

Lymphoma in Dogs and Cats^a

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KEY WORDS

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- canine
- feline
- chemotherapy

Lymphoma, also known as malignant lymphoma or lymphosarcoma, represents the most common hematologic malignancy in both dogs and cats.¹ The reported incidence ranges from 6 to 24/100,000 cases per year in dogs and 200/100,000 cases per year in cats. The mean age range is 5.5 to 9.1 years for dogs and 2 to 6 years for cats.

There does not appear to be a gender predilection in either species. Breeds at risk include the boxer, basset hound, Saint Bernard, Scottish terrier, Airedale terrier, and bulldog.

ETIOLOGY/RISK FACTORS

Canine lymphoma is considered to be a spontaneous neoplasm. Historically there have been suspicions of a retroviral etiology for the development of lymphoma. These suspicions were largely based on the presence of retroviral particles observed by electron microscopy, the demonstration of viral particles following experimental cellular transmission in beagles, and the identification of reverse transcriptase in supernatant fluids from cell cultures and crude tumor tissue preparations.² However, definitive proof of a viral etiology has not been found to date.

Genetic factors may appear to play a role in the etiology of canine lymphoma based on the breed predilections previously discussed. One family of bullmastiffs in Great Britain was reported to have an uncommonly high risk for the development of lymphoma. Environmental factors have been implicated in the development of non-Hodgkin's lymphoma in humans. The National Cancer Institute published an epidemiologic study in 1991, which suggested that the herbicide 2,4-dichlorophenoxyacetic acid may play a role in the development of lymphoma.³ In this study, dogs were twice as likely to develop lymphoma if

their owners sprayed their lawns with this herbicide four or more times a year.

Certain drugs and immunodeficiency states have been associated with an increased risk of lymphoma in humans. I have seen eight dogs develop lymphoma months to years after the diagnosis of immune-mediated thrombocytopenia. Unfortunately, most of these dogs received long-term azathioprine for the maintenance of remission for their thrombocytopenia. Azathioprine is carcinogenic and has been associated with the development of lymphoma in humans. Therefore it is uncertain whether the development of immune-mediated thrombocytopenia represented a preneoplastic process, the events had no relation, or the azathioprine contributed to the development of lymphoma in this subset of dogs.

Approximately 70% of cats with lymphoma are feline leukemia virus (FeLV) positive. Cats that are FeLV positive are usually less than 7 years old when lymphoma is diagnosed whereas FeLV-negative cats are usually older than 7 years of age when lymphoma is diagnosed. In addition, feline immunodeficiency virus (FIV) may contribute to the development of lymphoma, either secondary to the effects of the virus on immune regulation or possibly by a direct oncogenic mechanism.

FORMS OF PRESENTATION

Canine and feline lymphoma have been historically categorized based on five anatomic presentations as follows.

Multicentric Form

The multicentric form is the most common presentation in dogs, accounting for 84% of lymphoma in the species. It is characterized by lymph node enlargement and is further subclassified based on the presence or absence of systemic signs and stage of disease (see box on p. 110). Most dogs are asymptomatic at the time of presentation. Clinical signs may include lethargy, anorexia, weight loss, polyuria/polydipsia, vomiting, and abdominal distention. Physical examination reveals lymphadenopathy. The lymph nodes are typically 2 to 10 times their normal size, irregular, freely movable, firm, and nonpainful. Hepatosplenomegaly is common.

Cats uncommonly present with this form of lymphoma, although the prevalence varies geographically. A generalized lymphadenopathy resembling lymphoma has been reported in cats; in one report, five of six cats were evaluated for disease outcome and exhib-

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**CLINICAL STAGING OF CANINE
MULTICENTRIC LYMPHOMA^a**

Stage	Disease Extent
Stage I	Involvement limited to a single lymph node
Stage II	Involvement of more than one lymph node within the same side of the diaphragm
Stage III	Generalized lymph node involvement
Stage IV	Hepatic and/or splenic involvement
Stage V	Involvement of the blood or bone marrow

^aEach stage is further subclassified as (a) without systemic signs or (b) with systemic signs.

ited lymph node regression without treatment within 1 to 17 weeks.⁴ The etiology of this disease process is uncertain; however, there is some suggestion of an immune response to viral or chemical antigens. Lymph node biopsies from affected cats are similar to those from cats with lymphoma except for a lack of anaplastic changes, low rate of mitotic activity, abundant nodal vascularity, primary and secondary follicles with active germinal centers, and lack of capsular invasion.

