Canine lymphoma

Epidemiology and clinical presentations

Lymphoma is more correctly called lymphosarcoma (LSA) and it is a multifactorial systemic disease with many types. Canine LSA shares many similarities with non-Hodgkin's lymphoma (NHL) in humans. It is a haematopoietic neoplasia and is the most common cancer affecting the blood cells (lymphocytes) of dogs. It affects the lymphohaematopoietic organs (lymph nodes [LN], spleen, liver and bone marrow) more commonly than it is extra nodal. The most common presentation is multicentric with peripheral lymphadenopathy, with or without involvement of the spleen, liver and/or bone marrow. Other presentations include gastrointestinal, cutaneous, nasal, ocular, CNS and renal forms and these extra nodal forms differ in prognosis.

Just as cancer is not one disease but many, the same is true of lymphoma. LSA can affect many types of lymphocytes (B, T and NK [Natural Killer] cells) and this results in variable biological behaviour of the disease. Clonal proliferation of the affected cell type can occur at any stage of maturation. The malignant transformation that occurs is multifactorial and can be a result of chromosomal aberrations, breed predisposition, environmental, immunologic and other factors. While there are known breed predispositions to LSA, genetic predisposition does vary by country.

Diagnosis

The goal of lymphoma diagnosis is to identify the type of LSA as this affects prognosis and treatment decisions. This can be done after an initial cytological diagnosis of fine needle aspirates (FNAs) with ancillary tests and/or with histopathology of an excised LN. It is also important to use the white blood cell (WBC) dot plots that your CBC analyser gives you; it can help to increase the index of suspicion of a potential malignancy in cases without obvious peripheral lymphadenopathy.

Cytology

Cytologic diagnosis of lymphoma depends on the proportions of large (lymphoblastic), intermediate, and small (lymphocytic) lymphocytes assessed on multiple well-made, highly cellular FNA smears sampled from an entire lymph node or from multiple lymph nodes. Sample as many LNs as possible and make several slides so some are available for further testing if needed. It's important to submit good quality slides that have not been refrigerated. You can stain a slide in your practice to examine it for quality.

The key cytologic hallmark of most lymphomas in dogs is a cell population composed predominantly of a relatively homogeneous population of monomorphic, medium to large lymphocytes. Cytologic diagnosis of lymphoma involving small or intermediate lymphocytes can be more challenging, necessitating biopsy or molecular diagnostic testing. If cytology does not provide a diagnosis, it may be a result of a heterogenous lymphoid population, the presence of small cells that look like normal lymphocytes or a small population of malignant cells with a reactive/hyperplastic background of cells. This is where the ancillary tests can help with diagnosis. With the indolent types, one can find a mix of lymphocytes and some may not be distinguishable from lymphoid hyperplasia on cytology; these will require additional tests and/or histopathology on an excised LN.

Ancillary cytology diagnostic tests

Ancillary tests use molecular diagnostic techniques such as flow cytometry staining and analysis of lymphocytes in blood or FNAs, the PCR for antigen receptor rearrangement (PARR) assay of blood or FNAs for clonality and immunocytochemical staining of FNAs for phenotyping. These ancillary tests should not be used as standalone tests. Their use should be guided by cytological findings to help select the most appropriate test for each case. The results need to be evaluated in light of the full history and clinical picture together with cytological findings in order to obtain an accurate interpretation and guide therapeutic considerations (e.g. with indolent vs high grade lymphoma and phenotype).

The most basic division of lymphoma type is a result of whether the cancer arises from T or B cells. B lymphocytes produce antibodies while T lymphocytes perform many immune functions, including regulating immune processes and killing abnormal cells (for example, cancer cells or cells infected with viruses or bacteria). Knowing whether a lymphoma is predominantly B or T cell in origin is essential for prognosis and treatment. Each form has aggressive and less aggressive subtypes, and diagnostic testing can provide crucial additional information.

Flow cytometry can help differentiate reactive lymphocytosis/lymphadenopathy from neoplastic processes by identifying a monomorphic population of one immunophenotype in lymphoma, whereas a reactive node would have a mixed population of B-cells and T-cells. It helps to refine diagnoses, determine lymphoma subtypes, and assess clonality, which can guide treatment decisions and predict prognosis. Flow cytometry can differentiate between B-cell and T-cell lymphomas, identify specific cell surface markers such as CD markers (clusters of differentiation or classification determinants) that may be indicative of certain subtypes. Flow cytometry can also be used to monitor treatment response in lymphoma patients, by assessing changes in cell populations and marker expression over time.

Flow cytometry involves analysis of fresh cells in fluid aspirated from a suspect lymph node or organ and sent to a unique laboratory for review. Advantages of flow cytometry are that it includes a comprehensive panel of markers, a quick turnaround time and it may show a characteristic profile (e.g. T zone lymphoma) or it may provide prognostic information (e.g. CD34 expression, MCH class II and Ki-67). Disadvantages include the need for additional sampling of LNs after the initial cytology slide sample is taken and the strict requirement of a fresh sample as cells need to be viable at the time of analysis.

