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# Classification of Canine Malignant Lymphomas According to the World Health Organization Criteria

**V. E. Valli[1], M. San Myint[2], A. Barthel[3], D. Bienzle[4], J. Caswell[4], F. Colbatzky[5], A. Durham[6], E. J. Ehrhart[7], Y. Johnson[2], C. Jones[8], M. Kiupel[9], P. Labelle[10], S. Lester[11], M. Miller[12], P. Moore[13], S. Moroff[10], P. Roccabianca[14], J. Ramos-Vara[12], A. Ross[15], T. Scase[16], H. Tvedten[17], and W. Vernau[13]**

## Abstract

A study was carried out to test the accuracy and consistency of veterinary pathologists, not specialists in hematopathology, in applying the World Health Organization (WHO) system of classification of canine lymphomas. This study represents an initiative of the ACVP Oncology Committee, and the classification has been endorsed by the World Small Animal Veterinary Association (WASVA). Tissue biopsies from cases of canine lymphoma were received from veterinary oncologists, and a study by pathologists given only signalment was carried out on 300 cases. Twenty pathologists reviewed these 300 cases with each required to choose a diagnosis from a list of 43 B and T cell lymphomas. Three of the 20 were hematopathologists who determined the consensus diagnosis for each case. The 17 who formed the test group were experienced but not specialists in hematopathology, and most were diplomates of the American or European Colleges of Veterinary Pathology. The overall accuracy of the 17 pathologists on the 300 cases was 83%. When the analysis was limited to the 6 most common diagnoses, containing 80% of all cases, accuracy rose to 87%. In a test of reproducibility enabled by reintroducing 5% of cases entered under a different identity, the overall agreement between the first and second diagnosis ranged from 40 to 87%. The statistical review included 43,000 data points for each of the 20 pathologists.

## Keywords

dog, oncology

[1] VDx Veterinary Diagnostics, Davis, CA, USA
[2] Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, IL, USA
[3] Antech Diagnostics, Moab, UT, USA
[4] Department of Pathobiology, College of Veterinary Medicine, University of Guelph, Guelph, Ontario, Canada
[5] Department of Non-Clinical Drug Safety, Boehringer-Ingelheim Pharma GmbH &Co. KG, Biberach, Germany
[6] Department of Pathobiology, University of Pennsylvania, School of Veterinary Medicine, Philadelphia, PA, USA
[7] Department of Microbiology, Immunology and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, USA
[8] IDEXX Laboratories, Auburn, MA, USA
[9] Department of Pathobiology and Diagnostic Investigation, College of Veterinary Medicine, Michigan State University, East Lansing, MI, USA
[10] Antech Diagnostics, Lake Success, NY, USA
[11] Veterinary Pathology Consultants, Lake Stevens, WA, USA
[12] Department of Comparative Pathobiology, School of Veterinary Medicine, Purdue University, West Lafayette, IN, USA
[13] Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, UC Davis, Davis, CA, USA
[14] Animal Pathology, Faculty of Veterinary Medicine, University of Milan, Milan, Italy
[15] Australian Animal Pathology Standards Program, Frankston, Australia
[16] Bridge Pathology Ltd., Bristol, UK
[17] Department of Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden

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**Corresponding Author:**
Victor E. Valli, VDx Veterinary Diagnostics, 5622 Cowell Blvd, Davis, CA 95618-7212, USA
Email: vvalli@vdxpathology.com

## Introduction

Malignant lymphoma is the most common canine neoplasm treated by chemotherapy and a disease that affects dogs of all breeds and ages. Classifications that were developed for non-Hodgkin lymphoma in humans have been used in the past by veterinary pathologists to classify canine malignant lymphoma. Whereas early classification systems were based entirely on the morphologic characteristics of malignant lymphocytes, the ability to further differentiate cells immunophenotypically led to a revision of the historical classification systems. The Rappaport classification[28] from 1966 represents one of the earliest classification systems applied to canine malignant lymphomas, and according to this classification, the large cell lymphomas were termed *histiocytic*.[12]

With increasing knowledge of the immunologic aspects of malignant lymphomas, a better understanding of maturation and differentiation of lymphoid cells, and the advance of chemotherapy, new classification systems were developed. Almost simultaneously, the Lukes-Collins classification[20] in North America and the Kiel classification[18] in Europe were published. Both systems were based on immunologic concepts and only differed significantly in the position of centrocytes within the line of maturation in each classification. Despite these differences, translation from one to the other classification was still possible.[16] The Kiel classification was easily adapted for canine malignant lymphoma.[37]

To avoid further confusion and in an attempt to unify the European and North American classifications, the National Cancer Institute initiated a 1,400-case multi-institutional study published as the working formulation.[26] The working formulation represented a translational system for the existing human non-Hodgkin lymphoma classifications. The working formulation was primarily oriented on the clinical outcome and less on cellular criteria.[17] The various lymphoma entities in this classification were based on groups of human patients with similar survival curves, and the morphologic features for each group were described. Numerous studies addressed the limitations of the working formulation,[19] and in succeeding years, these deficiencies became more apparent as new entities were described.[3,6] The working formulation became widely used in North America with animal studies based on this system,[4,8,9] whereas the Kiel system became widely used in Europe for both humans and animals.[7,32]

The original Kiel classification was revised, and an ''updated'' version[31] was shown to be applicable to canine malignant lymphomas,[32] and multiple studies documented its prognostic utility.[13,32] The Kiel classification was limited to nodal pathology, and advances in immunology and histochemistry indicated the need for updating all of the previous systems. This prompted the formation of the International Lymphoma Study Group (ILSG), which proposed a Revised European-American Classification of Lymphoid Neoplasms (REAL).[11]

The objectives of the ILSG were to devise a system that did not have obvious ties to any country or region and greatly expanded criteria for disease recognition. The unique features of the ILSG proposal were that neoplasms were identified as diseases and not as cell types, with the diagnostic criteria including all relevant information: cellular morphology and cell lineage, as well as topography and general biology of each neoplasm that defined it as a specific disease entity. The REAL system was adopted largely intact as the revised World Health Organization (WHO) system of classification.[10] The efficacy of this classification was demonstrated by a group of medical pathologists in the Non-Hodgkin's Lymphoma Classification Project of 1997.[1] The results of that study on more than 1,400 cases of human leukemia and lymphoma showed that 5 expert hematopathologists obtained an 85% consensus on major types of lymphoma using the criteria of the ILSG classification system. These results immediately rendered other systems of classification obsolete and pointed to the need for a similar study to demonstrate the applicability of the WHO system to animal neoplasms.

The specific purpose of this study was to test the application of the WHO system for classification of canine malignant lymphomas by veterinary diagnosticians who were experienced but not expert in hematopathology. We also wanted to test the consistency (interobserver variability) and reproducibility (intraobserver variability) on a large group of canine lymphomas and determine the influence of immunophenotyping for making the correct diagnosis.

## Materials and Methods

### Case Material

Cases included in this study consisted of 285 excisional or incisional biopsies with 15 cases duplicated to test for consistency of interpretation. These biopsy specimens had been fixed in 10% neutral buffered formalin; most were broad Tru-cut biopsy specimens of lymph nodes. Cases were derived from 20 US states and Quebec with most (91) from California; 10 states were represented by only 1 case each. Tissues were routinely processed and sectioned at 3 microns and stained with hematoxylin and eosin (H&E). Serial sections of each case were placed on positively charged slides for further immunohistochemical labeling. To test intraobserver reproducibility 15 (5%) of the cases, including examples from the most common entities, were recut and included in this study with a similar signalment but different pathology accession numbers and American College of Veterinary Pathologists (ACVP) serial numbers. The total number of cases reviewed by each pathologist was 300, including the 15 duplicated cases.

