

FELINE LYMPHOMA

Amy C. Durham, MS, VMD, DACVP and Erika L. Krick, VMD, DACVIM (Oncology)

University of Pennsylvania School of Veterinary Medicine

Philadelphia, PA

Introduction

Lymphoma is the most common hematopoietic tumor in cats, and the incidence is reportedly the highest for any species. Despite this high incidence, diagnostic techniques, treatment options, and expected prognosis remained unchanged for decades. New information has recently emerged regarding different morphological variants of feline lymphoma, diagnostic options, treatments and prognosis. For better or worse, we are dealing with a new generation of cats with lymphoma and although some questions have been answered, new challenges have been identified as well.

Etiology

The retrovirus Feline Leukemia Virus (FeLV) has long been recognized as a cause of lymphoma in cats; the risk for lymphoma is increased sixtyfold in infected cats. Before the advent of a vaccine in 1985, approximately 70% of cats (mainly young animals) with lymphoma were FeLV positive. FeLV infects T cells and can cause myelodysplastic syndrome, acute myeloid leukemias, and T cell leukemia/lymphoma. In the latter, the mediastinum is the site most commonly involved (thymus, mediastinal, and sternal lymph nodes), although a multicentric distribution also occurs. Routine FeLV vaccination has led to a significant decrease in the prevalence of FeLV infection, which has resulted in a decrease in the proportion of mediastinal lymphomas. Cats infected with Feline Immunodeficiency Virus (FIV) have a fivefold to sixfold higher risk for developing lymphoma than in uninfected cats. Currently the most common location of lymphoma in cats is the gastrointestinal tract.

Histopathologic Types, Clinical Presentation, Diagnosis, and Staging

As more studies have examined our ability to diagnose lymphoma in cats using cytology, histopathology, immunohistochemistry, and/or PCR testing for antigen receptor rearrangement, conflicting reports have arisen regarding the frequency of small and large cell lymphoma in cats. When lymphoma cases diagnosed using cytology or histopathology are included, large cell lymphoma is the most common form diagnosed.¹ Cases classified according to the World Health Organization criteria found that mucosal T-cell lymphoma, also known as enteropathy-associated T cell lymphoma (EATCL type II) is the most common form.² This form of feline lymphoma arises from diffuse mucosal associated lymphoid tissue (MALT) of the small intestine. EATCL type II is associated with indolent clinical behavior and prolonged survival time and consists of small to intermediate-sized lymphoma cells, which is consistent with current terminology that refers to this type of lymphoma as small cell or low-grade lymphoma.

Transmural T cell lymphomas also occur focally or multifocally in the small intestine of cats and are classified as EATCL type I. By definition, these tumors must extend into the submucosa and muscularis, and some tumors invade the serosa and adjacent mesentery and can seed the abdomen in a similar manner to carcinoma (“lymphomatosis”). T cell large granular lymphocyte (LGL) lymphoma is often diagnosed, and B cell lymphomas are less prevalent in cats but occur in the stomach, jejunum, and ileoceocolic region as transmural lesions.²

Large cell lymphoma

This form of lymphoma has been recognized the longest, and it is the subject of the majority of research into feline lymphoma. Unfortunately we have been unable to break through the “locked cat door” regarding response rate, remission duration, and survival times that can be achieved with conventional chemotherapy, and new treatment strategies are needed. Large cell lymphoma can affect any area of the body, but the most common locations are the gastrointestinal tract, non-gastrointestinal tract abdominal locations such as the spleen or kidneys, nasal cavity, CNS, peripheral lymph nodes with or without liver and spleen involvement, and the mediastinum.³ Cats with large cell lymphoma typically exhibit clinical

signs referable to the anatomic location involved, and the physical examination abnormalities are related to the anatomic site as well.

Diagnosis of large cell lymphoma is often made during the work-up for an ill cat, and the presence of a palpable mass, facial deformity, pleural effusion, and positive FeLV status will raise the index of suspicion for large cell lymphoma. Because the neoplastic cells are large lymphoblasts that exfoliate well, fine needle aspiration and cytology is often sufficient to make the diagnosis. If cytology is unrewarding, then biopsy can be pursued to obtain a definitive diagnosis.

Most of the recommended staging tests for large cell lymphoma are typically performed during the diagnostic work-up that resulted in the diagnosis of lymphoma; however, it is typically recommended that cats diagnosed with large cell lymphoma have a complete blood count, chemistry panel, urinalysis, FIV/FeLV testing, chest radiographs, and abdominal ultrasound performed. Additional staging tests (such as CT scan or regional lymph node aspirate) may be recommended depending on the anatomic site involved. When I am presented with a cat with large cell lymphoma, if any of the above tests have not already been performed I will finish the staging process prior to initiating treatment.

