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INDOLENT LYMPHOMA

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As of 10-15 years ago, canine lymphoma was primarily considered to be a monolithic disease with two main subtypes - high grade B-cell and T-cell lymphoma. In veterinary school, it was taught that "B is bad, but T is terrible." Over time, this view has changed. Diffuse large B-cell lymphoma and peripheral T-cell lymphoma remain the two predominant subtypes, but we've come to recognize a population of more indolent lymphoid malignancies that share a slower clinical course.

In human medicine, over 90 different lymphoma subtypes are known, each with its own presentation, molecular characteristics, clinical course, treatment, and prognosis. In veterinary medicine, there are fewer recognized subtypes, but with the advent of larger clinical studies and better molecular diagnostics, we have begun to appreciate significant diversity in canine lymphoma as well.

Indolent lymphoma is a heterogeneous group of lymphoid malignancies that progress slowly over time. These represent about 20-30% of all diagnosed canine lymphoma cases. Indolent lymphomas generally develop over months instead of days or weeks. At presentation, patients are usually well and have mild-to-moderate lymphadenopathy. One or more nodes may be enlarged. Cytology may be suggestive but is rarely diagnostic. Demodex infestation and a secondary malignancy have been reported as common, concomitant diseases. Splenic forms of indolent lymphoma are often first noted incidentally as a splenic nodule or mass. Uncommonly, these splenic forms may enlarge and rupture, in which case a patient presents with a hemoabdomen, similar to a dog with hemangiosarcoma. Median survival times are usually prolonged - 15 months or much longer depending on circumstance.

By contrast, high grade lymphoma arises over days to weeks. Lymph nodes are often large at presentation (>3 cm), and multiple nodes are present (stage III). Cytology is usually diagnostic, or it will become diagnostic over a short course of time as a monomorphic population of atypical, intermediate-to-large lymph cells efface the normal nodal architecture. Patients with more advanced forms that involve the liver, spleen, and bone marrow often present more acutely ill. Median survival times without treatment are quite short (1-2 months).

Dr. Overley-Adamson

DIAGNOSIS

Cytology

Cell morphology may suggest an indolent lymphoma but will not definitively diagnose these diseases. Cytology is useful and can increase suspicion, but usually the diagnosis will be lymphoid hyperplasia. Features that increase suspicion for lymphoma

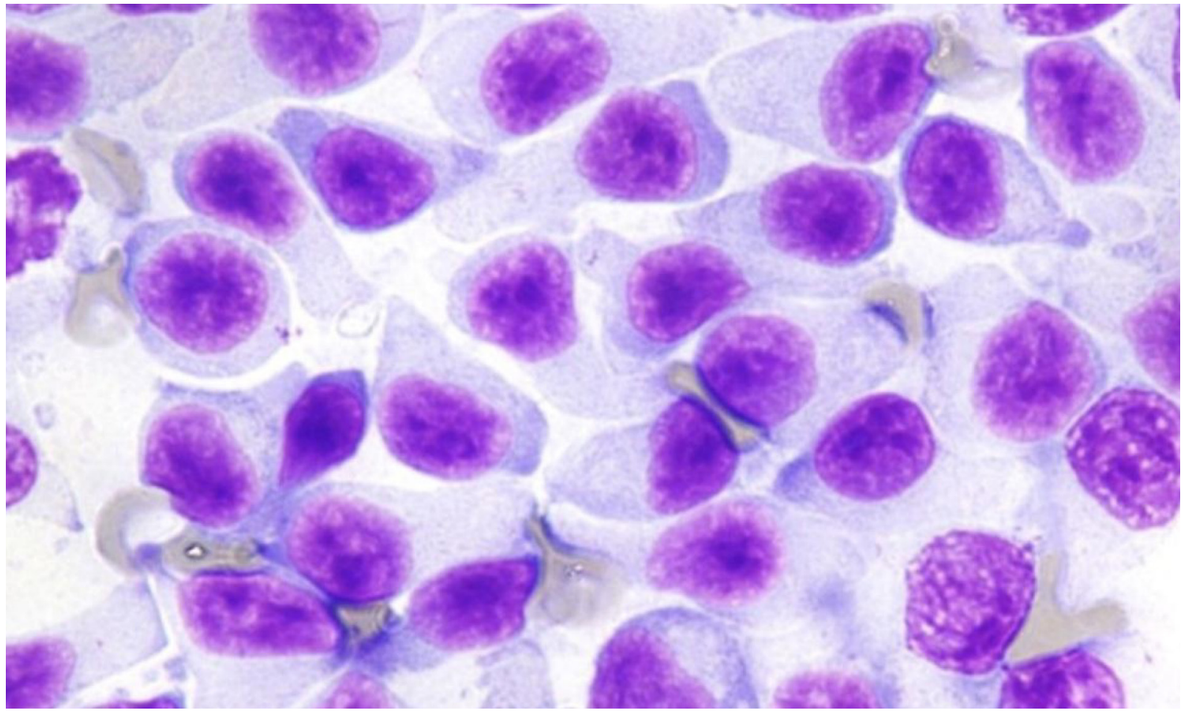

Figure 1. High power slide of T-zone lymphoma, Wright-Giemsa stain. Cells have round to oval nuclei and abundant clear cytoplasm with cytoplasmic extensions that appear panhandled or tear-dropped in shape. Mitoses are infrequent.