### Immunophenotyping

All cases were labeled immunohistochemically for B and T cell antigens following a routine protocol. Briefly, antigen retrieval was achieved by heating slides to 125°C for 30 seconds followed by 90°C for 10 seconds in citrate buffer at pH

6.0 in a commercial pressure cooker, Decloaker (Biocare Medical, Walnut Creek, CA). Endogenous peroxidase was blocked for 15 minutes with 3% hydrogen peroxide. Nonspecific immunoglobulin binding was blocked by incubation of slides for 10 minutes with a protein blocking agent (Dako, Carpinteria, CA) prior to application of the primary antibodies. The latter were allowed to react for 30 minutes at room temperature. Sections were stained in a Biogenex autostainer (BioGenex Laboratories, San Ramon, CA). The slides were incubated with a mouse monoclonal anti-CD79a antibody (clone HM57) for B cells at a dilution of 1:100 and a rabbit polyclonal anti-CD3 antibody for T cells at a dilution of 1:100 (both Dako). A supersensitive multilink kit was used for detection (BioGenex Laboratories). The immunoreaction was visualized with 3,39-diaminobenzidine substrate (BioGenex Laboratories). Sections were counterstained with Mayer's hematoxylin. Positive immunohistochemical controls included a normal canine lymph node to which the appropriate antisera were added. For negative controls, the primary antibodies were replaced with homologous nonimmune sera.

## Review Process

A total of 20 pathologists reviewed all 300 cases during August and November 2007. The study group included international participation with 7 of the pathologists currently residing outside of the United States and 5 pathologists currently residing in the United States who received their residency training in Europe or Australia.

The original diagnosis for each case was made by one pathologist (Valli). Two other pathologists (Moore, Vernau) worked as expert reviewers using a double-viewing microscope to develop the consensus interpretation by reviewing each case diagnosis against that of the first author. Each of the other pathologists worked independently. Each participant received a CD with annotated photographs of each lymphoma subtype, including immunophenotyic reactions, before the slide review period.

The 300 cases were divided into 8 groups of 37 to 38 cases each. Each review began with a general discussion of the process followed by distribution of the slides and individual work. All cases were classified by each reviewer into B and T cell subtypes as designated in the WHO classification system (see Table 1). A single group review after the first 2 hours of individual work was used to discuss complicated cases and reach consensus on how to classify specific tumor entities.

To classify each lymphoma into a distinct entity of the WHO classification, the following features were examined sequentially for each case: nodular versus diffuse growth pattern, the relation of cellular nodules to remnants of non-neoplastic follicles, nuclear size, the detailed nuclear morphology, the number of mitoses per high-power field, and the immunophenotype. Nuclear size was determined as small (<1.5× the size of a red blood cell), intermediate (1.5–2× the size of a red blood cell), or large (>2× the size of a red blood cell). The number of mitoses was identified in a microscopic field with a 40× objective. Lymphomas with 0 to 5 mitoses/400× field were graded as 1 or low grade (low), those with 6 to 10 mitoses/400× field were graded as 2 or medium grade (med), and those with greater than 10 mitoses/400× field were graded as 3 or high grade (high). Detailed morphological and clinical characteristics of each of these 6 entities are described in detail in the Results section.

**Table 1.** Summary of Canine Malignant Lymphoma Revised From the Revised European-American Classification of Lymphoid Neoplasms/ World Health Organization Classification of Lymphoid Neoplasms

| |
|---|
| B Cell Neoplasms |
| Precursor B cell neoplasms |
| Precursor B lymphoblastic leukemia/lymphoma |
| Mature (peripheral) B cell neoplasms |
| B cell chronic lymphocytic leukemia/prolymphocytic |
| Leukemia/small lymphocytic lymphoma |
| B cell prolymphocytic leukemia |
| Lymphoplasmacytic lymphoma |
| Splenic marginal zone B cell lymphoma |
| Plasma cell myeloma/plasmacytoma |
| Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue type |
| Nodal marginal zone lymphoma |
| Follicular lymphoma |
| Mantle cell lymphoma |
| Diffuse large B cell lymphoma[a] |
| Mediastinal large B cell lymphoma |
| Burkitt's lymphoma/Burkitt's cell leukemia |
| Provisional entity: high-grade B cell lymphoma |
| Burkitt's-like[a] |
| Primary effusion lymphoma |
| T Cell and Putative Natural Killer Cell Neoplasms |
| Precursor T cell neoplasm |
| Precursor T lymphoblastic |
| Lymphoma/leukemia |
| Mature (peripheral) T cell and natural killer cell neoplasms |
| T cell prolymphocytic leukemia |
| Large granular lymphocyte leukemia (LGL) |
| Aggressive natural killer (NK) cell leukemia |
| Peripheral T cell lymphomas, unspecified[a] |
| Adult T cell lymphoma/leukemia |
| Intestinal T cell lymphoma (±enteropathy associated) |
| Hepatosplenic γδT cell lymphoma |
| Subcutaneous panniculitis-like T cell lymphoma |
| Mycosis fungoides/Sezary syndrome |
| Anaplastic large cell lymphoma, T and null cell primary cutaneous type |
| Peripheral T cell lymphoma not otherwise specified |
| Angioimmunoblastic T cell lymphoma |
| Angiocentric T cell lymphoma |

[a] Peripheral T cell lymphomas are those that are not otherwise specified (NOS) to a specific subtype by further definition. See PTCL (Fig.3 a-d).

## Statistical Analysis

A Microsoft Access database was created from the 20 pathologists' reports. The data set contained 25 B cell lymphoma variables, 18 T cell lymphoma variables, and 3 phenotype selection

variables. A total of 43,300 data points were generated per pathologist for the 300 reviewed cases. Descriptive statistical analysis was conducted using Microsoft Excel software. Analytical statistics were conducted using Statistix 8 software. The consensus diagnoses reached by Drs Moore, Vernau, and Valli were used as the gold standard for comparison with the findings of the other 17 pathologists. For this study, sensitivity was defined as the rate of agreement for a positive diagnosis between each panel pathologist and the gold standard. The specificity was defined as the rate of agreement for ruling out a diagnosis between each panel pathologist and the gold standard. This initial analysis included many categories of unusual tumors that rarely occur. This may overestimate the specificity and underestimate the sensitivity of the diagnoses. To correct for this potential source of bias, a subset of the database consisting of only the 6 most common diagnostic entities (which constituted 79.5% of total cases) was analyzed separately.

## Results

The overall rate of consensus between panel pathologists and the gold standard was 83%. The mean sensitivity (rate of positive agreement) was approximately 70% with a range of 46 to 100%. The mean specificity rate was 99% with a range of 99 to 100%. The mean overall agreement between the first and second diagnosis on the 15 duplicate cases for the 20 test observers was 65.5% with a range of 40 to 86.7%.

The second analysis was based on the 6 most common neoplastic entities, which encompassed 79.5% of the total cases. For this group of cases, the overall rate of consensus between panel pathologists and the gold standard was approximately 87%, with an average sensitivity of 77% and a specificity of 96%. These 6 subtypes of lymphoma included the following entities: diffuse large B cell lymphoma (145 cases), marginal zone lymphoma (11), peripheral T cell lymphoma not otherwise specified (42), nodal T zone lymphoma (38), T lymphoblastic lymphoma (12), and disease other than lymphoma (20). Detailed morphological and clinical characteristics of each of the 6 most common entities are described in detail below.

### *Diffuse Large B Cell Lymphoma (Fig. 1a-d)*

The study included 145 cases of large B cell lymphoma (all CD79a positive), which comprised nearly half of the 300 cases studied. The defining features of diffuse large B cell lymphoma (DLBCL) are the diffuse arrangement of sheets of neoplastic B cells and the uniformly large nuclei (>2 red cells in diameter) and scant cytoplasm of the neoplastic cells. Nuclei are usually round or rarely cleaved or indented. Mitotic rates vary but are detectable in all fields at 40× magnification. For the purposes of this study and consistent with the Kiel classification, DLBCL was further divided according to the number and location of their nucleoli. Large B cells with multiple nucleoli, often located at the nuclear periphery, were referred to as *centroblastic* (DLBCL-CB). Those with a single central prominent nucleolus were termed *immunoblastic* (DLBCL-IB). The study included 111 cases of DLBCL-CB and 34 cases of DLBCL-IB. However, many cases had both types of nucleolar arrangement and were only assigned to DLBCL-IB if at least 90% of nuclei were of that type.

