Canine Lymphoma

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PROFILE

Definition
- Lymphoma is a diverse, heterogeneous disease that results from the uncontrolled clonal expansion of malignant lymphocytes.
- The B-cell phenotype is predominant; the remainder consists of T- or rarely NK-cell phenotypes.¹

Systems
- Lymphoma is generally considered a systemic disease.
- Sites of origin include lymphoid-rich tissues (ie, lymph nodes, spleen, thymus, bone marrow).
- Extranodal sites affected may consist of epithelium, intestinal tract, and CNS.
  • Because of the systemic nature of this disease, any tissue may be involved.

Incidence
- Lymphoma comprises 7% to 24% of all canine cancers; it is the most common hematopoietic cancer in dogs.²,³
- Incidence is estimated at 13-24 per 100 000 dogs at risk.²,³
- Incidence rate for dogs <1 year of age is 1.5 per 100 000; for dogs 10-11 years of age, incidence is 84 per 100 000.⁴

Geographic Distribution
- Lymphoma is diagnosed worldwide in the canine population.

Causes
- There is no known cause; the disease is likely multifactorial.⁵
- Hypothesized but unproven causes include retroviral infection with Epstein-Barr virus–like viruses, environmental contamination with phenoxyacetic acid herbicides (2,4-dichlorophenoxyacetic acid [2,4-D]), magnetic field exposure, and immune dysfunction.⁵

Lymphoma is generally considered a systemic disease.

Reference:
Genetic Implications
- Multiple genetic and molecular pathway aberrations have been noted, but none of these factors have translated into clinically relevant information.
  - Chromosomal aberrations reported include gain of chromosome 13 and 31, as well as loss of chromosome 14.5
  - Germline and somatic mutations, altered oncogene/tumor-suppressor gene expression, and epigenetic changes have been reported.7,8
  - Immunophenotypic differences among different breeds suggest heritable risks.9

Signalment
- Middle-aged dogs are most commonly affected, but young dogs can be affected.5
- No sex predisposition has been reported consistently.5
- Boxers, golden retrievers, basset hounds, Saint Bernard dogs, Scottish terriers, and mastiffs are overrepresented.5

Classification is based on anatomic location, staging, histologic criteria, and immunophenotype.

Risk Factors
- Dogs with impaired immune function are at increased risk for lymphoma.10
  - Dogs with immune-mediated diseases are at increased risk independent of age and sex.10
  - A case report of a dog that developed lymphoma following cyclosporine treatment has been reported.11
  - Infectious factors such as retroviral or Heli-cobacter infection may be involved though not definitive.5
  - Environmental factors include herbicides (eg, 2,4-D)12,13 and a weak association with magnetic fields.14

Pathogenesis
- Uncontrolled, clonal, neoplastic transformation and expansion of lymphocytes not restricted to specific anatomic sites
  - Disease progression in the lymph nodes, soft tissue, or extranodal sites leads to development of clinical signs.
  - Other signs may be related to paraneoplastic syndromes; the most common of these are anemia,15 hypercalcemia,16 and immune-mediated thrombocytopenia.17
  - Hypercalcemia, most commonly with T-cell variant of the disease18

Classification
- Classification is based on anatomic location, staging, histologic criteria, and immunophenotype.5,19
  - The most common form of the disease is the multicentric form; this most commonly involves the peripheral nodes but may also include liver, spleen, and bone marrow.
    - Other forms of the disease include GI (small or large bowel), mediastinal, cutaneous, and extranodal forms such as CNS, ocular, nasal, cardiac, lung, bladder, and bone.
  - World Health Organization’s Clinical Staging System for Lymphoma5:
    - **Stage I:** 1 Lymph node involved or lymphoid tissue in a single organ (excluding bone marrow).
    - **Stage II:** Involvement of many lymph nodes in a regional area.
    - **Stage III:** Generalized lymphadenopathy.
    - **Stage IV:** Liver and spleen involved ± stage III.
    - **Stage V:** Bone marrow involvement or extranodal disease.
  - **Substage**5, 20-24
    - a: without systemic signs.
    - b: with systemic signs.
**CLINICAL SIGNS**

