Alimentary Lymphoma in Cats and Dogs

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FELINE ALIMENTARY LYMPHOMA

Lymphoma is the most common feline malignancy, and the gastrointestinal (GI) tract is the most common location for this disease.\(^1\) Alimentary lymphoma may affect the upper or lower GI tract, liver, or pancreas, and is characterized by infiltration with neoplastic lymphocytes with or without mesenteric lymph node involvement. Lymphoma can be divided histopathologically into small cell (lymphocytic [LL]; low grade; well differentiated) or large cell (lymphoblastic [LBL]; high grade) types. At one institution, feline GI lymphoma was equally divided among those types,\(^2\) but in another study LL occurred 3 times more often than LBL.\(^3\) Large granular lymphoma (LGL) is a subtype that is characterized by the presence of natural killer T lymphocytes that have characteristic intracytoplasmic granules.\(^4,5\) Clinically these types of lymphoma are distinct entities with different clinical presentations, therapies, and outcomes.

Etiology and Pathogenesis

Although infection with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are major risk factors for the development of lymphoma, cats with GI lymphoma are usually negative for both viruses.\(^1,2\) Helicobacter infection may play a role in the development of feline GI lymphoma.\(^6\) In one study, gastric biopsy samples from 16 of 24 cats with lymphoma were positive for Helicobacter heilmannii. The potential importance of this infection is that eradication of the bacteria with antibiotics may resolve or hinder the progression of the underlying neoplasm. Exposure to cigarette smoke is another risk factor for development of lymphoma in cats. Cats living in households with any exposure to cigarette smoke have a 2.4-fold increased risk of developing lymphoma than cats from nonsmoking households, and the amount and duration of exposure is linearly correlated with increasing risk of lymphoma development.\(^7\)
Signalment, History, and Physical Examination

Alimentary lymphoma has been reported in cats ranging in age from 1 to 20 years (median 13 years), with most cats being middle-aged to older.¹

Lymphocytic lymphoma is typically a slowly progressive disease with a protracted history (Table 1). In one study, the median duration of clinical signs of illness before diagnosis was 6 months.⁸ Clinical signs included weight loss, vomiting, diarrhea, anorexia or hyporexia, and lethargy.² Physical examination findings in cats with LL may be unremarkable or can reveal diffusely thickened intestinal loops, a mass lesion consisting of mesenteric lymph nodes, and/or an intramural intestinal mass.²

Lymphoblastic lymphoma is most often characterized by an acute onset of weight loss, vomiting, diarrhea, anorexia or hyporexia, and icterus if concurrent liver involvement is present (see Table 1). The physical examination often reveals dehydration,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Lymphocytic versus lymphoblastic lymphoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical signs of illness</strong></td>
<td>Gradual weight loss, vomiting, diarrhea, decreased appetite</td>
</tr>
<tr>
<td><strong>Duration of clinical signs</strong></td>
<td>Typically prolonged (weeks to months)</td>
</tr>
<tr>
<td><strong>Physical examination findings</strong></td>
<td>May be normal; thickened bowel loops; palpable masses uncommon</td>
</tr>
<tr>
<td><strong>Diagnostic workup</strong></td>
<td>Rule out non-GI causes of weight loss; endoscopy versus full-thickness surgical biopsy required for definitive diagnosis</td>
</tr>
<tr>
<td><strong>Pitfalls of diagnostic testing and therapy</strong></td>
<td>False negatives common when enlarged mesenteric lymph nodes are aspirated; histopathology to differentiate from inflammatory bowel disease can be challenging</td>
</tr>
<tr>
<td><strong>Surgical intervention</strong></td>
<td>Useful to obtain samples for diagnosis</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Oral chemotherapy: prednisone and chlorambucil; radiation therapy may be useful to prolong survival</td>
</tr>
<tr>
<td><strong>Response to therapy</strong></td>
<td>75%–90% response rate</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Most cats live &gt;2 years and are managed long term with chemotherapy</td>
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hepatomegaly, an abdominal mass consisting of mesenteric lymph nodes or an intramural mass, and/or diffusely thickened intestinal loops.³