An additional subtype included in the category of DLCBL was the T cell–rich large B cell lymphoma (TCRLBCL). This neoplasm has variable numbers of neoplastic B cells amid a predominant population of small non-neoplastic T cells, and abundant fine stroma is present. These neoplasms are rare in dogs.

Architectural changes in DLBCL include thinning of the lymph node capsule and compression of the peripheral sinus. Fading germinal centers may be present in the outer cortex. There is destruction of normal nodal structures, filling of the medullary cords, and compression of medullary sinuses. Tingible body macrophages may be diffusely present, and their number varies with the mitotic rate.

DLBCL must be distinguished from marginal zone lymphoma, which has a characteristic arrangement of neoplastic B cells around atrophic fading follicles, intermediate-sized rather than large nuclei, more uniformly abundant cytoplasm, and an absence of mitotic figures in most cases. DLBCL must also be distinguished from large T cell lymphoma that may appear identical except for immunophenotype. Late-stage (grade III) follicular lymphoma may be similar cytologically but is distinguished on the basis of the uniformly diffuse architecture present in DLBCL.

DLBCL was the most common lymphoma of this case series, representing about 40% of cases. Most dogs present with one or more enlarged peripheral nodes, with involvement of abdominal nodes or viscera in 15 to 20% of cases and of skin in about 10% of cases. Up to 5% have primary involvement of the spleen or mediastinum. Overt leukemia is uncommon. DLBCL are strongly positive with CD79 and CD20 and are negative with CD3. It is likely that in dogs as in people, there is marked biological variation in DLBCL that is not detectable by morphological or limited immunophenotypic analysis.

### *Marginal Zone Lymphoma (Fig. 2a-d)*

Marginal zone lymphomas (MZL), whether in spleen or node, are indolent clonal proliferations of B lymphocytes of distinctive architecture in which aggregates of neoplastic cells surround fading remnants of germinal centers and thus resemble the marginal zone of the lymph node follicle. MZL has a distinctive cytological appearance characterized by nuclei of intermediate size with prominent single central nucleoli and abundant lightly stained cytoplasm and with mitoses absent except in advanced cases. MZL cells strongly express CD79 and CD20 and lack CD3.

This study included 11 (3.7%) MZL, of which 8 were biopsies from lymph nodes, 2 were from the spleen, and 1 involved both lymph node and spleen. In humans, MZL may be nodal[25] or splenic[27] or involve a mucosal surface as mucosal-associated lymphoid tumor (MALT).[25,30]

MZL occurs in mature dogs and in some reviews comprises up to 15 to 17% of canine lymphomas. MZL typically occurs in large breed dogs as a single enlarged submandibular or cervical

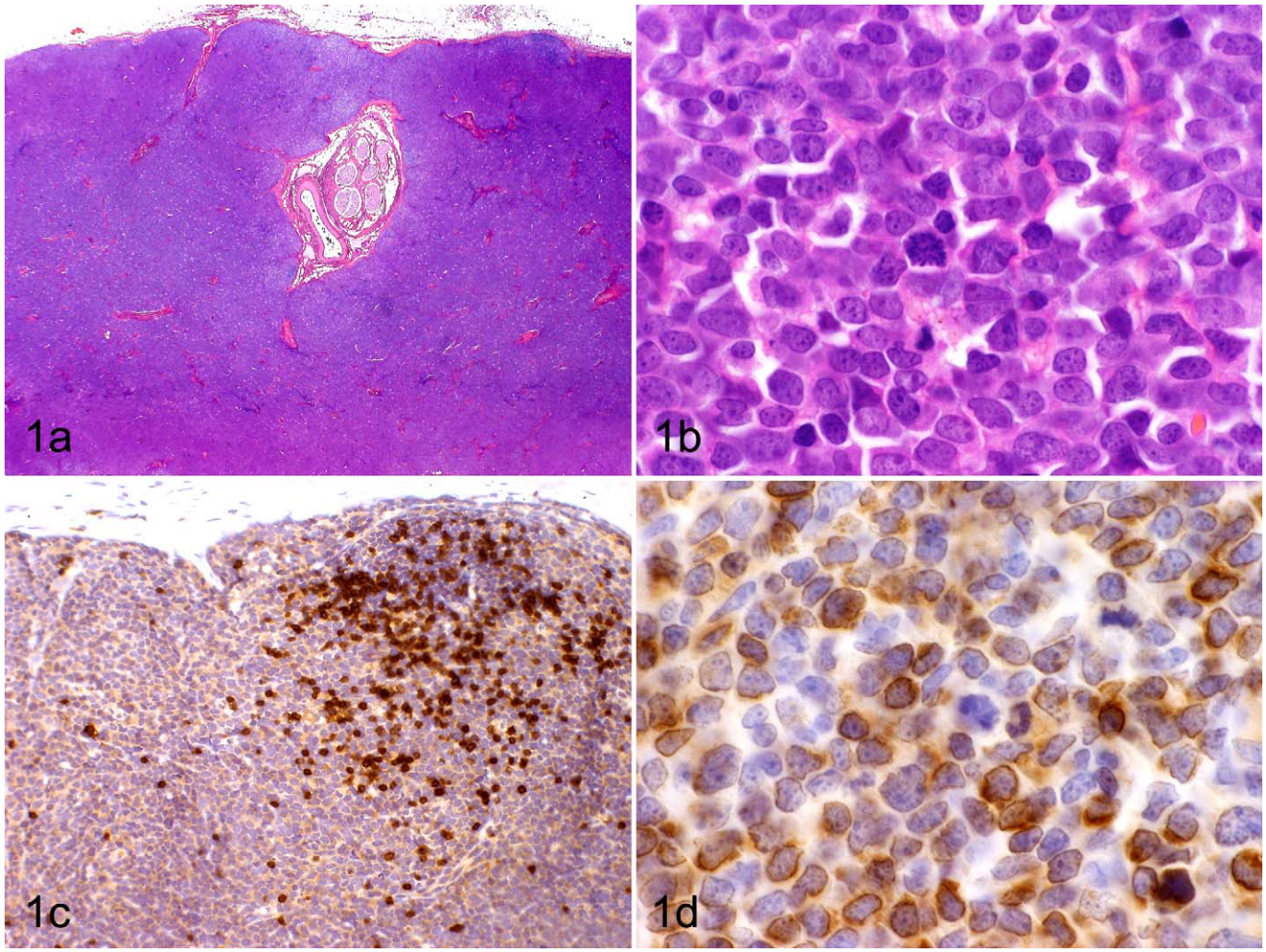


**Figure 1.** (a–d) Dog lymph node, diffuse large B cell lymphoma (DLBCL), high-grade centroblastic type. (a) Effacement of nodal architecture with thinning of the capsule and compression of the peripheral sinus. Hematoxylin and eosin (H&E). (b) Nuclei of neoplastic lymphoid cells are large (2 red cells in diameter) and have multiple prominent peripheral nucleoli that are often associated with the nucleolemma. H&E. (c) Neoplastic cells are negative for CD3. Numerous non-neoplastic T cells are associated with the involuted follicular structure. Immunolabeling with anti-CD3, hematoxylin counterstain. (d) Irregular cytoplasmic reactivity of neoplastic B cells with CD79a. Immunolabeling with anti-CD79a, hematoxylin counterstain.

lymph node that typically remains mobile beneath the skin. The dog usually retains normal appetite and activity.

