Gastrointestinal Lymphoma in Cats

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ABSTRACT:
Lymphoma is the most commonly diagnosed neoplasm in cats, and gastrointestinal (GI) lymphoma is now the most common anatomic form. Most cats with GI lymphoma test negative for FeLV and have a median age of 9 to 13 years. The most common clinical sign of GI lymphoma is weight loss followed by decreased appetite, vomiting, and diarrhea. Abdominal ultrasonography can be a strong diagnostic tool for GI lymphoma, but tissue samples are necessary for a definitive diagnosis. Histologic cell type (small versus large cell lymphoma) is a strong predictor of response to treatment and survival time.

LYMPHOMA
Lymphoma, the most commonly diagnosed neoplasm in cats, accounts for 90% of hematopoietic tumors and 33% of all tumors in cats. The incidence of feline lymphoma ranges from 41 to 200 cases per 100,000 cats. Cats of any age may be affected, with reported cases involving patients 4 months to 19 years of age. There is a bimodal peak in incidence, with one occurring at younger than 4 years of age and another at 8 years of age. Younger cats are more likely to have mediastinal lymphoma and test positive for FeLV. Some studies have found that Siamese cats are at higher risk of developing lymphoma. Male cats are more likely to have lymphoma, often in association with a higher incidence of FeLV and/or FIV infection.

PATHOGENESIS
FIV has been associated with an increased incidence of lymphoma. Cats infected with FIV are 5.6 times more likely to develop lymphoma than are FeLV-negative cats. Lymphoma develops in 25% of FeLV-positive cats. Lymphoma cells in cats infected with FeLV contain provirus and cytoplasmic and surface FeLV structural antigens. The malignant cells also express feline oncavirus-associated cell membrane antigen (FOCMA), a tumor-specific antigen. FeLV integrates into the myc oncogene, resulting in tumor formation. The following percentages of cats test positive for FeLV via ELISA: 85% with mediastinal lymphoma, 45% with renal lymphoma, 15% with alimentary lymphoma, and 20% with multicentric lymphoma. The true incidence of FeLV infection in cats with lymphoma may be underestimated by ELISA. In one study, polymerase chain reaction (PCR) testing to amplify viral nucleic acid sequences allowed detection of FeLV in 25% of cats with gastrointestinal (GI) lymphoma that were seronegative for FeLV antigen by ELISA. It has been proposed that some FeLV antigen-negative lymphomas involve latent or replication-defective FeLV. PCR testing can also detect low levels of FeLV that may be undetectable by less sensitive methods. FOCMA has also been found in lymphoma cells by ELISA in up to 20% of cats testing negative for FeLV.
antigen, indicating previous FeLV exposure. Lymphoma may develop without predisposing infectious disease (i.e., cases have been documented in specific pathogen-free cats). In cats testing negative for FeLV and FIV, mutations of the tumor suppressor gene p53 have been found in up to 40% of cases.

**CLINICAL PRESENTATION**

Lymphoma is a heterogenous disease in cats, and there is variation in anatomic classification systems between studies. Lymphoma is most commonly divided into four groups: GI, mediastinal, multicentric, and extranodal. Most studies classify hepatic, pancreatic, or splenic involvement as GI lymphoma, although some studies consider this form to be multicentric.

Disease presentation and anatomic site have changed with the decreasing prevalence of FeLV infection. Before 1980, lymphoma was most common in younger (<7 years of age) FeLV-positive cats presenting with mediastinal involvement. With the advent of widespread testing and vaccination for FeLV since 1980, GI lymphoma has become the most common anatomic presentation (i.e., 32% to 72% of cases) and occurs most frequently in older (median age: 10 years) FeLV-negative cats. For example, the incidence of GI lymphoma in New England has increased from 18% of lymphoma cases in 1983 to 32% in 1996, and the rate of occurrence of GI lymphoma in New York has ballooned from 27% in 1989 to 72% in 1995.