**Diagnosis of Lymphoma**

Lymphoma should be suspected in cats with thickened intestinal loops, mesenteric lymphadenopathy, intestinal masses, or multicentric organ infiltration. For cats with a history of gastrointestinal illness, weight loss, or hyporexia/anorexia, a thorough workup to identify primary and concurrent diseases is indicated. Baseline bloodwork including a complete blood count (CBC), chemistry panel, thyroid function testing, and urinalysis is essential. Testing for FeLV and FIV is generally indicated in any sick cat. For cats with suspected neoplasia, 3-view (ventrodorsal or dorsoventral, right and left lateral views) thoracic radiographs should be obtained to rule out gross metastatic disease. Abdominal radiography can be helpful to evaluate cats for the presence of abdominal masses, GI outflow tract obstruction, organomegaly, and constipation. Abdominal ultrasonography is indicated to evaluate intestinal wall thickness, to document the presence of GI outflow tract obstructions, to identify mass lesions and changes in liver/spleen parenchyma, and to evaluate mesenteric lymph nodes.

CBC abnormalities in cats with GI lymphoma may include anemia (usually nonregenerative anemia of chronic disease or regenerative anemia secondary to intestinal blood loss) and neutrophilia (secondary to inflammation, neoplasia, or stress). Biochemical abnormalities may include hypoalbuminemia and/or panhypoproteinemina secondary to intestinal loss; in one study, 49% of cats with LL and 50% of cats with LBL were hypoalbuminemic.³ Increased liver enzymes may indicate hepatic lymphoma or concurrent liver disease (hepatic lipidosis, cholangiohepatitis). Bone marrow aspiration and cytology is recommended as part of systemic staging for lymphoma in cats that are FeLV positive or in cats with cytopenias or circulating malignant lymphocytes. Polymerase chain reaction (PCR) of the bone marrow for detection of FeLV should be considered if a bone marrow aspirate is obtained.

Because the ileum is the sole site of cobalamin (vitamin B12) absorption, low serum cobalamin concentrations support a diagnosis of primary intestinal disease in cats with normal exocrine pancreatic function. In addition, determination of serum feline pancreatic lipase immunoreactivity may be useful, as the clinical signs of feline pancreatitis may be difficult to distinguish from those of GI lymphoma.

Ultrasound findings in cats with LL are usually indistinguishable from those with inflammatory bowel disease (IBD), and consist of normal or increased intestinal wall thickness with preservation of intestinal layers.²⁹ Mesenteric lymphadenopathy, intestinal intussusceptions, or distinct intramural mass lesions may also be noted. In a recent study evaluating differences in ultrasound findings between cats with LL versus IBD, thickening of the muscularis propria was present in 12.5% of normal cats, 4.2% of cats with IBD, and 48.4% of cats with LL.¹⁰ Cats with lymphoma were 18 times more likely to have a thickened muscularis layer than were cats with IBD (Figs. 1 and 2). Mesenteric lymphadenopathy was present in 47% of cats with LL and 17% of cats with IBD. Of the cats with lymphoma, 26% had both muscularis thickening and lymphadenopathy, whereas only 1 of 24 cats with IBD had this combination of findings. In another study of 16 cats with LL, mesenteric lymphadenopathy was present on ultrasonography in 12 cats, diffuse small intestinal wall thickening in 9, and a focal intestinal mass in 1.² The diagnostic value of cytologic evaluation of an ultrasound-guided aspiration of enlarged mesenteric lymph nodes for confirmation of LL was reported to be questionable: benign lymphoid hyperplasia was diagnosed in 9 of 12 cats with LL and abdominal lymphadenopathy. However, when surgical
biopsies were obtained of the affected lymph nodes, lymphoma was confirmed in 8 of 9 cases.²

Ultrasound findings in cats with LBL may include transmural intestinal thickening, disruption of normal wall layering, reduced wall echogenicity, localized hypomotility, abdominal lymphadenomegaly, and mass lesions (Fig. 3).¹⁰ Concurrent liver involvement may also be present, as evidenced by a hyperechoic or hypoechoic liver. Pancreatic and splenic involvement may also be noticed. The presence of diffuse echogenicity changes and/or nodular lesions in these organs supports possible infiltration with lymphoma.¹⁰