A second presentation of canine MZL is as a primary splenic tumor, and MZL is the most common primary lymphoma in the spleen in dogs and in humans. Spread from the spleen to abdominal lymph nodes occurs slowly, and spread to extra-abdominal lymph nodes occurs over several years. Leukemia is not a feature of MZL.[33] In the spleen, the tumor is multicentric and locally extensive.[33]

MZL is the most common lymphoma in dogs characterized by neoplastic expansion of marginal lymphocytes surrounding (''fading'') germinal centers, but a comparable arrangement can be seen with marginal zone hyperplasia, follicular lymphoma, and a faintly nodular form of DLBCL. MZL is distinguished from hyperplasia by a uniform population of medium-sized lymphocytes with peripheralized chromatin that accentuates a large central nucleolus and with abundant lightly stained cytoplasm with distinct cell boundaries. Hyperplasias have a mixture of smaller mantle lymphocytes that have less cytoplasm. MZL cells strongly express CD79 and CD20 and lack CD3. MZL can be distinguished from follicular lymphoma (FL) by having an inner remnant collapsed mantle cell cuff or a heterogeneous follicular center, whereas FL has a uniform proportion of centroblasts and centrocytes across the entire follicle. MZL is distinguished from a type of DLBCL that surrounds germinal centers, but DLBCL is of large cells with a higher mitotic rate; a single large nucleolus is a feature of both MZL and DLBCL-IB. Late-stage MZL retains the same cellular characteristics as the earlier stages, but the nodules coalesce, the mitotic rate increases, and tingible body macrophages become apparent.

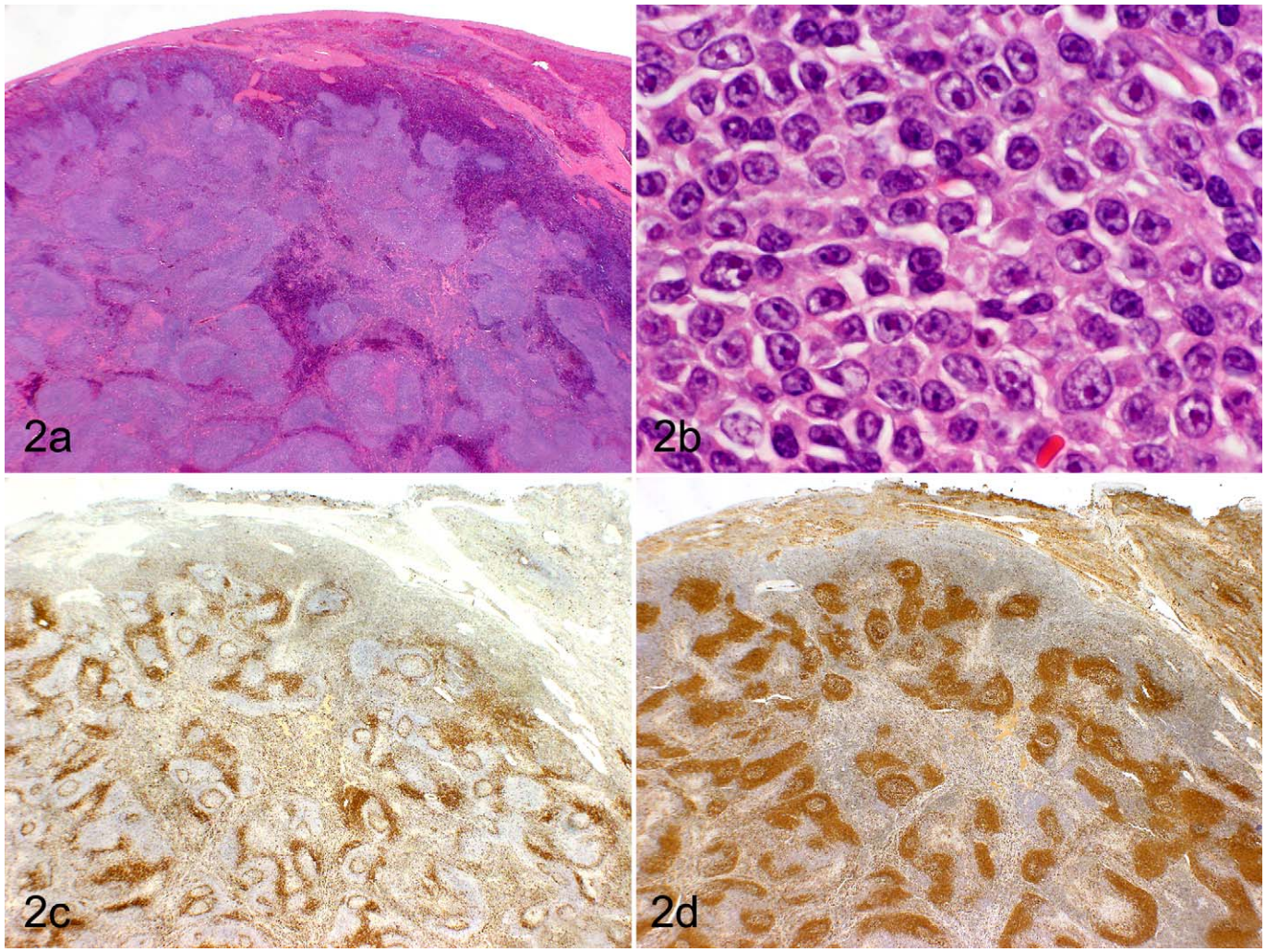


**Figure 2.** (a–d) Dog, spleen, marginal zone lymphoma (MZL). (a) Coalescing neoplastic lymphoid nodules have periodicity that indicates localization around terminal arterioles. There is lymphoid atrophy of the normal area of spleen. Hematoxylin and eosin (H&E). (b) Nuclei of neoplastic lymphoid cells are vesicular with peripheralized chromatin causing apparent thickening of the nuclear membranes. There is marked parachromatin clearing with thin chromatin bands and very prominent single central nucleoli. Cytoplasm is relatively abundant and of moderate staining density with cell boundaries irregularly distinct. Mitoses and tingible body macrophages are not present. H&E. (c) Fine CD3-positive inner rings of T cells remain within mantle cell cuffs of B cells surrounding fading germinal centers. Outer rings of T cells surround the unlabeled areas of neoplastic B cells of the marginal zone cell layer. Immunolabeling with anti-CD3, hematoxylin counterstain. (d) Strong focal labeling for CD79a of neoplastic B cells in areas of coalescing MZL proliferation, with sharp boundaries that interface with the areas of residual T cells. Some germinal centers are still apparent, and these are lightly labeled due to the presence of unlabeled dendritic cells and atrophy of benign B cells. The mantle cell cuff is inapparent and is labeled in continuum with the surrounding outer layer of MZL cells. Immunolabeling with anti-CD79a, hematoxylin counterstain.

### *Peripheral T Cell Lymphomas Not Otherwise Specified (Fig. 3a-d)*

Peripheral T cell lymphomas (PTCL) comprised 42 cases (nearly 15%) in this study. The category of PTCL not otherwise specified (PTCL-NOS) includes all T cell lymphomas that are not well categorized and cannot be further differentiated based on topography and cellular size. In human medicine, the term *NOS* is used less frequently, because many entities originally included are now given specific names. These include small T cell lymphomas such as mature T cell leukemia/lymphoma,[36] T zone lymphoma,[2,34] angioimmunoblastic T cell lymphoma (AILT),[29] the hepatosplenic and enteropathy types,[8] the subcutaneous panniculitis-like type,[14] and anaplastic large cell lymphoma[39] that in human conditions is specifically labeled for anaplastic lymphoma kinase (ALK) and CD30. Many of these diseases may be recognized in dogs on the basis of immunophenotype and topographical involvement but are still incompletely characterized.[7,23] The designation of peripheral refers to extrathymic location.