Alimentary Form

The alimentary form—characterized by gastric, intestinal, or mesenteric lymph node involvement⁵—is the second most common form of lymphoma in dogs and one of the most common forms in cats. Gastrointestinal lymphoma may present in the form of either a solitary mass lesion or as a diffuse infiltration of large areas of bowel. Clinical signs are generally nonspecific and include anorexia, vomiting, and diarrhea. The onset of signs is extremely variable, ranging from days to years. The development of gastrointestinal lymphoma in animals previously diagnosed with lymphoplasmacytic gastroenteritis has been reported. Gastrointestinal lymphoma typically involves the submucosa, and therefore full thickness biopsies may be necessary to confirm a diagnosis. Most cats with alimentary lymphoma are FeLV negative.

Mediastinal Form

The mediastinal form is characterized by enlargement of the cranial or caudal mediastinal lymph node.

It is the third most common form of presentation in dogs and one of the most common in cats. Most cats with mediastinal lymphoma are young and FeLV positive. Clinical signs may include dyspnea, exercise intolerance, and coughing secondary to the presence of pleural effusion or due to direct compression of the trachea by the presence of the mediastinal mass. This form is often associated with hypercalcemia in dogs.

Cutaneous Form

Cutaneous lymphoma is an infrequent form of presentation in dogs and is extremely rare in cats. Lesions may be solitary or multiple and vary in appearance from erythematous plaques and nodules to patches of alopecia and scaling. There are two main forms of cutaneous lymphoma recognized in the dog: (1) epitheliotropic lymphoma (mycosis fungoides), which is usually of T-lymphocyte origin and in which mucosal lesions are common, and (2) nonepitheliotropic lymphoma, which generally affects the middle and deep dermis and which is typically of B-cell origin. Lymph node involvement is more likely, and systemic involvement occurs in approximately 80% of dogs within 0.5 to 5 years. The prognosis for long-term survival is poorer with this form of cutaneous lymphoma. Cutaneous lymphoma typically occurs in older FeLV-negative cats.

Extranodal Form

The extranodal form includes all lymphomas that do not fall into any of the preceding categories and accounts for approximately 4% and 5% of lymphoma in dogs and cats, respectively. Ocular, neural, renal, and cardiac forms are the most common sites of involvement.

DIAGNOSIS

The minimum data base obtained from a dog suspected of having lymphoma should include a complete blood count (CBC), biochemistry profile, and urinalysis. Clinicopathologic abnormalities are often varied and nonspecific. Frequently detected abnormalities include the presence of atypical or immature lymphocytes, neutrophilia, thrombocytopenia, anemia, red blood cell fragments, and leukopenia. The finding of peripheral cytopenias warrants a bone marrow biopsy to differentiate myelophthisis from peripheral destruction, which may dictate the appropriate chemotherapy protocol to use. Increased liver enzyme activity, hypercalcemia, hypoglycemia, hyperproteinemia, and azotemia are occasionally detected.

Radiographic changes detected in dogs with lymphoma may include sternal, tracheobronchial, sublum-

INDUCTION PROTOCOLS FOR CANINE LYMPHOMA

COAP Protocol

Cyclophosphamide (Cytoxan®—Bristol-Myers Squibb Oncology): 50 mg/m² BSA PO every other day for 8 weeks
 Vincristine (Oncovin®—Eli Lilly and Company): 0.5 mg/m² BSA IV once a week for 8 weeks
 Cytosine arabinoside (Cytosar-U®—Upjohn): 100 mg/m² BSA IV or SQ divided bid for 4 days
 Prednisone: 40–50 mg/m² BSA PO sid for 1 week; then 20–25 mg/m² BSA PO every other day for 7 weeks

COP Protocol

Cyclophosphamide (Cytoxan®—Bristol-Myers Squibb Oncology): 50 mg/m² BSA PO every other day for 8 weeks
 Vincristine (Oncovin®—Eli Lilly and Company): 0.5 mg/m² BSA IV once a week
 Prednisone: 40–50 mg/m² BSA PO sid for 1 week; then 20–25 mg/m² BSA PO every other day