GI lymphoma usually involves the small intestine, resulting in either segmental or generalized thickening. The cecum and colon are rarely affected. Although lymphoma is the most common gastric tumor in cats, the stomach is an uncommon site for lymphoma. In most cats with GI lymphoma, the mesenteric lymph nodes are involved. The median age of cats with GI lymphoma is 9 to 13 years, with a reported range of 1 to 18 years. No breed predilection has been found, but male cats are slightly more likely to develop GI lymphoma. Cats with GI lymphoma have a lower incidence (15%) of FeLV infection than do cats with other anatomic forms of lymphoma, although the true incidence of FeLV infection might be higher if PCR testing were used.

Clinical signs in most cats with GI lymphoma are chronic and present for 1 to 3 months before presentation. The most common clinical signs are anorexia and weight loss. Vomiting is reported in fewer than 50% of cases. Diarrhea is present in approximately 30% of cases. Less common signs include lethargy, weakness, polydipsia, polyuria, pica, and abdominal swelling. Physical examination may reveal a poor body condition, an unkempt haircoat, a thickened bowel, or a palpable abdominal mass. The presence of an abdominal mass is more suggestive of high-grade lymphoma, whereas cats with low-grade lymphoma are more likely to have diffusely thickened bowel loops. Abdominal palpation yields normal results in many cats with GI lymphoma.

In fewer than 50% of cases, nonregenerative anemia is found via complete blood cell count (CBC). Nonregenerative anemia may result from chronic disease, neoplastic bone marrow infiltration, or FeLV infection. Regenerative anemia may result from GI blood loss. The most common serum chemistry abnormality is mild hypoalbuminemia, which occurs in approximately 50% of cats. When lymphoma invades the liver, serum alanine aminotransferase and alkaline phosphatase concentrations may be elevated. However, normal liver enzymes do not rule out liver involvement. Low serum cobalamin concentrations are associated with distal small intestinal disease and were present in 70% of cats with GI lymphoma in one study. Serum concentrations of folate were also decreased in three-fifths of cats with GI lymphoma and tended to be lower (<9 ng/ml) than the folate levels of cats with other diagnoses in this study. Hypercalcemia associated with lymphoma is rare in cats.

Plain abdominal radiographs in cats with GI lymphoma are often normal or have nonspecific findings. Decreased abdominal detail may be present, reflecting loss of body fat or abdominal fluid. A soft tissue mass may be present, or the small intestine may be dilated, suggesting intestinal obstruction or ileus.

Abdominal ultrasonography can be useful in localizing disease, which can be suggestive of a diagnosis of
lymphoma. Ultrasonographic findings may include thickening of the gastric wall (normal: <0.5 cm) or thickening of the intestinal wall (normal: <0.3 cm). Intestinal lesions are usually symmetrically thickened, but gastric lesions may be asymmetric. Lesions may be focal, multifocal, or diffuse. Loss of normal intestinal wall layering is common (Figure 1). Normal wall layering is more commonly preserved in cases of inflammatory disease than in neoplasia. Abdominal lymphadenopathy occurs in many cats with GI lymphoma (Figure 2). Localized masses associated with the intestine, regional bowel hypomotility, decreased intestinal wall echogenicity, and ascites have also been demonstrated in cases of GI lymphoma. “Target lesions” consisting of a hypoechoic ring surrounding a hyperechoic intestinal lumen may be seen but are not pathognomonic for lymphoma. In contrast to GI lymphoma, adenocarcinoma is often asymmetric or eccentric and has irregular contours, heterogeneous echogenicity, and a diminished lumen diameter at the site of the mass. Adenocarcinoma rarely involves mesenteric lymph nodes.

Normal ultrasonographic findings do not rule out a diagnosis of GI lymphoma.

**DIAGNOSIS**

Biopsies are required to definitively diagnose lymphoma. Biopsies may be procured by endoscopy or laparotomy. Many authors advocate laparotomy with full-thickness biopsies over endoscopy. Endoscopy is unable to evaluate the jejunum and ileum, where most lymphoma lesions are located. Biopsies of the mucosa may show inflammatory lesions but miss the underlying lymphoma, especially in cases of high-grade lymphoma, which commonly affects the submucosa most severely. Well-differentiated lymphoma is more likely to affect the superficial mucosal layers and may be more easily diagnosed by endoscopy. Laparotomy has the advantage of allowing full-thickness gastric and intestinal biopsies as well as inspection and biopsies of other abdominal organs. When laparotomy is performed, biopsy specimens of the liver, mesenteric lymph nodes, and pancreas should be obtained even in the absence of gross lesions.