- Patients typically are presented with a history of rapidly progressive, nonpainful, generalized lymphadenopathy ± hepatosplenomegaly.
  - Most are presented without signs of systemic illness (*substage a*).
- Clinical signs may be nonspecific (eg, mild lethargy, weight loss) or may represent the organ system that is infiltrated.
  - Dogs that are clinically ill (*substage b*) have profound inappetence, lethargy, weight loss, vomiting, and/or diarrhea.\(^5,20-24\)
  - Polyuria and polydipsia may be present in dogs with hypercalcemia of malignancy, secondary to other underlying disease or UTI.
- Other clinical signs related to the anatomic location of the disease include:
  - Uveitis
  - Cranial abdominal enlargement
  - Dyspnea
  - Mediastinal involvement or pleural fluid
  - Regional lymph edema
  - Dermal or subcutaneous masses
  - Vomiting or diarrhea
  - Bruising
  - Pallor
  - Stridor and stertor if retropharyngeal nodes are involved

**DIAGNOSIS**

- Complete physical examination, including rectal examination, should be performed.
- Complete staging before initiation of therapy is always recommended; however, in select cases, staging may not be performed in entirety because of owner financial constraints.
- Minimum database includes CBC, serum chemistry panel, urinalysis ± urine culture if clinically indicated.
  - CBC may indicate infection that requires treatment prior to chemotherapy or cytopenia consistent with myelophthisic or paraneoplastic syndromes.
  - Serum chemistry panel often reveals changes consistent with infiltrative disease such as:
    - Elevated ALP, ALT
    - Hyperbilirubinemia
    - Hypercalcemia
    - Azotemia
  - Urinalysis may indicate infectious cystitis that should be treated prior to initiation of chemotherapy.
- Three-view thoracic radiographs are recommended.
  - Mediastinal lymph node enlargement or tracheobronchial lymph node enlargement may be noted.
  - Occult pneumonia may be present.
  - Rarely, infiltrative disease (diffuse interstitial pattern) will be seen.
- Abdominal ultrasonography is recommended if GI signs are present or if no peripheral lymphadenopathy is appreciated.
- Echocardiography prior to doxorubicin may be recommended if patient is an at-risk breed for cardiomyopathy or if murmur or arrhythmias are noted.\(^5,24,25\)
- Lymphoma findings may be present on examination of a bone marrow aspirate.
  - Involvement conveys a worse overall prognosis.
  - Determine if marrow reserves are sufficient for chemotherapy.
- Fine-needle aspiration of affected node(s) or organs should be performed.
  - Results are often adequate to obtain diagnosis, as most cases are large-cell variant; monomorphic population of small or intermediate cells may require histopathology or molecular diagnostics to further characterize.
  - The author recommends avoiding areas of high reactivity if possible (eg, mandibular nodes).
  - Cells are generally >2 times the diameter of

\(\text{ALP} = \text{alkaline phosphatase}
\)
\(\text{ALT} = \text{alanine aminotransferase}
\)
\(\text{CNS} = \text{central nervous system}\)
a red blood cell or larger than neutrophils and appear as a monomorphic population.

- Histopathology is considered the gold standard and allows for evaluation of tissue architecture.
  - It also allows for classification into low-, intermediate-, and high-grade variants, which may affect treatment and prognosis.\(^{19}\)
  - Immunohistochemistry is provided through commercial laboratories.\(^{26}\)

- Molecular diagnostics may be recommended when cytology and histopathology are suggestive but confirmation or immunophenotyping is indicated.
  - PARR (PCR for Antigen Receptor Rearrangement) can determine if the majority of cells in the sample are derived from the same original clone vs multiple clones.\(^{26}\)
    - PARR assay is 94% specific for lymphoid neoplasia; sensitivity is 75%.
    - It can be performed on blood, lymph node, bone marrow, cavity fluid, and CSF.\(^{5,26}\)
  - Flow cytometry involves staining live cells with labeled antibodies that bind proteins expressed on the cell surface.
    - Flow cytometry is an interpretive test and can provide additional useful information regarding prognosis and treatment.\(^{27,28}\)
    - T-cells express CD3 (CD4 and CD8)
    - B-cells express CD21 (CD20, CD79a)
    - This can be performed on blood, lymph node, bone marrow, cavity fluid, and CSF.