PTCL are characterized by a diffuse proliferation of neoplastic T cells, but there is variable cellular morphology and

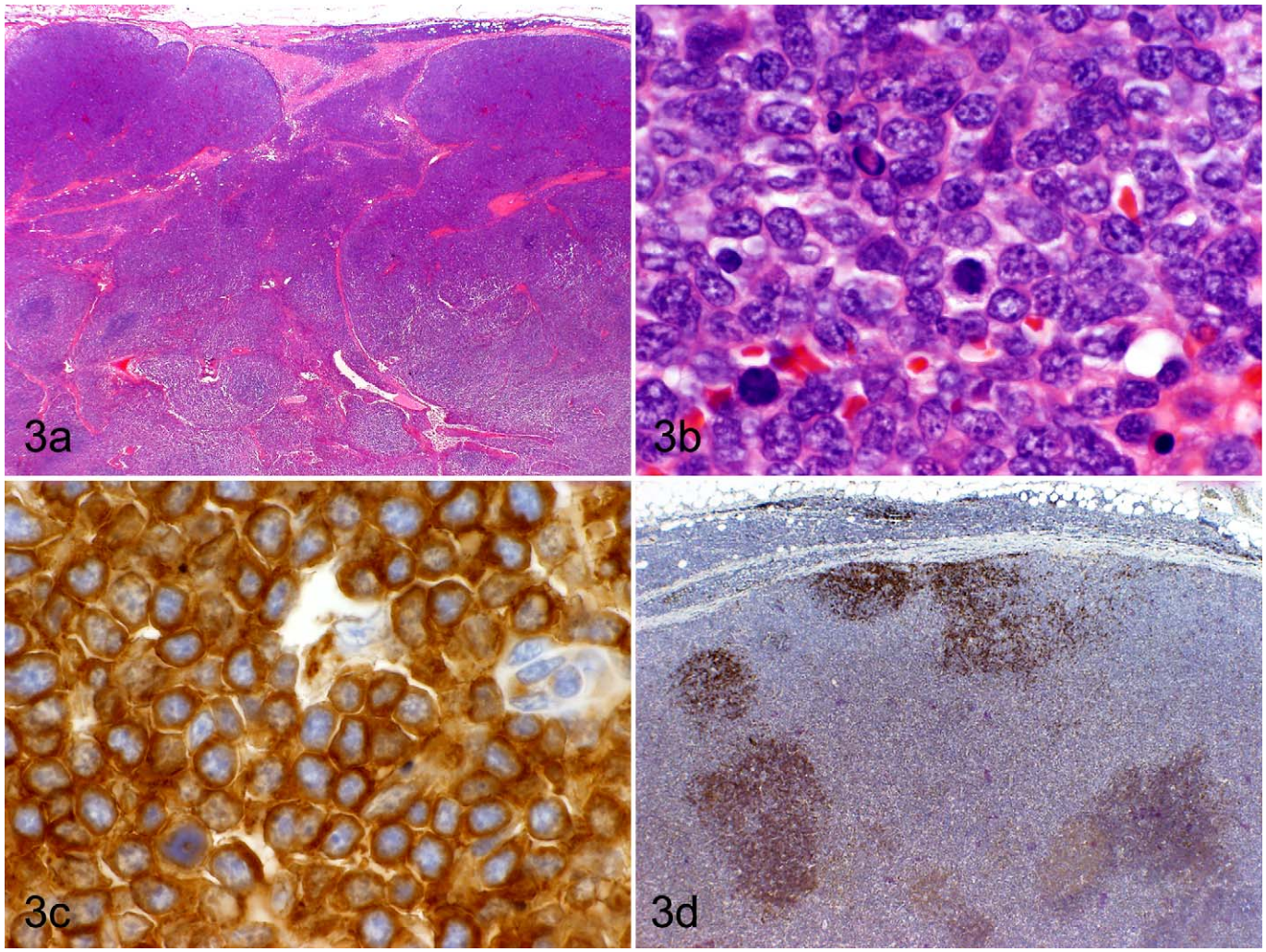


**Figure 3.** (a–d) Dog, lymph node, peripheral T cell lymphoma (PTCL). (a) The capsule is thinned and irregularly invaded. The peripheral sinus is compressed but only focally obliterated. Germinal centers are fading. Hematoxylin and eosin (H&E). b) Nuclei of neoplastic cells are closely aggregated and large (2 to nearly 3 red cells in diameter). The chromatin is branched with large chromocenters and marked parachromatin clearing. There are 2 to 4 quite prominent nucleoli in each cell with cytoplasm moderate in volume, lightly stained with cell boundaries indistinct. H&E. (c) Intense labeling of neoplastic T cells with CD3. Immunolabeling with anti-CD3, hematoxylin counterstain. (d) Irregular dense clusters of CD79a-positive B cells indicate the fading follicular centers. Immunolabeling with anti-CD79a, hematoxylin counterstain.

mitotic rate from case to case. They are associated with prominent high-endothelial venules, and an angioproliferative category has prominent fine vascular proliferation and focal ischemic necrosis. The presence of a mixture of cell types, including eosinophils or macrophages, is suggestive of PTCL.

Nodal peripheral T cell lymphoma is the most common form and exhibits diffuse paracortical expansion of the lymph node. The capsule is typically thin, and the sinus is compressed and focally obliterated with spread of neoplastic cells to perinodal tissue. The neoplastic cells are usually large but may be of variable cell size and frequently have cleaved or oval nuclei. Nucleoli are inconsistent in number and size. Mitotic rates are variable, and even those with many mitoses may lack numerous tingible body macrophages.

The extranodal form of PTCL is less common and may occur in the subcutis. The more aggressive forms of this disease have frequent vascular, especially arterial, invasion causing focal necrosis and edema.

Some of the less well-recognized types of peripheral T cell lymphoma include a rapidly progressive disease in young large breed dogs that presents with generalized skin disease and mimics an aggressive angioinvasive lymphoma of children.[21] In dogs, these masses are composed of strongly CD3-positive cells with large atypical nuclei, prominent nucleoli, marked irregular distribution of chromatin, and high mitotic rates. Another rare type of peripheral T cell lymphoma occurs in mature, healthy dogs that present with a single subcutaneous mass that may be interpreted as a puncture wound. The lesions are 1 to 2 cm in diameter with