**In cats with small cell GI lymphoma, a good therapeutic response can be achieved with the relatively nonaggressive chemotherapy combination of oral chlorambucil and prednisolone.**
STAGING AND GRADING

Although some authors advocate complete staging according to the World Health Organization’s Clinical Staging for Tumors of Domestic Animals (see box on this page), staging has not been shown to be predictive of outcome. The cost and invasiveness of complete staging should therefore be weighed against the benefit of the additional information.

GI lymphoma is separated into three grades:

- **Low**—Lymphocytic or small cell
- **Intermediate**
- **High**—Lymphoblastic, immunoblastic, or large cell

Most published reports do not specify the grade of lymphoma. In one study, the only difference in clinical signs between the grades was an increased frequency of a palpable abdominal mass in cases of high-grade lymphoma. In one study of 67 cats with GI lymphoma, 75% were classified as having low-grade lymphoma. In another study, intermediate-grade lymphoma made up 61% of cases of GI lymphoma. It can be difficult to differentiate well-differentiated lymphoma from severe inflammatory bowel disease in some cats. Many authors believe that inflammatory bowel disease leads to lymphoma in some cases. Immunophenotypic studies using CD3 and CD79a antibody stains can be conducted to assess T- and B-cell immunoreactivity, respectively, and can help differentiate between severe inflammatory lesions and lymphoma in some cases.

A monomorphic population of B or T lymphocytes supports a diagnosis of lymphoma, whereas a mixed population of T and B lymphocytes is more consistent with inflammatory bowel disease. In one study classifying 602 cases of lymphoma, 67% was derived from B cells, 27% from T cells, and 6% from null cells. FeLV infection was equally common in T- and B-cell lymphomas.

TREATMENT

Chemotherapy

Lymphoma is a systemic disease in cats, and chemotherapy is the treatment of choice (Table 1). Cyclophosphamide, vincristine and prednisolone (CVP protocol) form the basis of many treatment protocols for GI lymphoma in cats. GI toxicosis (e.g., vomiting, diarrhea, anorexia) is common with the CVP protocol but usually manageable with supportive treatment. Because vincristine and cyclophosphamide may cause severe myelosuppression, a CBC should be monitored weekly for the first several weeks of treatment. Cyclophosphamide can also cause sterile hemorrhagic cystitis; however, this problem is rare in cats.

Another common protocol combines CVP therapy with doxorubicin. CVP therapy should be administered as described in Table 2, and doxorubicin should be administered at a dose of 20 mg/m² IV every 3 weeks. Doxorubicin may cause bone marrow suppression, GI signs, and cardiac toxicity. Alopecia, involving mainly the whiskers in cats and slow regrowth of clipped hair, may occur.

The protocol used by The Animal Medical Center, New York (i.e., AMC protocol), combines L-asparaginase, vincristine, cyclophosphamide, doxorubicin, methotrexate, and prednisolone (Table 1). L-Asparaginase can cause hypersensitivity reactions; thus most oncologists recommend administering diphenhydramine (1 mg/kg SC) 30 minutes before administering L-asparaginase. Methotrexate has the GI and bone marrow toxicity common to most chemotherapy drugs.