The PARR assay enables the determination of clonality and is a sensitive method for confirming the neoplastic origin of lymphocytes and a diagnosis of lymphoma. Clonal testing with PARR assesses the diversity of lymphocyte antigen receptor rearrangement in order to differentiate a neoplastic from a reactive lymphoid proliferation. During development, cells undergo rearrangement of T-cell receptor (TCR) and immunoglobulin (Ig) receptor for a specific antigen. Every lymphocyte has a slightly different TCR or Ig receptor. In a reactive population, the population of lymphocytes is heterogenous and multiple-sized products (polyclonal) whereas in lymphoma, there is a clonal population of single-sized products (monoclonal). PARR can be performed on blood, fluid samples, cytology slides (pre-stained) and histology samples, provided there is sufficient lymphoid material. Advantages of PARR include differentiation of reactive vs neoplastic processes and it can be performed on samples already submitted (e.g. cytology stained slides). Disadvantages include the fact that it cannot differentiate indolent vs high grade forms and it is not ideal for phenotype (B- vs T-cell) as cross-lineage rearrangement is possible. PARR can give false negative results with a small sample and low numbers of clonal cells in a polyclonal background or with primer site mutation and it can give false positive results in chronic infectious diseases such as *Ehrlichia*, *Leishmania* or, rarely, thymoma or with non-specific amplification.

Immunocytochemistry (ICC) involves immunolabelling of cells with a stain applied to cytology smears to identify the immunophenotype as B- or T-cell; it requires a minimum of 3 good quality smears and can be performed on previously stained slides. Advantages include the fact that ICC can be done with a quick turnaround time on the slides used for the initial diagnosis if adequate and there is not need for special sample handling such as air-dried slides. Disadvantages are that there is a limited panel of markers and ICC cannot differentiate indolent vs high grade forms, meaning an association with cytological findings is essential.

Biopsy for histopathology and immunophenotyping

After a cytological diagnosis, histopathology is required for final classification of the type of lymphoma. An excisional LN biopsy is better than a wedge or tru-cut LN biopsy in maintaining tissue architecture for histopathology. Historically, histologic evaluation of tissue biopsy samples has been the gold-standard diagnostic test for morphological subtyping of canine lymphoma (diffuse versus follicular, cleaved versus noncleaved) and histologic grade (based on mitotic rate/400 field, with low-grade 0–5, intermediate 6–10, and high-grade >10). Mitotic rates tend to be low in indolent forms while the more aggressive non-indolent forms tend to have high mitotic rates. Immunophenotyping enables further categorization of lymphomas by immunohistochemical staining into B-cell (CD79a) or T-cell (CD3) types.

Classification and biologic behaviour

Historically, the types of LSA were thought to be either B-cell, T-cell, small cell or large cell and the prognosis was thought to depend on type of treatment with B-cell being ‘Bad’ and T-cell being ‘Terrible’ when it came to treatment. More recently, an accurate diagnosis is important as this affects prognosis and treatment. Applying the WHO classification of lymphoid neoplasia in humans to canine LSA gives a more precise classification based on morphology, immunophenotype, genetic features and anatomic location which is important for prognosis and treatment. Prognosis depends on the WHO lymphoma type and treatment recommendations change with the histologic subtype as specific therapies are needed for the different types of disease.

Lymphoma classification involves identifying the lymphocyte cell type as either B-cell or T-cell as well as whether the cells are of a small or large form. Large cell lymphoma is considered to be aggressive and fast moving. A large cell diagnosis means that more of the dog's body is being attacked by the cancer cells and, if left untreated, can prove fatal within 6-8 weeks. The presence of small cell lymphoma is less time sensitive and allows a bit of leeway to consider options before starting treatment. Indolent types of lymphoma are variations that can lead to different levels of intensity for managing the disease with a better prognosis; for some dogs with an indolent form of lymphoma, treatment may be more flexible and not as time-sensitive

The 5 main types of canine lymphoma account for ~80% of all canine lymphoma cases (76-95% depending on the study). Indolent canine lymphoma (low-grade), progresses slowly, may have fewer initial clinical signs and can often be managed more conservatively. Non-indolent (aggressive or high-grade) lymphomas progress quickly and often more require more immediate and intensive treatment.

Table 1. Lymphoma classification with median survival times (MST).