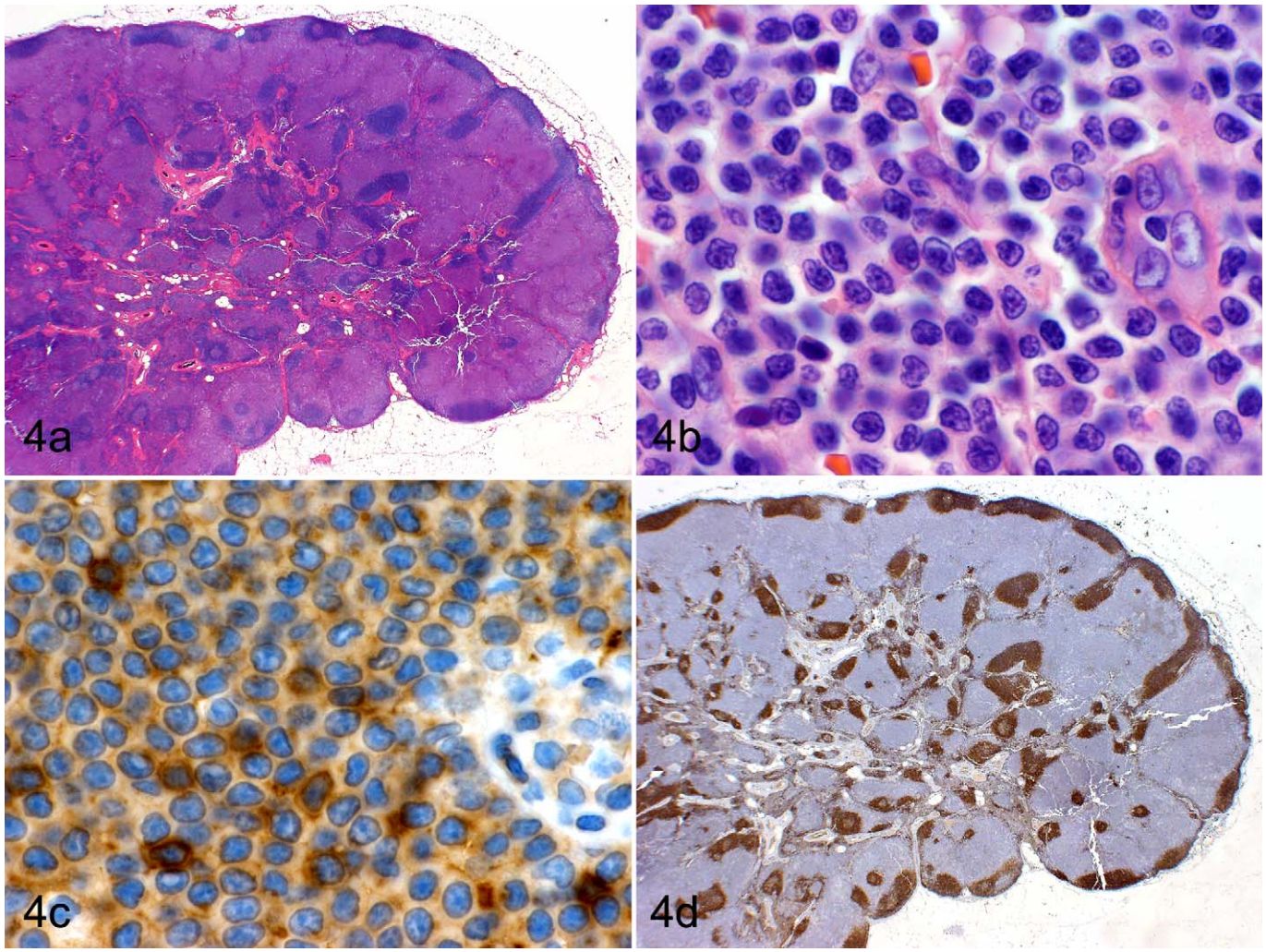


**Figure 4.** (a–d) Dog, lymph node, T zone lymphoma (TZL). (a) The nodal capsule is thinned without involvement of perinodal tissue. Neoplastic lymphoid cells are peripheralizing the fading germinal centers beneath the capsule. Fibrovascular supporting structures are prominent. Hematoxylin and eosin (H&E). (b) In this early stage, TZL nuclei are small (only slightly larger than red cells). Nuclei have sharp shallow indentations, and some nuclei have small central nucleoli. H&E. (c) Neoplastic T cells are uniformly CD3 positive; an occasional cell is more deeply labeled. Immunolabeling with anti-CD3, hematoxylin counterstain. (d) B cells in fading follicular structures are CD79a positive, and these fading follicles are adjacent to the capsule and to bands of fibrovascular connective tissue. Immunolabeling with anti-CD79a, hematoxylin counterstain.

large CD3+ neoplastic lymphocytes, often adjacent to small veins with mixed inflammatory cells, including eosinophils, and with diffuse fine sclerosis and foci of necrosis.[35] Proliferations of this type are usually considered of infectious origin before lymphoma is considered.

In this study, 39 PTCL were nodal, 2 were hepatic, and 1 was enteric. Of these, 31 were of large cell type, including 3 anaplastic; 9 were of intermediate size; and 1 each was of mixed and of small cell size. Of the 42 PTCL, 19 were of high grade, 7 were medium grade, and 16 were low grade. PTCL strongly expressed CD3 and was negative for CD79 and CD20. PTCL of diffuse large cell type cannot be distinguished from DLBCL on H&E stains. The mixed cellular types of PTCL are distinguishable from TCRLBCL since all cells express CD3 in PTCL but not TCRLBCL.

## *T Zone Lymphoma (Fig. 4a-d)*

The T zone lymphoma (TZL) category first appeared in the Kiel classification with a description of a nodal lymphoma that occurs rarely in humans.[2] In this study, there were 38 cases of TZL (12.7%). T zone lymphoma is defined as a nodal T cell lymphoma, in which neoplastic cells expand the paracortex and medullary cords but do not efface the nodal architecture. The neoplastic cells are small or intermediate in size, lack internal nuclear detail, and have shallow nuclear indentations, with mitoses absent in early cases and very low in advanced cases. There is consistent clonal rearrangement of T cell receptor genes. The architecture of TZL is characteristic. The capsule of the lymph node is at least focally thinned, but perinodal tissue is not involved. The peripheral sinus is compressed but not

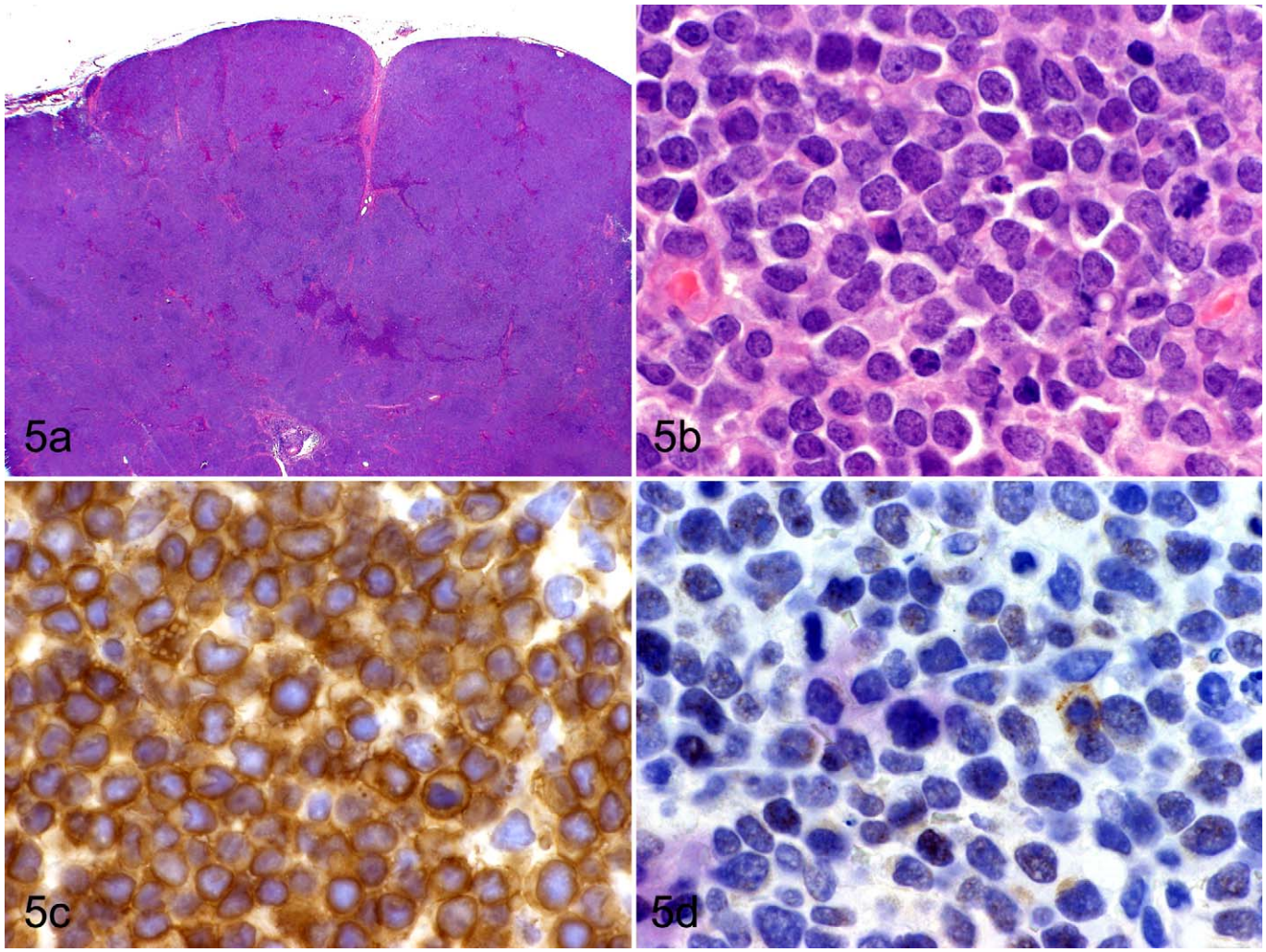


**Figure 5.** (a–d) Dog, node, lymphoblastic lymphoma (LBL). (a) The nodal capsule is thinned with a compressed peripheral sinus and focal colonization of the capsule. The medulla is filled with distended cords and compressed sinuses. Hematoxylin and eosin (H&E). (b) Nuclei of neoplastic cells are of intermediate size (1.5 times the size of red cells). There is moderate anisokaryosis, and the chromatin is finely dispersed. Nucleoli are present but not readily apparent because they are obscured by the dispersed chromatin. Cytoplasm is minimal and highly basophilic. H&E. (c) The cytoplasm of neoplastic T cells is densely positive for CD3. Immunolabeling with anti-CD3, hematoxylin counterstain. (d) Neoplastic T cells do not express CD79a. Without eosin staining, the nuclear shape is more easily identified. Nucleoli are inapparent after antigen retrieval. Immunolabeling with anti-CD79a, hematoxylin counterstain.

infiltrated. There typically are fading atrophic germinal centers in the outer cortex that are characteristically pressed against the outer sinus by the expanding population of neoplastic T cells. Fading germinal centers occur throughout the medulla, where they are peripheralized against the fibrovascular supporting structures.[34] The intervening areas of paracortex are filled with a uniform population of small- or intermediate-sized lymphocytes.