Small cell lymphoma

This form of lymphoma has been recognized for over 10 years as a morphologically distinct variant from large cell lymphoma. The clinical presentation and biological behavior of this form of lymphoma is also quite different from that of large cell lymphoma, as is the recommended treatment. Small cell lymphoma almost always affects the gastrointestinal tract with or without abdominal lymph node and other abdominal organ involvement.⁴⁻⁸ Cats with small cell lymphoma tend to present with a longer history and lower severity of clinical signs compared to cats with large cell lymphoma.

The neoplastic cells closely resemble normal small lymphocytes, so it is very difficult to diagnose small cell lymphoma on cytology alone. Even with full-thickness biopsy samples, making a definitive diagnosis of small cell lymphoma (versus inflammatory bowel disease/IBD) in the cat can be challenging. Additional diagnostic tests such as flow cytometry, immunohistochemistry (IHC), and PCR for antigen receptor rearrangement (PARR) can be used to help support or rule out small cell lymphoma; however, none of these tests is without flaws. Flow cytometry and IHC will both identify the type of lymphocytes in question (B or T cells). Unfortunately, both small cell lymphoma and inflammatory bowel disease are associated with T lymphocytes, so determining the type of lymphocytes is unlikely to distinguish between the two diseases except in the relatively uncommon situation of small cell B cell lymphoma.^{9,10} PARR will also identify the lymphocyte population but is primarily a test for clonality: monoclonal lymphocyte populations are more likely to be neoplastic compared to polyclonal populations, which are more likely to be reactive.¹¹ The sensitivity (78% in T cell lymphoma and 50% in B cell lymphoma) of PARR testing in distinguishing small cell lymphoma from inflammatory bowel disease is not high enough to allow PARR to be a stand-alone test to determine if a cat has small cell lymphoma or IBD.^{9,12} Current recommendations for distinguishing small cell lymphoma from IBD include a combination of histopathology, IHC, and PARR.¹¹ That paper reported that the specificity of histopathology for distinguishing small cell lymphoma from IBD is 99.9%, meaning that it is very unlikely that a pathologist would diagnose a cat with small cell lymphoma when the actual diagnosis is IBD. On the other hand, the specificity is 72%, meaning that a pathologist could diagnose a cat with IBD when the actual diagnosis is small cell lymphoma. As IHC and PARR are added to the diagnostic regime, the specificity increases to 78% then 83%, while the sensitivity remains unchanged. This information underscores the importance of incorporating all clinical and diagnostic information instead of relying on one specific test when attempting to determine if a cat has small cell lymphoma or IBD.

The recommended staging tests for cats with small cell and large cell lymphoma are similar with the exception of one additional test that is recommended for cats with small cell lymphoma. Cats with small cell lymphoma are at risk for cobalamin deficiency, which can exacerbate their clinical signs. One study of cats with small cell lymphoma found that 78% of them were cobalamin deficient, so measuring serum cobalamin and supplementing as indicated is recommended in these patients.⁶⁻⁵ Small cell lymphoma is unlikely to affect intrathoracic structures except for the sternal lymph node. An enlarged sternal lymph

node is unlikely to change the treatment plan, but monitoring how the lymph node changes (or not) with treatment can be a helpful addition to repeat abdominal imaging when assessing response to treatment.

Intermediate Cell Lymphomas

No studies specifically examine the diagnostic procedures, treatment, and expected outcome for cats with intermediate cell lymphoma. The WHO classification categorizes high-grade intermediate cell lymphomas as lymphoblastic lymphomas or Burkitt-like lymphoma; peripheral T cell lymphomas may also be in the intermediate to large cell size range and a subset of EATCL may also be in the small to intermediate cell size range. Likely due to the different subtypes, intermediate cell lymphomas appear to have a varied biological behavior and they can mimic the clinical picture of large or small cell lymphoma, which makes it difficult to decide upon a recommended course of treatment. At the author's hospital, if the clinical behavior of a cat with intermediate cell lymphoma is similar to large cell lymphoma, then chemotherapy for large cell lymphoma is recommended, and vice versa. All of these variants are uncommonly reported so it is difficult to make generalizations regarding recommended treatment protocols or prognosis for them.