The optimal approach to definitively diagnosing feline GI lymphoma varies among clinicians. Fine-needle aspiration and cytology of intestinal masses, enlarged mesenteric lymph nodes, or the liver may be diagnostic for lymphoma, and are relatively noninvasive and rapid diagnostic methods. However, the presence of inflammation and/or lymphoid reactivity may hinder a definitive diagnosis, and histopathology of

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**Fig. 1.** Abdominal ultrasonogram of a cat with lymphocytic lymphoma (LL). The hypoechoic small intestinal muscularis layer is diffusely thickened. Although this change is not specific, it has been reported to occur more frequently in cats with LL as well as in cats with IBD. (Courtesy of Dr L. Gaschen, Louisiana State University.)

**Fig. 2.** Moderately thickened jejunal segment with transmural loss of layering in an older cat with lymphocytic lymphoma. (Courtesy of Dr L. Gaschen, Louisiana State University.)
tissue biopsies may be necessary to confirm the diagnosis of lymphoma. Controversy exists regarding whether endoscopically or surgically obtained intestinal biopsies are most helpful to differentiate feline IBD from GI lymphoma.

**Surgically versus endoscopically obtained intestinal biopsies**

The obvious advantage of surgically obtained biopsies is that they are transmural and therefore include all of the layers of the GI tract, allowing the pathologist to evaluate the disease process thoroughly. In addition, the clinician can obtain biopsies of the mesenteric lymph nodes, liver, and pancreas during the laparotomy. Disadvantages of surgery include longer anesthesia time and a more invasive procedure followed by a period of wound healing in an often debilitated cat. In a recent study of 43 cats with chronic signs of illness related to the GI tract, full-thickness biopsies were obtained.11 Twenty-three percent of cats were diagnosed with LL; the majority of cats had IBD (46.5%), and fewer cats had fibrosis (9.3%), gastritis (7%), lymphangiectasia (7%), and mast cell tumors (4.7%).

In a study of 17 cats with LL diagnosed via full-thickness GI biopsies, lymphoma was detected in the stomach (33%), duodenum (83%), jejunum (100%), ileum (93%), mesenteric lymph nodes (59%), liver (27%), colon (20%), and pancreas (7%); however, not all sites were biopsied in all cats.2 All but one cat had lymphoma present in multiple biopsied sites and in 4 cats, IBD was present in other parts of the intestinal tract. Concurrent GI tract diseases including chronic pancreatitis (n = 1), neutrophilic cholangitis (n = 1), and hepatic lipidosis (n = 1) were also diagnosed.

The advantage of endoscopic biopsy is that it is a less invasive, shorter procedure that is often better suited to a critically ill feline than is exploratory laparotomy. Furthermore, it allows visualization of the mucosa, which helps to identify the best sites for collection of biopsies. The skills and persistence of the endoscopist are critical in obtaining diagnostic samples. In a recent study,12 “marginal” duodenal biopsy samples were defined as samples with the presence of at least one villus plus subvillous lamina propria, and “adequate” samples had at least 3 villi and subvillous lamina propria that extended to the muscularis mucosa. If 6 marginal or adequate samples of the feline stomach or duodenum were obtained, the correct histologic diagnosis was very likely to be achieved. Once endoscopic biopsies are obtained, sample handling to properly orient the samples for the pathologist is critical for optimal interpretation.

The disadvantage of endoscopy is that biopsies are limited to the gastric, duodenal, ileal, and colonic mucosa. In addition, detection of lymphoma in deeper tissues...
(submucosal/muscularis/serosal layers) is often difficult because of the limited depth of the biopsy specimen. A study of 22 cats (12 with IBD and 10 with LL) examined differences in histopathology results between endoscopic biopsy samples that had been collected immediately before exploratory laparotomy and full-thickness GI biopsy specimens collected during the surgical procedure.\textsuperscript{13} Of the 10 cats diagnosed with LL, full-thickness surgical biopsies revealed jejunal and ileal involvement, and 9 of 10 had duodenal involvement. Lymphoma was also detected in the mesenteric lymph nodes, the liver, or both. Evaluation of gastric biopsies revealed no significant difference in the ability to diagnose lymphoma between full-thickness and endoscopically obtained biopsies. Because the pylorus could not be passed in 8 of 22 cats because of the large size of the endoscope (chosen in an attempt to obtain large biopsy specimens), one-third of the duodenal biopsies had to be obtained blindly (with collection of only 3 samples per cat). When comparing the method used to obtain duodenal samples, 9 cats were diagnosed with LL via full-thickness biopsies and only 1 was definitively diagnosed via endoscopy. The study clearly demonstrates that the suboptimal endoscopic technique has a significant impact on the diagnostic accuracy of the method; however, it does not evaluate the diagnostic value of a thorough duodenoscopy with sampling of adequate numbers of good-quality samples. Overall, it underscores the fact that the quality of the endoscopist’s work significantly influences the diagnostic value of upper GI endoscopy.