There are 2 subtypes: TZL of small cells, with nuclei only slightly larger than red cells, and TZL of intermediate-sized cells. The nuclei have little internal detail and stain densely, and the nucleoli are inapparent. Sharp shallow nuclear indentations are characteristic and frequent. The cytoplasm is abundant, so that the nuclei of adjacent cells are not in contact. Mitoses are not present in most fields at 400×. The postcapillary venules are prominent. TZL cells are solidly CD3 positive and are negative for CD79 and CD20. Later stages of TZL will have areas of empty sinus ectasia.

TZL must be differentiated from small lymphocytic lymphoma (SLL) of T or B cell type. SLL are not associated with frequent fading germinal centers or sinus ectasia. Further, nuclei of SLL cells do not have consistent nuclear indentations. T cell proliferations result in peripheralized and fading germinal centers, whereas B cell proliferations symmetrically surround germinal centers. This feature gives TZL its architectural signature.

TZL comprises about 10 to 12% of lymphomas in dogs. Almost all cases of TZL occur in peripheral lymph nodes, usually submandibular,[34] and generally in animals that had a single enlarged node for as long as a year with normal appetite and

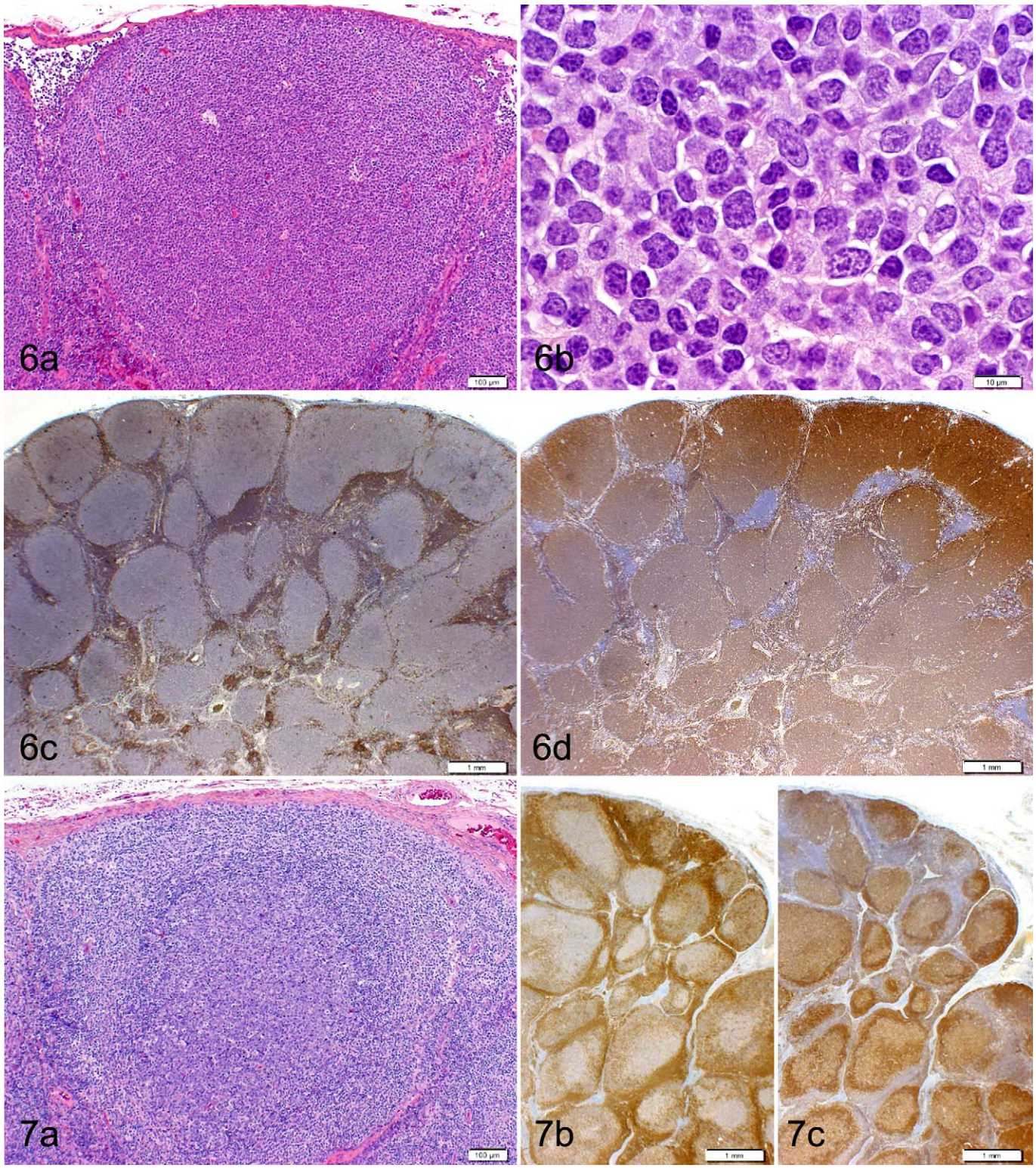


**Figure 6.** (a–d) Dog, lymph node, follicular lymphoma (FL). (a) The homogeneity of cell type and architecture, with an absence of tingible body macrophages throughout the follicle, identifies the proliferation as FL. Small arteries and postcapillary venules are interfollicular and peripheralized by neoplastic follicles. The capsule is thin, and the peripheral sinus is open between nodules. Hematoxylin and eosin (H&E). (b) Follicles are composed of intermediate-size centrocytes with indented, heterochromatic nuclei and large-size centroblasts that have large nucleoli impinging on the nuclear membrane. H&E. (c) The interfollicular areas consist of small areas of residual benign paracortex composed of CD3-positive T cells. There is complete absence of mantle cell cuffs. Immunolabeling with anti-CD3, hematoxylin counterstain. (d) Follicles

activity. Leukemia may occur in advanced cases of TZL. Examination of fine-needle aspirates may not distinguish malignant from benign small lymphocytes.

## T Cell Lymphoblastic Lymphoma (Fig. 5a-d)

T cell lymphoblastic lymphoma (T-LBL), in contrast to T cell lymphoblastic leukemia, is a neoplasm of peripheral tissues usually involving lymph nodes, and the cellular features are characterized by uniformly intermediate-sized nuclei with evenly dispersed chromatin that obscures nuclear detail and a high mitotic rate. There is with very rapid spread to visceral organs and marrow and characterized by short remission times in treated animals. In this study, there were 12 cases of T-LBL (4%).

The term *lymphoblastic* has not been used with precision in veterinary medicine and has been used in the hematologic context to indicate a large neoplastic cell in blood.[22] With newer classification systems for human tumors and their application in veterinary pathology, lymphomas of intermediate nuclear size with dispersed chromatin have become recognized as LBL that can be of either B or T cell type, indistinguishable without immunohistochemistry.[5]

Cytologically, the cells of LBL are similar to those of acute lymphoblastic leukemia (ALL) of B or T cell type. Dogs with ALL have overt leukemia and bone marrow involvement. LBL may be diagnosed on fine-needle aspiration where the diagnosis is based on the presence of uniformly large cells with few differentiating features. LBL cells are characterized by a dispersed chromatin pattern that obscures nucleoli in cells with nuclei of intermediate size. The chromatin appears uniformly dense in both cytology and histology. The mitotic figures are less sharply defined and may be underestimated.

