CASE IV: 2008906084 (JPC 3103338).**

**Signalment:** 11-year-old spayed female Japanese domestic, *Felis catus*.

**History:**

- 2008.3.25 This cat showed diarrhea lasting for one month and gradual weight loss for one year from 4.82kg to 3.76kg. Diarrhea disappeared immediately after general treatment with an anti-diarrheal drug.
- 2008.5.12 Repeated vomiting appeared from recent two weeks with complete loss of appetite. A mass lesion was found in the abdominal cavity by X-ray examination and echography.
- 2008.5.13 Intestinal obstruction was confirmed in the small intestine by barium contrast study.
- 2008.5.14 The mass was surgically removed. The enlargement of the mesenteric lymph node was observed during a laparotomy.

**Gross Pathologic Findings:** The affected part of the small intestine was a mass lesion and consisted of severely thickened intestine wall with narrowing of the lumen.

**Laboratory Results:** Fine needle biopsy findings: Comparatively uniform lymphoblast-like cells were observed on the smear from needle biopsy of the mesenteric lymph node.

**Histopathologic Description:** Lymphoid cells proliferated throughout the entire intestinal wall from the mucosa to the serosa and resulted in severe thickening of intestinal wall. Numerous lymphoid follicles of varying size were formed in the muscular and serosal layer among the severely infiltrated tumor cells. Some follicles had clear germinal centers and incomplete mantle zones. The tumor cells other than follicle-forming cells had small to medium-sized nuclei that are round to irregularly indented and have thick nuclear membrane. The nuclei had dense chromatin with multiple small distinct nucleoli (or with a small distinct nucleolus). The cytoplasm was pale and abundant. Mitotic figures were observed at rate of

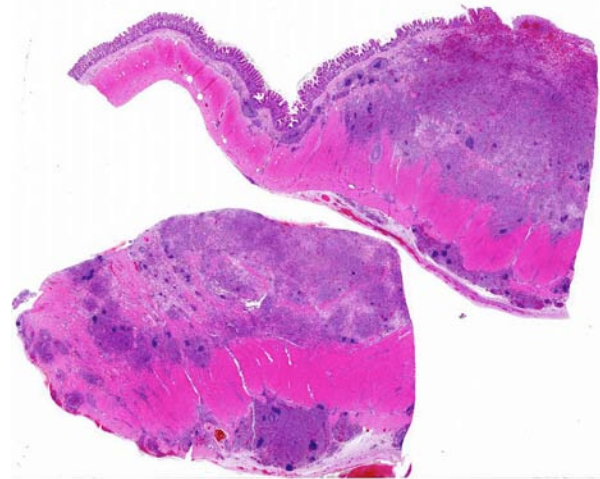
7 cells per 10 high power fields. Small number of eosinophils infiltrated among the tumor cells and fibrous stroma was slightly increased in some areas with proliferated tumor cell.

Immunohistochemically, the majority of tumor cells were positive for CD3 and TIA-1, negative for CD79a and CD20. In the muscular layer where the lymph follicles formed, many cells forming the follicles were positive for CD79a and CD20 and negative for CD3 and TIA-1, whereas a few cells of germinal center were positive for CD3 and TIA-1.

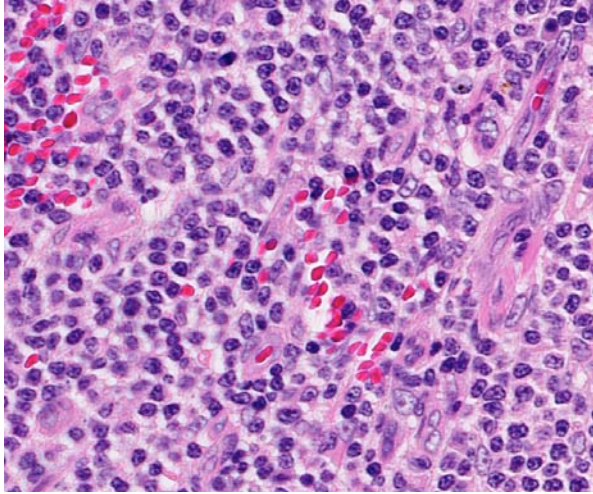
Based on immunohistochemical findings, tumor cells have a T-cell phenotype in this lymphoma but lymph follicles formed in the tumor mass consisted of B-cells.

**Contributor's Morphologic Diagnosis:** Small intestine: Malignant lymphoma, T cell lymphoma.

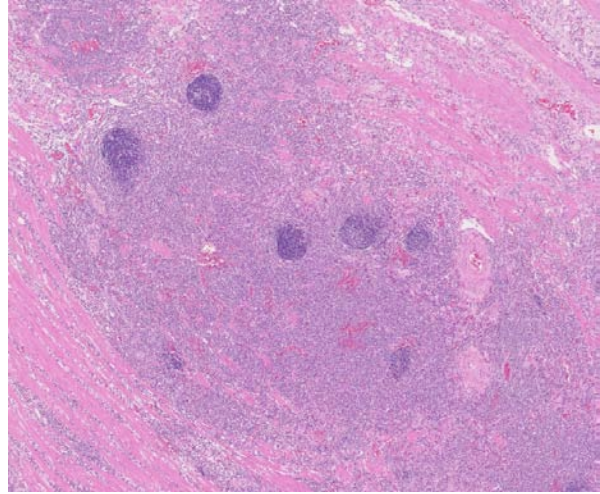
**Contributor's Comment:** Hematopoietic tumors (lymphoma and mast cell tumors) are the most common type of neoplasia in the feline intestine.<sup>7</sup> In alimentary lymphoma, the tumors are usually of the B-cell origin, with few being T-cell origin.<sup>4,7,11,15</sup> B-cell lymphoma arises from the germinal center of the gut, MALT, and drainage lymph nodes.<sup>6,7</sup> In contrast, T-cell type of multicentric lymphoma proliferates from the paracortical area,<sup>6,7</sup> and T-cell lymphoma of the intestine usually involves the lamina propria with epitheliotropism to the mucosal epithelium.<sup>2,8,15</sup>