In some veterinary clinics, the use of laparoscopy has largely replaced the need for laparotomy.\textsuperscript{14} This less invasive technique has many of the advantages of laparotomy, with a significantly shorter recovery period.

**Histopathologic evaluation of biopsy specimens**

Histologically, IBD is characterized by a diffuse infiltration of various proportions of lymphocytes, plasma cells, eosinophils, neutrophils, and/or macrophages that are primarily found in the mucosal layer of the intestine. Lymphoma causes mucosal infiltration by neoplastic lymphocytes that are often irregularly distributed between and among intestinal villi, with frequent progression to submucosal and transmural infiltration (Fig. 4).\textsuperscript{11,15} Lymphoma is not associated with mucosal edema or inflammation that typically occurs with IBD.\textsuperscript{2,3} LL and LGL typically consist of T cells, and LBL

![Fig. 4.](image_url) Section of the duodenal mucosa of an 11-year-old male neutered Siamese cat with an 8-month history of chronic diarrhea and intermittent vomiting. There is villus blunting, and the lamina propria is expanded by small neoplastic lymphocytes (hematoxylin-eosin stain, original magnification \( \times 100 \)). (Courtesy of Dr N. Wakamatsu, Louisiana State University.)
consists of B cells. \textsuperscript{2,8} Epitheliotropic intestinal lymphoma (EIL) is a subset of LL that is characterized by infiltration of malignant T cells into the mucosal epithelium of the intestinal tract. \textsuperscript{9} In one study, \textsuperscript{2} evidence of concurrent IBD was diagnosed in 3 of 19 cats diagnosed with LL.

The use of immunohistochemistry (IHC) for B-cell and T-cell markers may help to distinguish IBD from LL because cats with lymphoma should have a monoclonal population of B or T lymphocytes (Fig. 5). In one study, of 32 cats diagnosed with LL based on routine hematoxylin-eosin stains, 16\% of cases were reclassified as having IBD, based on a mixed population of B and T cells and plasma cells after IHC was performed. \textsuperscript{15} Immunohistochemistry results may be difficult to interpret because staining techniques and the antibodies used vary among laboratories, and there is often inconsistent stain uptake in cells of an individual tumor and between tumors from the same species. Also, the presence of T lymphocytes alone is not diagnostic for lymphoma because of MALT (mucosal-associated lymphoid tissue), which consists primarily of T cells and is expanded in cases of intestinal inflammation.

The use of PCR may be useful to confirm the diagnosis of GI lymphoma, because detection of a clonal expansion of either B or T lymphocytes would be diagnostic for lymphoma, while a mixed population of lymphoid cells supports a diagnosis of IBD. In a study of intestinal biopsies from 28 cats with intestinal T-cell lymphoma diagnosed by light microscopy and IHC, 22 had clonal rearrangements of their T-cell receptor gamma genes; this is in contrast to a polyclonal arrangement of receptors in 9 cats with IBD. \textsuperscript{16}

\textit{Treatment Options and Prognosis for Cats with Lymphoma}

Surgery for cats with obstructing GI masses is indicated to relieve the obstruction and discomfort associated with the mass. Complete resection may not be possible in some cases, however, and dehiscence of the anastomosis site must be considered as a possible complication. Surgical excision of intestinal masses should be followed by biopsy of other parts of the GI tract, liver, pancreas, and mesenteric lymph nodes, because it is rare to have a solitary mass of lymphoma with no concurrent organ involvement. Postoperative chemotherapy is indicated because lymphoma is almost always considered a multicentric disease, but a gold-standard protocol does not exist. Selection of a chemotherapy protocol depends on the type of lymphoma (lymphocytic