CLOP Protocol

COP + L-asparaginase (Elspar®—Merk & Co.): 10,000–20,000 IU/m² BSA SQ once every 4 weeks

CHOP Protocol

Cyclophosphamide (Cytoxan®—Bristol-Myers Squibb Oncology): 100–150 mg/m² BSA IV day 1
 Doxorubicin (Adriamycin®—Pfizer): 30 mg/m² BSA IV day 1
 Vincristine (Oncovin®—Eli Lilly and Company): 0.75 mg/m² BSA IV days 8 and 15
 Prednisone: 40–50 mg/m² BSA PO sid days 1–7; then 20–25 mg/m² BSA PO every other day for days 8–21

BSA = body surface area.

bar, or mesenteric lymphadenopathy, pleural effusion, pulmonary infiltrates, or hepatosplenomegaly. The extent of involvement is generally dependent on the form of presentation. Bone marrow biopsy and radiographic evaluation of the chest and abdomen are helpful to adequately stage the disease.

The diagnosis of lymphoma can be suggested by a fine-needle aspirate of the lymph nodes or abdominal or thoracic masses or by evaluation of any effusions that may be present. Accurate histologic classification

INDUCTION PROTOCOLS FOR FELINE LYMPHOMA

COAP Protocol

Cyclophosphamide (Cytoxan®—Bristol-Myers Squibb Oncology): 300 mg/m² BSA PO every 3 weeks
 Vincristine (Oncovin®—Eli Lilly and Company): 0.5 mg/m² IV once a week for 6 weeks
 Cytosine arabinoside (Cytosar-U®—Upjohn): 100 mg/m² IV or SQ divided for 2 days
 Prednisone: 40–50 mg/m² BSA PO sid for 1 week; then 20–25 mg/m² BSA PO every other day for 5 weeks

COP Protocol

Cyclophosphamide (Cytoxan®—Bristol-Myers Squibb Oncology): 300 mg/m² BSA PO every three weeks
 Vincristine (Oncovin®—Eli Lilly and Company): 0.5 mg/m² BSA IV once a week
 Prednisone: 40–50 mg/m² BSA PO sid for 1 week; then 20–25 mg/m² BSA PO every other day

BSA = body surface area.

can only be determined with lymph node biopsies. When performing a lymph node biopsy, it is important to obtain an entire lymph node. The popliteal and prescapular lymph nodes are preferred.

CLASSIFICATION

A variety of attempts have been made to categorize lymphoma in an effort to predict response to therapy and survival. There are four general classification systems: the Lukes-Collins, Rappaport, Kiel, and the Working Formulation.⁶ The Working Formulation is the most recent system and was devised to allow a common classification system among researchers. The Lukes-Collins system takes into consideration architectural, histocytologic, and immunologic aspects while the Rappaport, Kiel, and Working Formulation systems take only cell type and architecture into consideration. The predominant cell type differs depending on which classification system is used. To date, none of the systems is effective in predicting the response to therapy, survival time, or length of remission. Most lymphomas in dogs are high grade and immunoblastic. High grade lymphomas are more chemoresponsive than low grade lymphomas and are associated with poorer survival times.

MAINTENANCE PROTOCOLS**LP Protocol**

Chlorambucil (Leukeran®—Glaxo Wellcome): 20 mg/m² BSA PO every other week
 Prednisone: 20–25 mg/m² BSA PO every other day

LMP Protocol

Chlorambucil (Leukeran®—Glaxo Wellcome): As above
 Prednisone: As above
 Methotrexate: 2.5–5 mg/m² BSA PO 2–3 times a week

COP Protocol

COP protocol used every other week for 6 cycles and once a month thereafter

BSA = body surface area.

RESCUE PROTOCOLS**If Animal Relapses on LMP Maintenance Protocol**

Add vincristine (Oncovin®—Eli Lilly and Company): 0.5 mg/m² IV every 7 days

D-MAC Protocol

Day 1: Dexamethasone: 0.5 mg/lb PO or SQ
 Actinomycin: 0.75 mg/m² IV push
 Cytosine arabinoside: 200 mg/m² IV drip over 4 hours

Day 8: Dexamethasone: 0.5 mg/lb PO
 Melphalan 20: mg/m² PO

ADIC Protocol

Doxorubicin: 30 mg/m² BSA IV every 3 weeks
 Dacarbazine (DTIC): 1 g/m² BSA IV drip for 6–8 hours every 3 weeks

BSA = body surface area.