T Cell Rich Large B Cell Lymphoma

T cell rich large B cell lymphoma, also referred to as feline Hodgkin-like lymphoma in some studies, is composed of a mixture of reactive small lymphocytes and large neoplastic B lymphocytes (resembling the Hodgkin cells or Reed-Sternberg cells of human Hodgkin's lymphoma). Cats with this disease often present with a slow-growing unilateral enlargement of the cervical lymph nodes, which spreads to adjacent nodes within the chain. However, a proportion of cases may go on to develop into a more aggressive disease that can affect peripheral and visceral nodes and multiple organs.

First Line Treatment

Large cell lymphoma

Combination chemotherapy with COP or CHOP protocols is considered the standard of care for the treatment of large cell lymphoma in cats. An exception is the option of first line radiation therapy for cats with nasal or mediastinal lymphoma. One thing to keep in mind when treating cats with large cell lymphoma, particularly gastrointestinal large cell lymphoma, is that the clinical signs of progressive lymphoma (decreased appetite, vomiting, weight loss) are very similar to common chemotherapy side effects (decreased appetite, vomiting, weight loss). That can make it challenging to determine if a cat being treated for large cell lymphoma and who is acting ill is doing so because of tumor progression, poor tolerance to chemotherapy, or both. One potential solution to this quandary is to alter chemotherapy protocols to include other drugs that are less likely to cause these side effects.

One of the authors has recently completed and published a prospective randomized clinical trial comparing the efficacy and tolerance of vinblastine versus vincristine for feline lymphoma.¹⁴ Briefly, 40 cats with treatment-naïve large cell lymphoma or progressive small cell lymphoma were randomized to receive a COP based protocol that contained either vincristine or vinblastine. Owners were blinded to their cat's study group to minimize bias in their reporting of clinical signs. Cats that experienced clinically significant gastrointestinal toxicity (end points established *a priori*) could be crossed over to the other treatment group in an effort to maintain dose intensity if one of the two drugs was poorly tolerated. Response rate, progression free survival, lymphoma specific survival, and the number of cats in each group that crossed over to the other group due to gastrointestinal toxicity were compared between the two groups. Response rate and outcome was very similar between the two groups. The number of cats that switched from vincristine to vinblastine due to gastrointestinal toxicity was significantly higher compared to the number of cats that switched from vinblastine to vincristine due to gastrointestinal toxicity. Neutropenia was more common in the vinblastine group, but the number of dose reductions due to neutropenia was not significantly different between the two groups.

Small cell lymphoma

Multiple reports have confirmed the efficacy of prednisone/prednisolone and chlorambucil for cats with small cell lymphoma (Table 1). These protocols are typically well tolerated. Reported toxicities include mild to moderate gastrointestinal signs and myelosuppression, but the benefits of treatment outweigh the

risks in the majority of patients with small cell lymphoma, particularly in the absence of co-morbidities such as chronic kidney disease or diabetes mellitus.

Table 1. Published chemotherapy protocols, response rates, and outcome for small cell lymphoma. *If reference provided outcome information in days, the value was converted to months for this table.

Protocol	Response Rate	Outcome (months)*	Reference
Prednisolone 10 mg PO q24h Chlorambucil 15 mg/m ² PO daily for 4 days every 3 weeks	69% CR	CR duration 16 Survival 17	8
Prednisone 5-10 mg PO q12-24h Chlorambucil 2 mg PO q48-72 hours	56% CR 39% PR	CR duration 29.4 PR duration 14 Survival 23	5
Prednisolone 3 mg/kg PO q24h until CR, then 1-2 mg/kg q24h Chlorambucil 15 mg/m ² PO q24h for 4 days every 3 weeks	76% CR	CR 18.9 Survival 14.9	6
Prednisone or prednisolone varied doses for 1 week, then tapered to 1 mg/kg PO q48h Chlorambucil 20 mg/m ² PO every 2 weeks	96% clinical remission	Clinical remission duration 25.8 Survival not reported	7

Rescue Therapies

Large cell lymphoma

Few studies have been published regarding rescue chemotherapy options for cats with large cell lymphoma, and the efficacy is poor. Lomustine (CCNU) appears to be the most promising option for cat with non-gastrointestinal large cell lymphoma, while the response rate to doxorubicin in the rescue setting was 0% for cats with large cell lymphoma.^{15,16} Radiation therapy to the abdominal cavity has been reported as a rescue therapy in 11 cats with intestinal lymphoma.¹⁷ Cats with small and large cell lymphoma were included in that retrospective study. Radiation therapy was delivered in 2 daily fractions of 4 Gy in most cats. One of the cats died shortly afterwards related to extensive hepatic infiltration of lymphoma, and one cat experienced a decreased appetite for a few days. Otherwise the treatment was well tolerated. The 10 cats that survived after treatment responded to therapy and had a median survival time after treatment of 214 days. There were too few cats to compare outcome according to lymphoma cell type, and more studies are needed in cats with large cell lymphoma to determine how beneficial it would be to include radiation therapy more routinely in the treatment of cats with intestinal lymphoma. Radiation therapy is more likely to be used in cats with nasal or mediastinal lymphoma as either first line or rescue therapy.

