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.

2,4=D = 2,4-dichlorophenoxy-acetic acid

CNS = central nervous system

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.[6]
- 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 *Helicobacter* 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 disease[18]

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 Lymphoma[5]:
  - **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

ALP = alkaline phosphatase

ALT = alanine aminotransferase

CNS = 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

CSF = cerebrospinal fluid

PARR = PCR for Antigen Receptor Rearrangement

PCR = polymerase chain reaction

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[34]
  - ≈40%-50% response rate
  - Median survival of ≈4 months
  - Frontline therapy for canine cutaneous lymphoma[35]
- Prednisone monotherapy[30]
  - ≈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[36]
  - 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[37]
    - 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.[38-40]
- 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.[31]

Radiation Therapy

- The role of radiation therapy in the management of lymphoma remains under investigation, and no protocols are well-established in clinical practice.[41-42]
- 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 $

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

COST KEY

$$$$$ = >$4500
$$$$ = $2001-4500
$$$ = $501-2000
$$ = $251-500
$ = <$250

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