Architecturally, T-LBL typically has a thin capsule with focal perinodal colonization, diffuse cortical and medullary filling, and lack of tingible body macrophages. Cytologically, there is a high mitotic rate (>10/400× field), and the cells appear densely stained because of the dispersed chromatin that obscures nucleoli. There is moderate anisokaryosis, and nuclei range from round to oval or irregularly indented.

LBL is the most aggressive lymphoma regularly encountered in veterinary practice, with T-LBL more common than B-LBL. Dogs with LBL are visibly ill but in good body condition, indicating rapid onset with reduced appetite and activity. Most cases present with one or more peripheral nodes enlarged. There is marked similarity between canine mediastinal T cell lymphoma that rapidly involves the bone marrow and human adolescent acute lymphocytic leukemia.[15]

T-LBL can be distinguished from PTCL of similar cell size since the latter has more prominent nucleoli and mitoses. T-LBL must be differentiated from B-LBL through immunohistochemistry (IHC) for CD3, CD79, and CD20 and from T-ALL on the basis of topographical involvement.

## Follicular Lymphoma (Fig. 6a-d) Versus Follicular Hyperplasia (Fig. 7a-c)

Diseases other than lymphoma totaled 20 cases in this study. Eleven (3.7%) of these cases were lymphoid hyperplasia; 9 cases were benign atypical follicular hyperplasia (BAFH), identified by having coalescing follicles, and 2 cases were benign follicular hyperplasia (BFH). BFH needs to be differentiated from the indolent lymphomas of dogs (FL, MZL, mantle cell lymphoma [MCL], and TZL).[38] None of these, with the possible exception of BFH, is associated with clinical illness. Both humans and dogs with FL tend to present with widespread involvement but lack clinical illness. FL in humans constitutes more than 30% of all lymphomas in North America but represent only about 1% of lymphomas in dogs. The morphologic features of these groupings are sufficiently well defined that they can be distinguished on H&E staining.[9,38]

Architecturally, BFH, in contrast to FL, usually retains a thin mantle cell cuff, and many may have antigen-related polarity with larger cells at one side of the follicle.[24] Perinodal extension may occur in both BFH and FL. BFH is characterized by the presence of intrafollicular tingible body macrophages, whereas FL, having disabled the apoptotic gene, has few or none. Both FL and BFH label strongly with CD79 and CD20. CD3 labeling is primarily interfollicular. There are a few residual T cells in FL follicles and many in those of BFH.

FL is a rule out in nodes with follicular architecture and is confirmed on the basis of an identical mixture of centrocytes and centroblasts across each individual follicle and between follicles anywhere in the node. Additional criteria are loss of mantle cell cuffs and absence of antigen-related polarity. FL may only partially involve the lymph node and only rarely develops into diffuse areas in advanced cases.

FL must be distinguished from BFH on the basis of the absence of antigen-related polarity, loss of the mantle cell cuff, and homogeneity of centrocytic and centroblastic proportions. The proportion of the centrocytes and centroblasts is the basis on which the FL is graded from I to III, and with time, the

**Figure 7 (continued)** are composed of strongly and uniformly CD79a-positive B cells. There are irregular areas of follicular coalescence present in the outer cortex. Immunolabeling with anti-CD79, hematoxylin counterstain. (a–c) Dog, lymph node, benign atypical follicular hyperplasia (BAFH). (a) A perceptible mantle cell cuff encircles the germinal center, with a broad surrounding area of marginal zone hyperplasia that greatly increases the follicle size. The follicle has retained antigen-related polarity, characterized by lighter staining of the more superficial follicular lymphocytes and more dense staining of the lymphocytes in the deeper aspect of the follicle. Hematoxylin and eosin (H&E). b) The marking of the periphery of follicles is due to numerous scattered CD3-positive T cells within the mantle cell layer. Immunolabeling with anti-CD3, hematoxylin counterstain. (c) Small CD79a-positive B cells of the mantle cell cuff have greater cytoplasmic density than large CD79a-positive B cells of follicular centers. Immunolabeling with anti-CD79, hematoxylin counterstain.

proportion of large cells of the centroblastic type increases and the proportion of small cells of the centrocytic type decreases.[10]

## Discussion

This study confirms that veterinary pathologists, even those who are not specialists in hematopathology, can achieve a high degree of accuracy in applying the WHO classification system to canine lymphomas. The histologic diagnosis of specific subtypes of non-Hodgkin lymphoma in humans is widely believed to be imprecise.[1] We believe that the same can be said for the histologic diagnosis of canine malignant lymphoma. Since only follicular lymphoma can be accurately diagnosed on H&E staining and that subtype constituted less than 1% of total cases in this study, immunophenotyping is essential for an accurate diagnosis of canine lymphoma. The accuracy of the 17 reviewing pathologists can best be assessed by comparing this study to that carried out by the medical pathology group.[1] It is important to recognize that in that study, the reviewers did not work independently as their daily results were tracked, and if all 5 reviewers did not provide the same diagnosis on each case, they were required to review all of these to reach a consensus diagnosis. An odd number of pathologists (5) was chosen precisely to facilitate reaching agreement in cases in contention. No consensus agreements were reached in this current study except those between the 3 pathologists who established the diagnostic interpretation for each of the 300 cases. The fact that the overall accuracy by this diverse group so closely mirrored that of the human study is a remarkable achievement.

The prognostic significance of each morphologic entity will be reviewed in a future article. A preliminary evaluation of clinical data from this study shows that dogs with indolent lymphoma retain normal appetite and activity, even with advanced stages of lymphoma. The specific lymphomas with these characteristics include nodal and splenic marginal zone lymphoma, follicular lymphoma, small cell lymphoma of B and T cell types, T cell–rich large B cell lymphoma, and T zone lymphoma.

To our knowledge, no other system of veterinary diagnostic classification has been tested in a system of equivalent rigor and detail. The success of this study exemplifies an important concept. Experience provides pathologists with a breadth of knowledge that is difficult to gain other than by hands-on activity. However, an equivalent need is access to diagnostic criteria for specific lymphoma entities by which they can be accurately distinguished by observers who are talented but not experienced. The critical value of well-described and illustrated disease entities was apparent in the analysis of this study, where a senior resident scored higher than many experienced and certified pathologists. Thus, experience may also bring a bias that impedes use of new diagnostic criteria. This demonstrates that careful application of well-described criteria is paramount for accuracy in diagnosing canine lymphoma or any other disease entity. In the historical development of lymphoma classifications, it was those that had well-defined and easily applicable criteria that gained use. This study is an affirmation of the WHO criteria that are generally directly applicable to canine lymphomas.

The basic premise behind the development of the WHO classification system for human leukemias and lymphomas deserves comment. In reviewing the existing disease classification systems, the working group saw how new knowledge made each of the preexisting systems obsolete. Therefore, a goal was to develop a classification system that was capable of absorbing new knowledge without requiring a complete revision of the system. Their strategy of classifying human lymphomas on the basis of well-defined diseases rather than on cellular type recognized that there was no gold standard by which round cell tumors can be classified. Thus, every aspect of these diseases, including topography, cell type, immunophenotype, cytogenetics, and molecular analysis, were all included. Fortunately, the first 3 of those criteria provide most of the information required to arrive at a specific diagnosis of lymphoma in a dog. The open-ended aspect of the WHO classification system is valuable to veterinary pathology since it permits application of oversight criteria and allows addition of newly derived information. By this process, large diagnostic categories, such as DLBCL, will be subdivided as diagnostic specificity increases. This process is apparent in the initial list of human peripheral T cell lymphomas: those listed as not otherwise specified (NOS) have become progressively fewer as more of these diseases were found to have specific criteria by which they could be identified.

It is pragmatic for veterinary pathologists to apply the current WHO criteria, recognizing that this is a work in progress that will advance as more information becomes available. In summary, because the 6 disease categories described in detail here include nearly 80% of all canine lymphomas, application of this system is practical for most veterinary pathologists.

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The authors declared that they had no conflicts of interests with respect to their authorship or the publication of this article.

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