Source: Mizutani N, Goto-Koshino Y, Takahashi M, Uchida K, Tsujimoto H. Clinical and histopathological evaluation of 16 dogs with T-zone lymphoma. The Journal of Veterinary Medical Science. 2016 Sep;78(8):1237-1244. DOI: 10.1292/jvms.15-0688. PMID: 27098109; PMCID: PMC5053923.

include a monomorphic population of small-to-intermediate lymphoid cells with mild to moderate atypia. A paucity of plasma cells (which are more common with inflammation), may be noted as well. Other atypical features might include subtle nuclear alterations and/or abundant, clear cytoplasm with an occasional "panhandled" appearance. Though not usually diagnostic, cytology remains one of the first steps toward diagnosis, as it can rule out other disease states.

DIAGNOSIS

Biopsy

Surgical biopsy with immunohistochemical analysis remains the gold standard for diagnosis, most particularly if a B-cell lymphoma subtype is suspected (such as marginal zone, mantle zone, or follicular lymphoma). Less invasive diagnostics, such as flow cytometry and PARR, do not at this time distinguish among B-cell lymphoma subtypes, and small-to-intermediate cell size does not always indicate indolent disease. For example, there is a recently recognized, aggressive, canine B-cell subtype, which is called diffuse small B-cell lymphoma, and this subtype has a median survival time of only 140 days. Other diagnostic methods, such as flow cytometry, can be diagnostic for indolent forms T-cell lymphoma (such as T-zone lymphoma, the most common form), and so cytology, flow cytometry, and PARR are often recommended, particularly if an owner declines biopsy, if it is unclear whether it is high or low grade, or as an initial diagnostic starting point.

PCR for Antigen Receptor Rearrangements (PARR)

PARR is a PCR-based, clonality test that can be run on cellular DNA obtained from a biopsy sample or a cytology submission. A PARR test uses primers that select a section of DNA that encodes both the immunoglobulin heavy chain (IgH) of B cells and the gamma subunit of the T cell receptor of T cells (TCRγ). The amplified snippet of DNA shows whether there is an identical antigen receptor rearrangement that is characteristic of a clonal B-cell or T-cell population. This test can be particularly useful for diagnosis, as it helps to differentiate a cancerous (usually clonal) versus inflammatory (usually polyclonal) population of lymph cells. This test is relatively easy to "add on" to cytology, because it can be run on the cells submitted on slides, and these cells do not have to be viable. It is ideal to submit at least four slides, however, so enough material is available. No test is perfect, and it's important to note that false positives include infection with certain tick-borne diseases (such as Ehrlichia). False negatives are possible as well. However, it can strongly support or refute a concern for lymphoid malignancy. PARR does not distinguish further among subtypes, however, and it will not distinguish between an indolent and high grade lymphoma.

Flow Cytometry

Flow cytometry (FC) is a multi-parametric test used to better characterize lymphoma populations in the blood, bone marrow, or other tissues (lymph nodes, skin, or other). FC requires viable cells; therefore, live cells in fluid suspension must be kept cooled and shipped immediately so that samples can be processed within 12-48 hours of collection. FC characterizes cells based on their size and also on the pattern of cell surface markers that they express. Information is often used in addition to cytology and PARR and can be both prognostic and diagnostic in many situations. It is a good test to distinguish thymoma from lymphoma and to characterize suspected leukemias. For indolent lymphomas, flow cytometry can be diagnostic for the most common form, called T-zone lymphoma. For B-cell indolent lymphomas, flow cytometry is less useful. There are aggressive small cell B-cell forms and the available cell surface markers cannot reliably distinguish between subtypes.