\textbf{Fig. 5.} Same biopsy as in \textbf{Fig. 4.} The majority of neoplastic cells stain positive for CD3. Diagnosis: T-cell lymphoma, LL (CD3 immunohistochemistry, original magnification $\times 100$). (Courtesy of Dr N. Wakamatsu, Louisiana State University.)
vs lymphoblastic), as well as patient-associated factors such as finances, ability to medicate the cat, and ability to return for rechecks. In general, cats with LL have better responses to therapy and longer survival times than those with LBL. In one study of cats with alimentary lymphoma treated with various chemotherapy protocols, 50 cats with LL had a complete response (CR) rate of 69% and a median survival time (MST) of 17 months as compared with an 18% CR rate and an MST of 3 months for 17 cats with LBL.³

Lymphocytic lymphoma is typically a slowly progressive disease, and chlorambucil, a chemotherapeutic agent that targets slowly dividing lymphocytes, is used along with steroids such as prednisone or prednisolone (Table 2). There is some debate about whether chlorambucil should be administered as a bolus dose (a single large dose every 3 weeks) or every other day continuous dosing. Because cats will potentially be treated with chlorambucil for several months to year(s), the clinician must determine a therapeutic plan that is suitable for both the cat and the client. The potential advantages of the bolus-dosing regimen include (1) less owner exposure to chemotherapy and (2) less continuous exposure of the cat to chemotherapy.¹⁷

In one study of 42 cats with LL treated with prednisone (5–10 mg orally [PO] every 24 h) and chlorambucil (2 mg PO every 48–72 h), there was an overall response rate of 95% with a 56% CR rate (ie, 100% resolution of clinical signs and detectable tumor) and 39% partial response (PR) rate (ie, >50% but <100% decrease in the amount of measurable disease).⁸ For cats achieving a CR to therapy, the median remission duration was 897 days as compared with 428 days for cats achieving a PR. Twelve cats died of lymphoma during the study period (median follow-up time of 476 days). Overall, the MST of affected cats was 704 days. In another study of 17 cats with LL treated with either prednisone (1–2 mg/kg PO every 24–48 hours) and chlorambucil (15 mg/m² PO every 24 hours for 4 consecutive days every 3 weeks) or a multidrug injectable chemotherapy protocol (including vincristine, cyclophosphamide, doxorubicin, and L-asparaginase), the CR rate was 76% with a median remission duration of 19 months (range, 3.5–73 months).²

In one study of 28 cats with LL (24 were diagnosed via full-thickness biopsy) treated with prednisone and chlorambucil, the clinical response rate was 96%.¹⁷ In this study, IHC confirmed that 94% of cases were of T-cell origin. Rescue therapy with cyclophosphamide was successful in 7 of 9 cats that developed recurrence of clinical signs of their disease during treatment with chlorambucil (complete restaging was not always performed). The median duration of clinical remission was 786 days. Of interest, 4 of 28 cats developed a second, unrelated malignancy.

There are few studies that address rescue chemotherapy for cats with LL, because many cats do not develop clinical relapse and survival times are typically long (Table 3). Cyclophosphamide has been used as a rescue therapy, with good responses.¹⁷ Other drugs typically used to treat LBL including (but not limited to) vincristine, vinblastine, doxorubicin, and L-asparaginase could be used to attempt reinduction of clinical remission. Additional considerations for cats with recurrent clinical signs include repeat staging (ultrasonography, endoscopy) to look for new concurrent diseases and/or the progression of LL to the lymphoblastic form; this has not been well described, however.