THERAPY

Lymphoma is considered a systemic disease and therefore requires systemic chemotherapy to achieve long-term survival. A number of chemotherapeutic protocols are described in the literature,^{7–10} but none is consistently better than others. Most researchers, however, agree that combination chemotherapy is superior to single agent therapy with the exception of single agent doxorubicin. Extent of disease, presence of cytopenias or other paraneoplastic syndromes, patient cooperation, owner availability, and financial aspects should all be taken into consideration when choosing a chemotherapeutic protocol.

Response rates and duration depend on the extent of disease. Most combination chemotherapeutic protocols used to treat dogs with multicentric lymphoma result in an 80% to 85% probability of attaining a complete remission for an average of 10 months. In cats, FeLV status also plays a role in response rate and duration. Combination chemotherapy protocols in cats are not as effective as they are in dogs. Only 60% to 70% of cats exhibit a complete response to combination chemotherapy, with a median survival time of only 5 to 7 months.

Both dogs and cats tolerate chemotherapy quite well. Dose-limiting adverse effects are primarily gastrointestinal and hematologic in the form of myelosuppression. In general a CBC should be performed prior to every intravenous chemotherapeutic injection.

Neutrophil counts should be greater than 2000/ μ l prior to the administration of drug. If the neutrophil count is less than 2000/ μ l and the animal is nonfebrile, it is best not to treat at this time. Instead, have the owners monitor the animal for lethargy and anorexia, wait 2 days, and then repeat the CBC. If the animal is neutropenic and febrile, emergency treatment for potential sepsis is indicated.

The three general phases of treatment for lymphoma include the induction of remission, maintenance of remission, and rescue.

During induction of remission, an aggressive therapeutic approach is used in an effort to destroy the majority of tumor cells, thereby producing a clinical remission (see boxes on p. 111). Clinical remission is not synonymous with cure but rather is defined as disappearance of all clinically detectable tumor. Many induction periods last 8 to 10 weeks. If the patient is in complete remission, maintenance therapy is then initiated.

The purpose of maintenance therapy is to continue exposing the tumor cells to chemotherapeutic agents. Its goals are to minimize toxicity and to maintain remission for as long as possible. A variety of maintenance protocols are available (see box on left on p. 112). During this phase, I recommend teaching owners how to palpate their animals' lymph nodes for evidence of enlargement and reevaluate the animals every 4 to 6 weeks. An animal receives maintenance therapy until gastrointestinal toxicity occurs, its dis-

ease relapses, or it has been on the regimen for more than 2 years.

In most cases, the disease relapses while the animal is receiving maintenance therapy, at which point rescue therapy is indicated. The purpose of a rescue protocol is to reinduce remission, and a number of protocols are available (see box on right on p. 112). Unfortunately, the reinduction of remission is not as successful and response durations tend to be short.

PROGNOSIS/SURVIVAL TIMES

Numerous efforts have been made to determine prognostic factors and treatment responses for dogs with lymphoma. Although these reports are often conflicting, it has been suggested that dogs with stage I lymphoma have longer survival times and remission durations. Younger dogs and those weighing less than 15 kg may also have longer survival times. Neutered females have a tendency to have longer survival, whereas intact females exhibit the poorest survival times. Sequential combination chemotherapy protocols that include doxorubicin have improved remission duration and survival compared to protocols that do not use doxorubicin. Animals with immunoblastic lymphomas have longer remission durations compared to those with other forms when treated with doxorubicin or COP. Dogs with pretreatment hypoalbuminemia may have shorter remissions. Historically, it has been suggested that dogs with hypercalcemia

have a poorer prognosis; in a more recent study, however, the only significant factor associated with the survival of dogs with lymphoma was the presence of a mediastinal mass. Hypercalcemic dogs with a mediastinal mass had an average survival of only 3 months versus 8 months when no mass was present.

The prognosis and treatment outcomes reported for cats vary with the anatomic site, geographic location, FeLV status, presence of azotemia, and presence of cytopenias. The average median survival for FeLV-negative cats regardless of anatomic location is 9 months versus 4.2 months for FeLV-positive cats.

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