Imprimed

Imprimed is a company founded in 2017 by two Stanford PhDs (engineering science), Sungwon Lim and Jamin Koo. Imprimed tests cell samples with flow cytometry, PARR, and an ex vivo chemosensitivity assay to provide further characterization of the cancer cells along with a drug sensitivity analysis to allow for more personalized treatment for lymphoid malignancies. Viable cells in liquid media are required for testing, which means that fine needle aspirate samples should be collected in the appropriate medium and sent immediately for processing. To date, Imprimed has been primarily used and recommended for high grade lymphomas. However, its use may be considered for treatment of indolent forms of lymphoma given we have no optimized standard of care treatment recommendation for these subtypes as of yet. As cool as this test sounds, please remember that no test is perfect, and chemosensitivity assays have their flaws. Continued validation is required. Nonetheless, the clinical utility of a drug sensitivity assay for these patients is provocative and interesting.

STAGING

Staging remains the same for both aggressive and indolent lymphomas. Indolent lymphoma can arise in multiple spots, and patients can also present with two different lymphoma subtypes, which is presumably due to immune system suppression caused by the indolent lymphoma. If dermatology lesions are present, testing for Demodex may be in order. Staging diagnostics include physical examination, complete blood count, serum chemistry analysis, urinalysis, 3-view chest radiographs, abdominal ultrasound, liver and splenic aspirate cytology (as warranted), and possible bone marrow aspirate (as warranted).

TYPES OF INDOLENT LYMPHOMAS

Using human World Health Organization (WHO) classification, the most common canine variants include T-zone lymphoma (TZL), marginal zone lymphoma (MZL), follicular lymphoma (FL), and mantle cell lymphoma (MCL). TZL is of T-cell lineage. MZL, MCL, and FL are all of B-cell lineage. .

T-zone lymphoma (TZL)

TZL is the most common form of indolent lymphoma in dogs and represents roughly 60% of all diagnoses. It arises most commonly in middle-aged to older dogs (8-10 years). Common breeds include Golden Retrievers and Shih Tzus. Patients usually present with one or more mildly to moderately enlarged lymph nodes. These nodes

may wax and wane in size. They may seem to respond initially to antibiotics but persist over weeks to months. Most patients will present feeling well. Upon staging, mild-to-moderate lymphocytosis is common. Hepatosplenomegaly is possible. Significant cytopenias are rare. Other disease states (Demodex) may be present.

TZL can be diagnosed by both histological and cytological means. Histology requires biopsy and immunohistochemical staining. Cytology requires flow cytometry (and, ideally, PARR). Cancer cells are characterized by small-to-intermediate size, a clear cell cytomorphology, an occasional “panhandled” appearance, T-cell phenotype, and the loss of cell CD45 expression. As for treatment, there is, as of yet, no true standard of care for this disease. However, monitoring is most often recommended initially. Monitoring includes periodic examination and complete blood counts with additional testing as warranted. Treatment is recommended if a patient is ill, if there is significant tumor burden, if the tumor behaves more aggressively than expected, or if the lymphocyte counts rise above a certain threshold. Most oncologists choose to start with a lower grade, oral protocol of prednisone and chlorambucil. TZL is usually thought to be incurable but is managed for an extended period of time as a chronic disease.

Splenic Marginal Zone Lymphoma (MZL)

Splenic marginal zone lymphoma (MZL) is the second most common form of indolent lymphoma. It is characterized histologically by proliferation of atypical, small lymphocytes in the marginal zone of lymphoid follicles. Diagnosis is achieved with a biopsy and immunohistochemical staining. These lesions arise most commonly in middle-aged dogs. They are often found incidentally on a physical exam (enlarged spleen) or by abdominal sonography performed for other concerns. However, it’s important to know that MZL can present acutely with hemoabdomen secondary to a bleeding splenic mass. It is also common for patients to present with concurrent medical problems or other neoplastic diseases (reported in 35% in one study). Anemia and thrombocytopenia are the most common abnormal blood work results. Patients can do well long term with surgical treatment and monitoring. However, it’s best to have a follow up oncology consultation as there are specific situations in which this disease may behave more aggressively than expected. These include high lymph cell counts, illness at presentation, and nodal or more systemic involvement. Median survival times are generally reported to range 1-3 years, and the use of chemotherapy depends on the situation.

Canine Nodal Marginal Zone Lymphoma

Though considered indolent, reports indicate that many of these cases present for diagnosis at a more advanced stage, and these patients can have a poorer outcome (<1 year) despite having indolent disease. Patients may present systemically unwell with significant bone marrow involvement, and the magnitude of peripheral blood involvement or bone marrow infiltration is prognostic. However, patients diagnosed with earlier stage disease are still expected to do well longer term.

Other

Mantle zone lymphoma and follicular lymphoma are much less common. Mantle zone lymphoma arises most frequently in the spleen. Follicular lymphoma arises more commonly in the lymph nodes, but cases of colorectal masses have been reported. From personal, anecdotal experience, I had one follicular lymphoma patient survive 10 years after diagnosis, but she ultimately died of drug-resistant, aggressive, muco-cutaneous lymphoma.