Because cats with LBL are often severely ill at the time of diagnosis, intensive supportive care in addition to chemotherapy is warranted. This treatment may include intravenous (IV) fluid therapy, blood products, IV antibiotics, and enteral or parenteral nutrition. For cats with LBL, multidrug protocols are the most widely studied, and COP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone ± L-asparaginase ± methotrexate) based protocols
<table>
<thead>
<tr>
<th>Chlorambucil Dose (PO)</th>
<th>Prednisone Dose (PO)</th>
<th>Response Rate</th>
<th>Median Response Duration (months)</th>
<th>Median Survival Time (months)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg every 48–72 h</td>
<td>5 or 10 mg/cat/d</td>
<td>56% CR</td>
<td>30 mo if CR</td>
<td>14 mo if PR</td>
<td>n/a</td>
<td>8</td>
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<tr>
<td></td>
<td></td>
<td>39% PR</td>
<td></td>
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<td></td>
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<tr>
<td>15 mg/m² every 24 h</td>
<td>3 mg/kg every 24 h</td>
<td>76% CR</td>
<td>19 mo</td>
<td>19 mo if CR; 4 mo if not CR</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>x 4 d every 3 wk</td>
<td>then 1–2 mg/kg when remission is achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg/m² every 24 h</td>
<td>3 mg/kg every 24 h</td>
<td>69% CR</td>
<td>16 mo</td>
<td>17 mo overall; 23 mo if CR</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>x 4 d every 3 wk</td>
<td>then 1–2 mg/kg when remission is achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/m² every 2 wk</td>
<td>Variable</td>
<td>96% CR</td>
<td>26 mo</td>
<td></td>
<td>Good response to cyclophosphamide when clinical relapse occurred</td>
<td>17</td>
</tr>
<tr>
<td>(round to nearest 2 mg tablet size)</td>
<td></td>
<td></td>
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</table>

*Abbreviations*: CR, complete response (100% of clinically evident disease resolved); n/a, no data available; PO, by mouth; PR, partial response (>50% but <100% of clinically evident disease resolved).
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Response Rate</th>
<th>Median Response Duration (months)</th>
<th>Median Survival Time (months)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>18% CR</td>
<td>n/a</td>
<td>2.7 mo</td>
<td>Part of a larger study comparing lymphocytic and lymphoblastic alimentary lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>COP</td>
<td>75% CR</td>
<td>8 mo</td>
<td>9 mo</td>
<td>If CR, 51% clinical remission rate at 1 y and 38% at 2 y; cats that did not achieve CR usually did not live 1 y</td>
<td>26, a, b</td>
</tr>
<tr>
<td>COP</td>
<td>32% CR</td>
<td>7 mo if CR</td>
<td>n/a</td>
<td>If CR, 51% clinical remission rate at 1 y and 38% at 2 y; cats that did not achieve CR usually did not live 1 y</td>
<td>32, a</td>
</tr>
<tr>
<td>COP or COP then</td>
<td>n/a</td>
<td>3 mo if COP; 9 mo if COP then</td>
<td>n/a</td>
<td>Study comparing COP to doxorubicin maintenance therapy</td>
<td>18, a, b</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>n/a</td>
<td>3 mo if COP; 9 mo if COP then</td>
<td>n/a</td>
<td>Study comparing COP to doxorubicin maintenance therapy</td>
<td>18, a, b</td>
</tr>
<tr>
<td>CVM</td>
<td>52%</td>
<td>4 mo</td>
<td>n/a</td>
<td>Addition of prednisone and l-asparaginase did not improve results</td>
<td>24, a, b</td>
</tr>
<tr>
<td>CVM-L</td>
<td>62% CR</td>
<td>7 mo if CR</td>
<td>n/a</td>
<td>Cats with minimal response to therapy: MST 1.5 mo; FeLV + worse prognosis; cats with stages I and II lymphoma had a better prognosis</td>
<td>23, a, b</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>42%</td>
<td>Median 2 mo; 3 mo if CR</td>
<td>n/a</td>
<td>Cats with CR to therapy and FeLV-negative cats have a better prognosis</td>
<td>19, a, b</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>22% response</td>
<td>n/a</td>
<td>n/a</td>
<td>Doxorubicin used as a rescue therapy; small cell lymphoma and cats receiving drugs in addition to doxorubicin were more likely to respond to therapy; not thought to be an effective rescue therapy</td>
<td>33, a, b</td>
</tr>
<tr>
<td>CHOP-L-M</td>
<td>47% CR</td>
<td>22 mo if CR</td>
<td>22 mo if CR</td>
<td>Cats with CR to therapy and FeLV-negative cats have a better prognosis</td>
<td>27, a, b</td>
</tr>
<tr>
<td>CHOP-L-M</td>
<td>37% PR</td>
<td>22 mo if CR</td>
<td>22 mo if CR</td>
<td>Cats with CR to therapy and FeLV-negative cats have a better prognosis</td>
<td>27, a, b</td>
</tr>
<tr>
<td>CHOP-L-M</td>
<td>n/a</td>
<td>4 mo if PR</td>
<td>4 mo if PR</td>
<td>Longer duration of first remission resulted in longer survival time</td>
<td>25, a</td>
</tr>
<tr>
<td>CHOP-L-M</td>
<td>74% CR</td>
<td>4 mo if CR</td>
<td>4 mo if PR</td>
<td>Longer duration of first remission resulted in longer survival time</td>
<td>25, a</td>
</tr>
<tr>
<td>CHOP-L-M</td>
<td>14% PR</td>
<td>9 mo if CR</td>
<td>10 mo</td>
<td>Longer duration of first remission resulted in longer survival time</td>
<td>25, a</td>
</tr>
</tbody>
</table>