<table>
<tr><th>Form</th><th colspan="2">Category</th><th>MST (days)</th></tr>
<tr><td rowspan="2">Indolent</td><td colspan="2">TZL = T-cell T-zone</td><td>412</td></tr>
<tr><td colspan="2">Small cell B-Cell – follicular, mantle cell and marginal zone</td><td>168</td></tr>
<tr><td rowspan="4">Non-indolent</td><td rowspan="2">DLBCL = Diffuse Large B-Cell Lymphoma</td><td>Centroblastic</td><td>213</td></tr>
<tr><td>Immunoblastic</td><td>308</td></tr>
<tr><td colspan="2">PTCEL-NOS</td><td>162</td></tr>
<tr><td colspan="2">LBL</td><td>160</td></tr>
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* centroblastic with multiple central nucleoli and immunoblastic with single large nucleolus in each nucleus

Prognosis

The prognosis for canine lymphoma depends on several factors, including the type of lymphoma (B-cell or T-cell), stage of the disease, treatment protocol and response to treatment. Most B-cell lymphomas are large cell forms that tend to respond better to treatment and generally have a better prognosis than T-cell lymphomas that tend to be more aggressive small cell forms and that do not respond as well to treatment. Early-stage lymphoma is more likely to respond to treatment than advanced-stage lymphoma. While most dogs achieve remission with chemotherapy, the length of remission and overall survival can range from a few months to over a year. Dogs that achieve complete remission with chemotherapy have a significantly longer survival time than those that do not. Paraneoplastic signs such as hypercalcemia tend to be associated with a poorer prognosis.

Treatment

Canine lymphoma is generally responsive to conventional systemic chemotherapy (initial response rate ≥ 90%); most dogs achieve improved quality of life and greater overall survival time. However (except in some forms of indolent lymphoma), eventual disease relapse is expected in most dogs, with disease that progressively becomes refractory to continued treatment. Given that only a small fraction of dogs achieve a cure with conventional treatment options, the primary goal for treatment is palliative. With no treatment, dogs die or are euthanized within 4–6 weeks.

Multicentric lymphoma

In the treatment of high-grade lymphoma in dogs, the most common chemotherapeutic agents administered in combination protocols are cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone (ie, CHOP-based protocols; the "O" in "CHOP" comes from one trade name for vincristine). The addition of l-asparaginase is optional, although this drug is usually reserved for clinically ill dogs or cases of relapse. With systemic multidrug chemotherapy protocols, median survival times in dogs are ~12 months for B-cell lymphoma and ~6–8 months for T-cell lymphoma.

Other common chemotherapeutic agents with activity against naive and relapsing lymphoma include lomustine, mitoxantrone, and rabacfosadine. A recent paper was published reporting on the use of cyclophosphamide, lomustine, vincristine, and prednisone protocol (CLOP) in 26 dogs with naïve non-indolent T-cell lymphoma.

Compared with combination protocols, single-agent chemotherapy, with the exception of doxorubicin treatment, does not typically achieve durable remission. Doxorubicin monotherapy can achieve complete remission, with a median survival time of 6–8 months, albeit with lower response rates than CHOP-based protocols achieve. Extravasation of doxorubicin can be catastrophic and cumulative cardiotoxicity results in a lifetime dose limit. Prednisone monotherapy can improve quality of life and can induce remission for a time (typically 1–2 months, but some dogs can have better outcomes). However, multidrug resistance can develop.

Other forms of lymphoma

Despite the favorable outcomes expected in treating high-grade multicentric lymphoma, the successful management of other anatomical forms of lymphoma is often more difficult and less rewarding.

Recently, the use of two new protocols for the treatment of canine gastrointestinal/hepatosplenic lymphoma, high-grade lymphomas traditionally associated with a very poor response to chemotherapy and a poor prognosis, has been reviewed: L-LOP (L-asparaginase, lomustine, vincristine, and prednisolone) and L-LOPP with the addition of procarbazine. These new suggested protocols turned out to be well tolerated with mild and transient adverse events and longer median survival time and progression-free survival.

Alimentary lymphoma, if focal, can be treated effectively with surgical resection and combination chemotherapy. However, diffuse involvement of the intestinal tract, low constitutional reserve, severe malabsorption of nutrients, and loss of proteins often result in poor clinical responses and short survival times (< 3 months).

For mediastinal lymphoma, chemotherapy alone or combined with focal ionizing radiotherapy (in patients that might have appreciable pleural effusion or space-occupying complications—ie, those with associated dyspnea) can achieve favorable survival times and good quality of life.

Cutaneous lymphoma can be controlled for limited amounts of time, often < 3–6 months, by treatment with lomustine, doxorubicin, or rabacfosadine, or a combination protocol.

For indolent lymphoma, low-intensity oral chemotherapy protocols (chlorambucil and prednisone) often provide prolonged survival times (> 2 years). In some dogs with localized and low-grade disease such as only splenic involvement (B-cell mantle cell) or indolent B-cell marginal zone form, splenectomy can be an effective treatment option without requiring adjuvant chemotherapy.

Unfortunately, while many papers have been published, there are few comprehensive literature reviews of the remission and survival times following chemotherapy and the associated prognostic factors. Additionally, while individual papers have shown a much better survival than others, the overall improvement in outcome has not changed much in the last 40 years.

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