TREATMENT

There is no optimized, “standard of care” treatment, and monitoring is usually the first recommendation unless a patient presents ill or with advanced stage disease. Treatments may ultimately become different for each entity and depend on a tumor’s clinical behavior and stage. Surgical removal as the sole treatment may be recommended for a solitary splenic mass or lymph node. Monitoring and delay of treatment may be considered for patients with mostly normal, stable blood work and stable multi-centric lymph nodes. Oral therapies are usually considered for progressive indolent lymphoma, and multi-agent cytotoxic chemotherapy may be considered for patients with rapid clinical progression despite cell size or diagnosis.

PROGNOSIS

Indolent lymphoma is not curable. A smaller, splenic marginal zone lymphoma lesion may be removed surgically, and a patient may go on to live a long and happy life and die of something else. However, for most of the multicentric indolent lymphomas, the goal of therapy is chronic disease management - a good quality of life and prolonged stabilization of disease. Complete response is uncommon, yet extended survival is possible. With monitoring and/or oral therapy protocols, studies show that median survival times are fair to good and in the range of 15-44 months. The most common treatment protocol involves the use of an oral alkylator (chlorambucil) and prednisone, and survival times have been reported as long as 7.5 years. Dogs with elevated lymph cell counts generally have poorer outcomes. About 10% of indolent lymphoma cases will go on to develop a secondary malignancy, often another lymphoid malignancy. If diagnosis has been made without histology and immunohistochemical staining, it’s important to remember that not all small cell lymphomas are indolent, and so clinical tumor behavior may better predict outcome.

Monitoring for these patients usually includes physical examination and complete blood count every 4-12 weeks depending on the situation. Periodic ultrasound, serum chemistry analysis, and chest radiographs would also be recommended as well. Ideally, monitoring (exam and CBC) starts at 4-week increments for the first few months to ensure that tumor behavior accords with diagnosis. Once an indolent nature is confirmed, monitoring can be spread out to every 2-3 months.

LAPAROSCOPIC PROCEDURES AT MVA

Dr. Litterine-Kaufman, VMD, DACVS-SA

Dr. Litterine-Kaufman joined MVA in 2022, and is excited to help provide a wide range of surgical services. He has a special interest in minimally invasive surgery, but enjoys being in the OR with a wide variety of orthopedic, neurologic, and soft tissue cases. He also offers laparoscopic ovariectomy, cryptorchid neuter, liver biopsy, and laparoscopy-assisted gastropexy. While these techniques are used most to help with older and larger dog procedures, smaller animal spays and cryptorchid neuters can also be performed with these techniques. Dr. LK is happy to discuss any case that may benefit from these techniques.

WELCOME TO OUR EMERGENCY TEAM

Dr. Danielle O'Brien

Dr. Danielle O'Brien grew up in McKinney, Texas. She attended the University of Oklahoma for her undergraduate degree, but was fortunate enough to be accepted into the University of Edinburgh's Royal (Dick) School of Veterinary Studies prior to graduating. She obtained a Bachelor of Veterinary Medicine and Surgery (BVM&S) before returning stateside. She spent a year working at a hybrid general practice and emergency clinic in the panhandle of Florida before uprooting her life further north to Philadelphia. She has continued her career as an emergency clinician in the emergency/specialty and referral community in the area before joining MVA in 2023. Her professional interests include urethral obstruction, emergency stabilization and mental health within the veterinary profession.

In her spare time, she enjoys traveling, going to concerts, hiking, playing volleyball, and home decorating. She and her husband share two cats, Steve Kerr and Binks, and a dog, Potter.

CalPro RESEARCH

In past years, we've received feedback that allowed us to grow and better support our referral relationships. Coming soon, we'll be asking our referring partners to participate in a survey on Metropolitan that will be sent via e-mail from CalPro. All participants will be put into a drawing, and the winner will receive lunch for their entire practice as a thank you from MVA!

HERE TO HELP YOUR MANAGEMENT TEAM

P V M G

Pennsylvania Veterinary Managers Group

Serving The Needs of Veterinary Management Professionals Throughout Pennsylvania

The Pennsylvania Veterinary Managers Group is an organization of veterinary management professionals responsible for the leadership and direction of today's veterinary hospitals. Comprised of hospital administrators, practice managers, HR managers, and office managers our mission is to come together to share experiences and ideas and support the advancement of veterinary management.

Meetings are held at Maggiano's in King of Prussia and cover a wide range of topics, from practice financials and human resources to strategic planning, health and safety, and federal regulations and compliance. Membership is free.

If you are interested in coming together with other veterinary management professionals throughout Pennsylvania please contact Patrick Fabricatore at pfabricatore@perkiomenanimalhospital.com.