*Abbreviations: C, cyclophosphamide; CR, complete response (100% of clinically evident disease resolved); FeLV, feline leukemia virus; H, hydroxydaunorubicin, doxorubicin; L, l-asparaginase; M, methotrexate; MST, median survival time; O, vincristine; P, prednisone or prednisolone; PR, partial response (>50% but <100% of clinically evident disease resolved); V, vincristine.

*a* A diagnosis of lymphoma was confirmed in these studies; however, it was not documented whether it was lymphocytic or lymphoblastic.

*b* Not all cats in these studies had alimentary lymphoma.
have been shown to have better efficacy than single-agent protocols and steroids alone.\textsuperscript{18,19} Recently, CCNU (lomustine) used as a single agent or in combination with steroids has been shown to be effective in the treatment of feline lymphoma, and appears to be a reasonable treatment option for many cats.\textsuperscript{20} In general, cats are less responsive to chemotherapy than dogs when they are treated for LBL. Most studies document response rates for cats with LBL at approximately 50% to 75% with an MST of 7 to 9 months.\textsuperscript{21–28} One of the few consistent prognostic indicators in cats treated for LBL is response to therapy; several studies have documented that cats that have a CR to therapy have longer survival times than those that only have a PR to therapy.\textsuperscript{23,25} Other possible indicators of prognosis include the World Health Organization stage of disease. Cats with stage 1 (single extranodal or lymphoid site) and stage 2 (regional lymphadenopathy or resectable GI mass) lymphoma have longer survival times than other stages.\textsuperscript{23} Finally, a positive FeLV antigen test is considered a negative prognostic factor, because cats infected with this virus typically die of viral-associated syndromes even if therapy for lymphoma is effective.\textsuperscript{21}

LGL is an uncommon form of feline alimentary lymphoma that has a poor prognosis.\textsuperscript{5} In a study of 45 cats with LGL, all cats tested negative for retroviruses. Twenty-three cats were treated with chemotherapy. Thirty percent responded, and the MST was 57 days (range, 0–267 days). Prognostic factors for improved survival were not detected.

In general, cats tolerate chemotherapy very well and clinically significant neutropenia is uncommon.\textsuperscript{22} In a recently published survey of 31 owners whose cats were undergoing COP chemotherapy, 83% of owners were happy that they treated their cats and 87% stated they would treat another cat.\textsuperscript{22}

Dietary modifications should be considered as part of the treatment protocol for cats with lymphoma. Diets should be highly digestible and palatable. For cats with concurrent IBD, hypoallergenic diets should be considered. For cats that are anorexic or hyporexic, enteral nutritional support should be provided by means of an esophageal or gastric feeding tube. Appetite stimulants such as cyproheptadine and mirtazapine may also be helpful. For many cats, once chemotherapy (including steroids) is initiated, the appetite improves and the tube can be removed.