Small cell lymphoma

Although most cats with small cell lymphoma respond well to treatment, not all of them do. In addition, some cats may eventually relapse and be resistant to chlorambucil. The primary choices for rescue chemotherapy in cats with small cell lymphoma are other alkylating agents: cyclophosphamide and lomustine. Two papers describing treatment of small cell lymphoma with prednisone/prednisolone and chlorambucil comment on observed responses to rescue treatment with cyclophosphamide.^{7,8} One reports that all 7 of 7 cats responded to cyclophosphamide rescue treatment.⁷ Three of those cats eventually died of causes unrelated to lymphoma, and another 3 were lost to follow up, so the duration of response to rescue is difficult to interpret. The second study does not describe objective outcome parameters but states that “rescue extended the life of some of the cats.”⁶ When doxorubicin was examined in the rescue setting for cats with lymphoma, responses were noted only in cats with small or intermediate cell lymphoma.¹⁷ Similarly, cats with small cell lymphoma were reported to have longer response duration to rescue therapy with lomustine compared to cats with large cell lymphoma.¹⁵ A more recent study evaluating rescue chemotherapy for cats with relapsed small cell lymphoma found that both lomustine and reintroduction of prednisolone and chlorambucil (if chlorambucil had been discontinued) were associated with long survival times, with the survival time being longer for cats that received reintroduction of prednisolone and chlorambucil versus lomustine.¹⁹

Body Weight and Body Condition Score

The prognostic impact of lower body weight in feline lymphoma has been well documented, with cats that have a lower body weight experiencing shorter survival times.^{14,15,19} A prospective study examining the effect of body condition score (BCS) as well as weight on survival in cats with cancer found that cats with a BCS less than 5 had a significantly shorter survival time for all cats as well as specifically for cats with lymphoma (3.3 versus 16.9 months, $p = 0.001$).²⁰ Remission status was also significantly correlated with BCS, as cats in remission had a mean \pm SD BCS of 5.2 \pm 1.7 compared to a mean \pm SD BCS of 2.8 \pm 1.9 for cats not in remission ($p = 0.0008$).

It is plausible that cats that weigh less and have a poorer body condition score will have more advanced disease and be less responsive to and tolerant of cancer treatment. The next question to ask, then, is can weight changes over time be used as a surrogate marker for response? It is likely that cats that are not responding to or tolerating treatment will continue to lose weight, while patients that are responding to and tolerating treatment well may gain weight. A recent study evaluated the impact of weight changes over time on survival time of cats with lymphoma.²¹ Cats with large and small cell lymphoma were included, and weight measurements at baseline and 1, 2, 3, and 6 months after starting treatment were recorded from the medical records. Interestingly, this study found that baseline weight was not predictive of survival. Changes in weight at the time points recorded did not correlate with survival for cats with small cell lymphoma; however, changes in weight at the 1 month time point for cats with large cell lymphoma did. Specifically, cats that lost $\geq 5\%$ of their body weight compared to baseline at the 1 month time point had a significantly shorter survival time compared to cats with stable or increased weight. A similar trend was found at the 2 month time point, but the difference was not statistically significant.

Ongoing Challenges

Advances have been made in the diagnosis and classification of feline lymphoma and associating lymphoma type with treatment recommendations and outcome. In addition, investigation of different treatment strategies, such as radiation therapy and different chemotherapy protocols (vinblastine instead of vincristine), have provided some alternatives to standard treatment for these patients. However, several significant challenges for the successful treatment of cats with lymphoma, particularly large cell lymphoma, remain.

As more studies have focused on specifically including cats with either small or large cell lymphoma, the distinction in clinical behavior and prognosis between these two forms of lymphoma has become more obvious. In general, the reported outcome for cats with large cell lymphoma appears to be less promising than it was 15 years ago; however, the current numbers are likely a more accurate assessment because the bias of including cats with small cell lymphoma on survival times has been removed. The next challenge then is to investigate new treatment strategies to improve the outcome of cats with large cell lymphoma and to increase our ability to identify cats that are more and less likely to respond to treatment. Effective supportive care and accurately determining response to treatment remain challenges, and the recent studies that suggest that body weight and/or body condition score can be used as surrogate markers for response underscore the importance of this aspect of feline lymphoma treatment.