**Differential Diagnoses**

- Reactive lymphoid hyperplasia
- Systemic infection
  - Bacterial (eg, Rickettsial disease)
  - Fungal
  - Parasitic
  - Viral
- Immune-mediated disease

**Prognostic Factors**

- The prognostic factors with the most significance regarding overall survival time are phenotyping and clinical substaging.
  - Median survival times for dogs without treatment is 4-6 weeks\(^{29,30}\); with gold standard therapy, survival times are 1 year with 25% chance for 2-year survival.\(^{5}\)
  - The most significant negative prognostic factors are substage b, T-cell phenotype, mediastinal location, and hypercalcemia.
  - Other negative factors include the presence of anemia, gastrointestinal location, and stage V disease (bone marrow involvement).
  - Small cell/low grade/indolent lymphomas are associated with longer survival times because of slow progression of disease but are considered less chemoresponsive.
  - Clinical staging is controversial; in general, I=II>III=IV>V.
  - Dogs with a longer initial remission generally have a better long-term outcome and often respond favorably to re-induction therapy when relapse is noted.

**TREATMENT**

**Chemotherapy**

- Because of the systemic nature of disease, chemotherapy is considered the mainstay of therapy for large-cell lymphoma.
  - There are many protocols available, and the individual protocol should be tailored to patient and owner.
  - However, current standard of care consists of CHOP-based protocols.
  - The following protocols are recommended as a starting point when discussing therapeutic options with owners:
    - CHOP-based therapy\(^{5,22,29-31}\)
      - 80%-90% of patients experience remission within the first 4 weeks of therapy
      - Median survival time of 12 months with 25% survival at 2 years\(^{5}\)
      - 70% response and 6-8 month survival for stage V or T-cell disease
    - Single-agent doxorubicin therapy\(^{32,33}\)
‒ 50%-75% response rate
‒ Median survival of 6-9 months
• Single-agent CCNU therapy
  – ≈40%-50% response rate
  – Median survival of ≈4 months
  – Frontline therapy for canine cutaneous lymphoma
• Prednisone monotherapy
  – ≈50% response rate
  – 1-3 month survival time

The author strongly recommends reviewing the necessary personal protective equipment, administration techniques, and chemotherapy side effects/adverse events before consideration of any chemotherapeutic agent.

Consultation with a board-certified medical oncologist is recommended.

There is not a one-size-fits-all protocol, and new protocols, treatment options, and clinical trials may be available.

New Options

♦ Monoclonal antibody therapy for large T-cell lymphoma
  • This is being used on a clinical trial basis under a conditional USDA license in combination with chemotherapy.
  • AT005, first T-cell biological therapeutic
    – Caninized monoclonal antibody
    – Targeted immunotherapy that specifically recognizes CD-52 expressed on T-Cell
  • No known contraindications for use in T-cell lymphoma.
  • Standard hypersensitivity reactions (eg, vomiting, nausea, cutaneous erythema swelling, pruritus) are uncommon.
  • Efficacy data is pending trial results.
  • Monoclonal antibody therapy for large B-cell lymphoma
  • Canine Lymphoma Vaccine, DNA (merial.com; conditional licensure by USDA)
    – Targeted immunotherapy that specifically recognizes CD20.

  – Therapeutic immunization to be used on achieving remission with chemotherapy.
  – Survival time of vaccinates after completion of 25-week CHOP protocol is >734 days, median not reached, which represents a significant improvement over previously reported historical survival times of 1 year.

Radiation Therapy

♦ The role of radiation therapy in the management of lymphoma remains under investigation, and no protocols are well-established in clinical practice.
  • Discussion with a board-certified radiation oncologist is strongly recommended prior to referral for this modality.
  • Radiation therapy may be used in select cases:
    • Localized (nasal, CNS) or stage I disease (1 node involved)
    • Palliation of local disease (solitary location or refractory node)
    • Whole-body radiation with bone-marrow transplant
    • Staged half-body irradiation after chemotherapy

Costs

♦ Staging test costs are dependent on decision-making between owner and clinician, depending on the degree of work up: $$-$$$$
  • Diagnosis, cytology $$
  • Diagnosis, histopathology $$$
  • Diagnosis, IHC-Flow cytometry $$$

  • Treatment
    • Multi-agent protocol $$$$$
    • Monoclonal therapy $$$$$
    • Single-agent doxorubicin $$$$-
    • Radiation therapy $$$$-
    • Single-agent CCNU $$$
    • Prednisone therapy $
References