4-1. Small intestine, cat: The intestinal wall is markedly expanded and transmurally effaced by sheets of neoplastic cells. (6X)



4-2. Small intestine, cat: Neoplastic cells have small amounts of cytoplasm and irregularly round nuclei with small blue nucleoli. Mitotic figures are rare. (HE 350X)



4-3. Small intestine, cat: Non-neoplastic lymphoid follicles are scattered throughout all layers of the intestinal wall, including the muscular tunics. (HE 70X)

The present case was characterized by formation of lymph follicles in the mass of tumoral proliferation. These lymph follicles were not original lymphoid tissue, because they were formed in muscular and serosal layers where there is no lymphatic tissue in the normal condition. In addition, this lymphoma had a T-cell phenotype and the follicles were composed of B-cell phenotype. Therefore, it was likely that lymphoid follicles were formed due to the reactive response to tumor cells or immunologic stimuli by the altered environment resulting in proliferation of tumor cells. The neoplastic cell proliferation forming lymph follicles was similar to lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in morphologic growth pattern. MALT lymphoma and marginal zone lymphoma are B-cell lymphoma,<sup>14</sup> and the tumor cells encircle follicles outside the mantle cell layer in these types of lymphoma. Cytologically, T-cell lymphoma consists of smaller cells with low mitotic rate as in the present case. However, MALT lymphoma is usually composed of small lymphocytes with indented nuclei, or there may be a more mixed pattern with some larger lymphoid cells similar to the centrocytes and centroblasts of benign germinal centers.<sup>14</sup>

Intestinal T-cell lymphoma is characterized also by epitheliotropism of tumor cells.<sup>2,8,15</sup> Neoplastic lymphocytes usually are small round cells that resemble mature lymphocytes. However, epitheliotropism was not seen in the tumor cells of the present case. In a report of canine intestinal T-cell lymphoma, approximately 25% did not

show epitheliotropic behavior.<sup>14</sup> In addition, in humans, MALT lymphoma usually forms lymphoepithelial lesions and tumor cells invade between mucosal epithelium. Lymphoepithelial lesions resemble epitheliotropism, but are characterized by centrocyte-like cell invasion and destruction of the epithelium. Therefore, epitheliotropism is not specific for T-cell lymphocytes and formation of lymph follicles is also not specific for B-cells.

**JPC Diagnosis:** Intestine, ileum: Lymphoma, intermediate size, low grade, transmural.

**Conference Comment:** The cellular morphology and epitheliotropic behavior presented in the small intestine of a cat is distinctive for T-cell lymphoma (TCL). Intestinal lymphomas can be further classified as mucosal or transmural based on depth of invasion. Epitheliotropism can occur in both types, and occurs most commonly in the villous epithelium. Mucosal T-cell lymphoma closely matches the WHO entity enteropathy-associated T-cell lymphoma (EATCL) type II. Transmural T-cell lymphomas more often can lead to intestinal obstruction and perforation and closely match the WHO entity EATCL type I.<sup>9</sup>

The most common presentation of lymphoma in cats has evolved as the success of FIV/FeLV testing and vaccination programs have been realized. In the 1970's, 70% of feline lymphoma cases in the U.S. were attributed to FeLV infection which dropped to less than 15% twenty years later.<sup>1</sup> Interestingly, as the prevalence of

these known oncogenic viruses have diminished, the incidence rate of lymphoma in cats appears to be increasing.<sup>1,9</sup> Retroviral-associated lymphomas commonly presented as mediastinal or multicentric forms in young cats.<sup>3,12</sup> The majority of lymphomas in cats now occur in the gastrointestinal tract.<sup>9</sup> Recent literature has also described a shift in prevalence from B-cell to T-cell lymphomas in intestinal lymphoma in cats.<sup>9,12</sup> Diffuse large B-cell lymphomas are considered most common in the stomach of cats.<sup>9</sup> Other subclassifications of significance in cats include large granular lymphocyte lymphoma which also occurs in the intestinal tract but often with more systemic involvement and is associated with a poor prognosis. T-cell rich large B-cell lymphoma is an indolent type with a mixed cell population to include bizarre giant or multinucleated cells and typically presents in a single lymph node.<sup>3</sup>

Conference participants were interested in the unique histologic presentation of lymphoma in this case, with the formation of multiple lymphoid follicles dispersed throughout all levels of the muscularis mucosa. Theories regarding their formation were exchanged, including immune stimulation by antigens or toxin absorption through the disrupted mucosal epithelium.

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