Another commonly used protocol, VCM + L-asparaginase, combines vincristine, cyclophosphamide, methotrexate, and L-asparaginase (Table 1). Oral chemotherapy with the slow alkylating agent chlorambucil combined with prednisolone for low-grade lymphoma has been advocated. Prednisolone should be administered at a dose of 10 mg/cat/day PO. Different doses of chlorambucil have been recommended. One protocol calls for a dose of 15 mg/m²/day PO for 4 days, then every 3 weeks. Long-term chlorambucil at a dose of

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement limited to a single node of lymphoid tissue in a single organ (excluding bone marrow)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of multiple lymph nodes in a regional area (± tonsil)</td>
</tr>
<tr>
<td>III</td>
<td>Generalized lymph node involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Liver and/or spleen involvement (± stage III)</td>
</tr>
<tr>
<td>V</td>
<td>Manifestation in the blood, and involvement of bone marrow and/or other organ systems (± stages I–IV)</td>
</tr>
</tbody>
</table>

Each stage is further subclassified as:

- a Without systemic signs
- b With systemic signs

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October 2005
2 mg/cat every other day is also commonly used. Adverse reactions to chlorambucil are rare but can include GI toxicity, bone marrow suppression, and hepatotoxicity. A CBC and serum chemistry profile should be conducted before treatment, then weekly for the first month of treatment and every 3 months thereafter.

Current studies evaluating treatment of GI lymphoma are limited because of the small number of cats studied and lack of reporting the histologic grade in many studies. Also, many studies do not report outcomes in cats with GI lymphoma separately from those of cats with other anatomic types of lymphoma. A summary of several studies, the protocols used, and the median survival times is presented in Table 2. Jeglum et al treated nine cats with GI lymphoma with a combination of vincristine, cyclophosphamide, methotrexate, and L-asparaginase. A 55% remission rate was achieved, with a median remission interval of 6 months and a median survival time of 9.6 months. Rassnick treated 31 cats with the AMC protocol (i.e., a combination of L-asparaginase, vincristine, cyclophosphamide, doxorubicin, methotrexate, and prednisolone), achieving remission in 16 cats. The median remission time was 4 months, and the median survival time was 8.6 months. Zwahlen et al treated 21 cats with GI lymphoma using the AMC protocol: 38% achieved complete remission, 57% achieved partial remission, and 5% had stable or progressive disease. Cats achieving remission had a median remission time of 10 months. The average survival time for all cats in the study was 10.3 months. Lomustine (CCNU), an oral alkylating agent, was used in a phase I trial to treat six cats with GI lymphoma and achieved only a partial response in two cats.

Teske et al described 11 cats with GI lymphoma treated with cyclophosphamide, vincristine, and prednisolone (CVP). Seven cats achieved complete remission, with a median remission time of 32 weeks; the median survival time of all cats in the study was 25 weeks. In two other studies, cats with GI lymphoma were treated using the CVP protocol. Cotter treated seven cats, six of which achieved complete remission with a median duration of 19 weeks and a median survival time of 26 weeks. Mahony et al treated 25 cats with high-grade GI lymphoma using the CVP protocol. Eight cats achieved complete remission with a median duration of 7.2 months; the median survival time was 7.5 weeks. Fondacaro et al also presented results of cats treated for high-grade lymphoma. In this study, 11 cats with high-grade lymphoma were treated using the CVP protocol with or without doxorubicin. As in Mahony’s study, cats with high-grade GI lymphoma fared poorly. The overall median survival time was only 10 weeks, whereas the
median disease-free interval of the 18% that achieved remission was only 2.5 months. These studies indicate a poorer prognosis and shorter survival time for cats with high-grade lymphoma. These findings contrast with those of cats with low-grade lymphoma. Fondacaro et al treated 29 cats with low-grade GI lymphoma using oral prednisolone and chlorambucil. Sixty-nine percent of cats in this study achieved complete remission with a median disease-free interval of 20.5 months. The median survival time for all cats was 17 months. Twelve of the 20 cats that achieved complete remission responded to a “rescue” treatment with oral cyclophosphamide after relapse, achieving a median disease-free interval of 24 months and a survival time of 29 months. Seven of the original 29 cats were alive at the time of data collection, and all but one of them had undergone “rescue” therapy.

The response to doxorubicin alone is generally poorer than that to other protocols; thus this drug should not be used as a sole chemotherapy agent for GI lymphoma. Kristal et al used doxorubicin as the sole agent in seven cats with GI lymphoma and achieved remission in only 28%. Peaston and Maddison also administered doxorubicin alone in four cats with GI lymphoma, and remission was not achieved in any of them. One study of 145 cases of lymphoma of unspecified grade and location showed a significantly longer remission time with CVP plus doxorubicin (9 months) than with CVP alone (3 months).