Parenteral cobalamin supplementation should be considered even if serum concentrations are not measured, because the prevalence of hypocobalaminemia in cats with GI lymphoma was reported to be 78% in one study.\textsuperscript{8} In another study of cats with a history of clinical signs related to the GI tract and confirmed severe hypocobalaminemia (<100 ng/L), the serum cobalamin concentrations and mean body weight increased, and signs of GI disease improved in the majority of animals after 4 weeks of administration of cobalamin at a dose of 250 μg subcutaneously once weekly.\textsuperscript{26} Limitations of this study included that the cats did not have biopsy-confirmed diagnoses of GI disease and that the majority of cats were receiving other therapy (steroids, antibiotics) concurrently with vitamin B12 supplementation.

Radiation therapy for alimentary lymphoma may be an underutilized treatment modality in cats, because lymphoma is generally a radiation-responsive disease. Radiotherapy is used successfully for the treatment of solitary site lymphomas, including nasal and spinal lymphoma. In a pilot study of 8 cats with LBL treated with 6 weeks of standard multidrug chemotherapy followed by 10 daily 1.5-Gy fractions of radiation, 5 of 8 cats had long-term (>266 days) progression-free survival.\textsuperscript{29} Radiation therapy was well tolerated. Further studies are warranted that will hopefully result in prolongation of survival times in cats with alimentary lymphoma.
CANINE ALIMENTARY LYMPHOMA

Alimentary lymphoma is less common in dogs than in cats, representing only 7% of all canine lymphomas. Alimentary lymphoma in dogs may be part of the syndrome of multicentric lymphoma (ie, peripheral lymph nodes ± other organ systems), but most commonly, it is confined to the GI tract. In one study of 18 dogs with alimentary LBL, 13 (72%) had lymphoma confined to the intestinal tract, and lymphoma was part of multicentric disease in the remaining 5 (28%). Unlike in cats, lymphocytic lymphoma of the alimentary tract is rare. The majority of dogs have rapidly progressive clinical signs associated with lymphoblastic lymphoma, including (in decreasing order of frequency) vomiting, diarrhea, weight loss, anorexia, and lethargy. Physical examination findings in dogs with LBL may include ascites, poor body condition, a palpable abdominal mass, abdominal pain, and thickened intestinal loops. Staging tests are similar to those for feline lymphoma. The most common biochemical abnormality is hypoalbuminemia (which occurs in 61%–80% of dogs); and hypercalcemia is uncommon. The majority of alimentary lymphomas in dogs are of T-cell origin.

Chemotherapy and supportive care are the mainstays of the treatment of alimentary lymphoma in dogs. The overall response rate to treatment with a multidrug chemotherapy protocol (vincristine, L-asparaginase, cyclophosphamide, doxorubicin, prednisone, lomustine, procarbazine, mustargen) was 56% in the largest published study of dogs with alimentary lymphoma. For the responders, the overall median first remission duration was 86 days and the MST was 117 days. Dogs that did not respond to treatment were euthanized a median of 10 days after initiation of therapy. Dogs with diarrhea as a presenting complaint had a worse prognosis, with 13 diarrheic dogs having an MST of 70 days versus 700 days for 5 dogs without diarrhea. Similar to cats with alimentary LBL, intensive fluid therapy and nutritional support (enteral or parenteral) is indicated concurrently with chemotherapy in clinically ill dogs with alimentary lymphoma.

SUMMARY

This article presents a review of feline and canine alimentary GI lymphoma. Gastrointestinal lymphoma should be suspected in animals with an acute or prolonged history of clinical signs of disease related to the GI tract. Systemic staging tests (CBC/chemistry/urinalysis/thyroxin levels/thoracic radiographs) are used to identify concurrent disease. Abdominal ultrasonography is useful for the documentation of intestinal wall thickening, mass lesions, concurrent organ involvement, lymphadenopathy, and abdominal lymphadenopathy. The ultrasonographic findings can be used to decide whether the next diagnostic test should be laparotomy, laparoscopy, or endoscopy, with the goal of obtaining diagnostic histologic specimens. Histopathologically, lymphoma may be lymphoblastic or lymphocytic; these diseases have different therapies and prognosis. Chemotherapy, including steroids and nutritional support, are essential in the management of alimentary lymphoma.

REFERENCES