References

1. Russell KJ, Beatty JA, Dhand N, et al.: Feline low-grade alimentary lymphoma, how common is it? *J Feline Med Surg* 14(12):910-912, 2012.
2. Moore PF, Rodriguez-Bertos A, Kass PH. Feline gastrointestinal lymphoma: mucosal architecture, immunophenotype, and molecular clonality. *Vet Pathol* 49:658, 2012.
3. Louwerens M, London CA, Pederson NC, et al: Feline lymphoma in the post-feline leukemia virus era. *J Vet Intern Med* 19:329, 2005.
4. Carreras JK, Goldschmidt M, Lamb M, et al.: Feline epitheliotropic intestinal malignant lymphomas: 10 cases (1997-2000), *J Vet Intern Med* 17:326-331, 2003.
5. Kiselow MA, Rassnick KM, McDonough SP, et al: Outcome of cats with low-grade lymphocytic lymphoma: 41 cases (1995-2005). *J Am Vet Med Assoc* 232:405, 2008.
6. Lingard AE, Briscoe K, Beatty JA et al.: Low-grade alimentary lymphoma: clinicopathological findings and response to treatment in 17 cases, *J Feline Med Surg* 11:692, 2009.

7. Stein TJ, Pellin M, Steinberg H, et al.: Treatment of feline gastrointestinal small cell lymphoma with chlorambucil and glucocorticoids, *J Am Anim Hosp Assoc* 246:413, 2010.
8. Fondacaro JV, Richter KP, Carpenter JL.: Feline gastrointestinal lymphoma: 67 cases (1988-1996), *Eur J Comp Gastroenterol* 4:5, 1999.
9. Moore PF, Rodriguez-Bertos A, Kass PH: Feline gastrointestinal lymphoma: mucosal architecture, immunophenotype, and molecular clonality, *Vet Pathol* 49:658, 2012.
10. Carreras JK, Goldschmidt M, Lamb M, et al.: Feline epitheliotropic intestinal malignant lymphomas: 10 cases (1997-2000), *J Vet Intern Med* 17:326, 2003.
11. Avery AC: Molecular diagnostics of hematologic malignancies in small animals, *Vet Clin Small Anim* 42:97-110, 2012.
12. Moore PF, Woo JC, Vernau W, et al.: Characterization of feline T cell receptor gamma (TCRG) variable region genes for the molecular diagnosis of feline intestinal T cell lymphoma, *Vet Immunol Immunopathol* 106:167, 2005.
13. Kiupel M, Smedley RC, Pfent C, et al: Diagnostic algorithm to differentiate lymphoma from inflammation in feline small intestinal biopsy samples. *Vet Path* 48:212, 2011.
14. Krick EL, Cohen RC, Gregor TP, Sorenmo KU. Prospective clinical trial to compare vincristine and vinblastine in a COP-based protocol for lymphoma in cats. *J Vet Intern Med* 27:134, 2013.
15. Dutelle AL, Bulman-Fleming JC, Lewis CA, et al.: Evaluation of lomustine as a rescue agent for cats with resistant lymphoma, *J Feline Med Surg* 10:694, 2012.
16. Oberthaler KT, Mauldin E, McManus PM, et al.: Rescue therapy with doxorubicin-based chemotherapy for relapsing or refractory lymphoma: a retrospective study of 23 cases, *J Feline Med Surg* 11:259, 2009.
17. Parshley DL, LaRue SM, Kitchell B, et al: Abdominal irradiation as a rescue therapy for feline gastrointestinal lymphoma: a retrospective study of 11 cats (2001-2008). *J Feline Med Surg* 13:63, 2011.
18. Pope KV, Tun AE, McNeill CJ. Outcome and toxicity assessment of feline small cell lymphoma: 56 cases (2000-2010). *Vet Med Sci* 1:51-62, 2015.
19. Hadden AG, Cotter SM, Rand W, et al: Efficacy and toxicosis of VELCALP-C treatment of lymphoma in cats. *J Vet Intern Med* 22:153, 2008.
20. Baez JL, Michel KE, Sorenmo K, et al.: A prospective investigation of the prevalence and prognostic significance of weight loss and changes in body condition in feline cancer patients, *J Feline Med Surg* 9:411, 2007.
21. Krick EL, Moore RH, Cohen RB, et al.: Prognostic significance of weight changes during treatment of feline lymphoma, *J Feline Med Surg* 13:976, 2011.