Some general conclusions can be drawn from the results of these studies. The response rate and survival time with chemotherapy for high-grade GI lymphoma are poor, whereas the response rate and remission dur-

**Table 2. Remission Rates and Survival Times of Cats with GI Lymphoma**

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>No. of Cases</th>
<th>Complete Remission Rate (%)</th>
<th>Median Remission Time (mo)</th>
<th>Median Survival Time (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeglum et al</td>
<td>VCM + L-asparaginase</td>
<td>9</td>
<td>55</td>
<td>6</td>
<td>9.6</td>
</tr>
<tr>
<td>Rassnick</td>
<td>AMC</td>
<td>31</td>
<td>51</td>
<td>4</td>
<td>8.6</td>
</tr>
<tr>
<td>Zwahlen et al</td>
<td>AMC</td>
<td>21</td>
<td>38</td>
<td>10</td>
<td>10.3</td>
</tr>
<tr>
<td>Teske et al</td>
<td>CVP</td>
<td>11</td>
<td>63</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Cotter</td>
<td>CVP</td>
<td>7</td>
<td>85</td>
<td>4.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Mahony et al</td>
<td>CVP ± doxorubicin</td>
<td>25 with high-grade lymphoma</td>
<td>32</td>
<td>7.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Fondacaro et al</td>
<td>CVP ± doxorubicin</td>
<td>11 with high-grade lymphoma</td>
<td>18</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Fondacaro et al</td>
<td>Prednisolone and chlorambucil</td>
<td>29 with low-grade lymphoma</td>
<td>69</td>
<td>20.5</td>
<td>17</td>
</tr>
<tr>
<td>Kristal et al</td>
<td>Doxorubicin</td>
<td>7</td>
<td>28</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Peaston and Maddison</td>
<td>Doxorubicin</td>
<td>4</td>
<td>0</td>
<td>—</td>
<td>1.1</td>
</tr>
</tbody>
</table>

AMC = L-asparaginase, vincristine, cyclophosphamide, doxorubicin, methotrexate, and prednisolone; CVP = cyclophosphamide, vincristine, and prednisolone; VCM + L-asparaginase = vincristine, cyclophosphamide, methotrexate, and L-asparaginase.

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Decreased serum cobalamin and/or folate levels can help localize disease to the small intestine in cats presenting with weight loss as the sole clinical sign of GI lymphoma.
tion are much better for low-grade lymphoma.\textsuperscript{17} Cats with low-grade GI lymphoma can have a good response to a relatively nonaggressive chemotherapy protocol of oral prednisolone and chlorambucil.\textsuperscript{17} It is unknown whether survival times and remission rates would be longer with a more aggressive chemotherapy protocol. However, administering a slow alkylating agent such as chlorambucil may be endorsed with regard to the lower mitotic rate of low-grade lymphoma.\textsuperscript{7} Doxorubicin may prolong remission times when used in combination with other chemotherapy protocols\textsuperscript{20} but is not effective when used as the sole agent to treat GI lymphoma in cats.\textsuperscript{28,29} Unlike dogs with lymphoma, cats that had received previous corticosteroid treatment before a diagnosis of lymphoma had neither a better nor worse prognosis than cats that had not previously been treated with corticosteroids.\textsuperscript{18}

**Surgery**

Surgery is indicated in treating GI lymphoma when partial or complete intestinal obstruction or intestinal perforation is present. Because lymphoma is generally a systemic disease with diffuse or multifocal microscopic involvement, chemotherapy is warranted after resection of a focal GI mass. Cytotoxic chemotherapy may result in delays in wound healing or dehiscence; it is recommended that chemotherapy be delayed for 10 to 14 days after surgery. Surgery in cases of GI lymphoma has not been correlated with increased or decreased survival times.\textsuperscript{7}

**Supportive Care**

Supportive care plays a vital role in treating GI lymphoma in cats. Oral appetite stimulants such as cyproheptadine can be useful in increasing voluntary food intake. Placing an esophagostomy or gastrostomy feeding tube in anorectic cats that are not vomiting can allow delivery of adequate nutrition, especially during induction of remission. Surgical placement of a jejunostomy tube is warranted if intractable vomiting occurs. As previously mentioned, a large proportion of cats with GI lymphoma are severely deficient in cobalamin. The main clinical finding with cobalamin deficiency is anorexia, which often improves with cobalamin supplementation. Cobalamin supplementation at a rate of 250 µg SC once weekly can help stimulate the appetite and improve a cat’s general condition. Although it has been speculated that cobalamin supplementation can lead to increased proliferation of neoplastic cells, this finding has not been substantiated in controlled studies.\textsuperscript{2} Oral metoclopramide may control nausea and vomiting in many cats. In cats with continued nausea, constant rate infusion of metoclopramide or oral ondansetron may be necessary.

**PROGNOSIS**

Few prognostic factors have been well defined for cats with GI lymphoma. In one study,\textsuperscript{17} histologic grade was shown to be a strong indicator of outcome. Cats with low-grade lymphoma treated with oral prednisolone and chlorambucil had significantly better remission rates (69% versus 18%) and survival times (17 versus 2.7 months) than did cats with high-grade lymphoma treated with multiagent chemotherapy. In most studies,\textsuperscript{15,17,18,23–25,27,28,30} the most significant prognostic indicator was initial response to chemotherapy. Cats that achieved complete remission generally had longer survival times than did cats failing to achieve remission. Stage of disease has not been shown to predict outcome.\textsuperscript{7,17} Negative FeLV status has been correlated with longer survival time in several studies,\textsuperscript{4,5,20} but FeLV status was not a predictor of survival in one study.\textsuperscript{30} One study\textsuperscript{20} that classified cats as sick at the time of treatment (i.e., substage b) versus generally healthy (i.e., substage a) showed a significantly longer survival time in “well” cats (9.5 months) versus clinically

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October 2005

**COMPENDIUM**

Gastrointestinal Lymphoma in Cats \textsuperscript{749}
ill cats (3.5 months). Similar findings were found in another study. However, this classification may be less applicable to cases of GI lymphoma, as virtually all cats are clinically ill at the time of diagnosis.

Molecular markers as predictors of prognosis have been studied. Assays measuring tumor cell proliferation, such as argyrophilic nucleolar organizer region (AgNOR) frequency, have not been shown to correlate with response to chemotherapy or survival time in feline lymphoma. The immunophenotype (B versus T cell) of tumor cells also does not correlate with response to therapy or survival in cats.

REFERENCES

3. Cats infected with FeLV have a _______ times higher risk of developing lymphoma than do cats that test negative.
   a. five  
   b. 22  
   c. 62  
   d. 100

4. Which finding suggests large cell, high-grade lymphoma?
   a. poor body condition  
   b. palpable abdominal mass  
   c. history of vomiting  
   d. anorexia

5. Which ultrasonographic finding(s) is not consistent with a diagnosis of lymphoma?
   a. target lesions (i.e., hypoechoic ring surrounding a hyperechoic intestinal lumen)  
   b. asymmetric thickening of the bowel  
   c. multifocal bowel thickening  
   d. enlarged mesenteric lymph nodes

6. Disadvantages of endoscopically procured biopsy specimens include the inability to
   a. evaluate the jejunum and ileum.  
   b. evaluate abdominal organs outside the GI tract.  
   c. take full-thickness specimens.  
   d. all of the above

7. Most cases of GI lymphoma are ____ cell in origin.
   a. B  
   b. T  
   c. null  
   d. none of the above

8. The median survival time of cats with small cell GI lymphoma is reportedly
   a. 8 weeks.  
   b. 6 months.  
   c. 8 months.  
   d. 17 months.

9. Which site is most commonly involved in GI lymphoma?
   a. jejunum  
   b. ileum  
   c. colon  
   d. stomach

10. The most common clinical sign of GI lymphoma is
    a. vomiting.  
    b. weight loss.  
    c. diarrhea.  
    d. abdominal enlargement.